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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

MITSUBISHI TANABE PHARMA CORPORATION and METUCHEN PHARMACEUTICALS, LLC Plaintiffs, vs. EMPOWER PHARMACEUTICALS LLC, EMPOWER CLINIC SERVICES LLC and ARTA SHAUN NOORIAN Defendants	Civil Action No. 2:18-cv-11406-JLL-SCM Hon. José L. LINARES, Chief Judge **AMENDED COMPLAINT** ***JURY TRIAL DEMANDED***

Plaintiffs METUCHEN PHARMACEUTICALS LLC of Cranford, New Jersey and MITSUBISHI TANABE PHARMA CORPORATION of Osaka, Japan state as follows:

1. Plaintiffs developed and now sell STENDRA® avanafil, a patented prescription pharmaceutical. Defendants are fully aware of the patent. Yet nonetheless covertly import avanafil and market it to patients in New Jersey. This infringes Plaintiffs' patent. Compounding the harm, Defendants peddle their knock-offs using Metuchen's copyrighted package insert, and misuse

Plaintiffs' trademark and quality-testing data to confuse patients, falsely passing-off their knock-offs as genuine STENDRA® avanafil and/or as equivalent to it. Further compounding the harm, Defendants use avanafil which appears to be defective, tarnishing the reputation of genuine STENDRA® avanafil. This action therefore claims infringement of Federal patent, copyright and trademark rights, New Jersey state trademark and unfair competition rights and New Jersey State Board of Pharmacy regulations.

THE PARTIES

2. Plaintiff Mitsubishi Tanabe Pharma Corporation is a corporation organized and existing under the laws of Japan. Mitsubishi has a principal place of business at 3-2-10 Dosho-Machi, Chuo-ku, Osaka 541 8505 JAPAN. Mitsubishi is the assignee of record for Koichiro YAMADA *et al.*, *Aromatic Nitrogen-Containing 6-Membered Cyclic Compounds*, United States Letters patent No. 6656935 ("the '935 patent"). *See* **EXHIBIT A** (copy of the '935 patent); **EXHIBIT B** (copy of recorded assignments).

3. Plaintiff Metuchen Pharmaceuticals LLC is a limited liability company organized and existing under the laws of the State of Delaware. Metuchen has its principal place of business at 4400 Route 9 South, Ste 1000 Freehold, NJ 07728. Metuchen is the exclusive licensee of the '935 patent. As the exclusive licensee, Metuchen has the exclusive right to make, use, offer to

sell, sell and import avanafil in The United States of America. *See* 35 U.S.C. § 271(a). As the exclusive licensee for the '935 patent, Metuchen also enjoys the right to enforce the '935 patent. *See e.g., Waterman v. Mackenzie*, 138 U.S. 252, 255 (1891).

4. Defendant Empower Clinic Services LLC d/b/a Empower Pharmacy operates under New Jersey State Board of Pharmacy license #28RO00095200. **EXHIBIT C**. Empower Clinic Services LLC d/b/a Empower Pharmacy is a limited liability company organized and existing under the laws of the State of Texas and also has a place of business at 5980 West Sam Houston Parkway North, Suite 300, Houston TX 77041. **EXHIBIT D**.

5. Defendant Empower Pharmaceuticals LLC is a limited liability company organized and existing under the laws of the State of Texas. It maintains a place of business at the same location as Empower Clinic Services LLC d/b/a Empower Pharmacy, *i.e.*, 5980 West Sam Houston Parkway North, Suite 300, Houston TX 77041.

6. Defendant Arta Shaun Noorian uses the aliases "Arta S. Noorian" and "Shaun Noorian" in his 2017 annual report to the Secretary of State of the State of Texas for Empower Clinic Services LLC. **EXHIBIT D**. He now concedes these various aliases all refer to himself. *See* CM/ECF #7-2 ¶ 2. He is

the sole owner of, sole member of, and registered agent for Empower Clinic Services LLC and Empower Pharmaceuticals LLC. **EXHIBIT D**.

7. Empower Pharmaceuticals LLC and Empower Clinic Services LLC share the same office address, ownership, and management. Further, on information and belief, Empower Pharmaceuticals acts as an alter ego of Empower Clinic Services LLC. The two entities are therefore here referred to collectively as "Empower."

JURISDICTION

8. This Court has subject matter jurisdiction pursuant to 28 U.S.C. § 1338, 15 U.S.C. § 1121, 28 U.S.C. §§ 1331-32 and 28 U.S.C. § 1367.

9. Empower Clinic Services LLC d/b/a Empower Pharmacy has since 2014 maintained a pharmacy license in this District, **EXHIBIT C**, and continues to purposefully solicit business in this District, *see* **EXHIBIT E**. This Court therefore enjoys personal jurisdiction over Empower, *See* Fed. R. Civ. Proc. Rule 4(k).

10. This Court has personal jurisdiction over Arta Shaun Noorian because his repeated, egregious behavior (described in detail below) justifies holding him personally liable for his companies' actions. *See* Fed. R. Civ. Proc. Rule 4(k).

VENUE

11. Venue is proper in this District pursuant to 28 U.S.C. § 1391.

12. Furthermore, venue is proper in this District pursuant to 28 U.S.C. § 1400. Section 1400 provides that patent cases may be brought where the defendant has committed acts of infringement and has a regular and established place of business:

> Any civil action for patent infringement may be brought in the judicial district where the defendant resides, or where the defendant has committed acts of infringement and has a regular and established place of business.

See 28 U.S.C. § 1400(b).

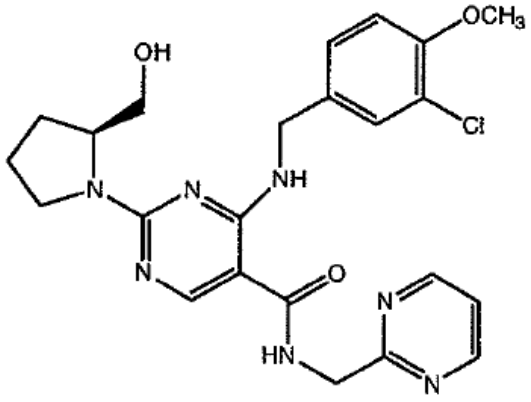
13. In the instant case, Empower Clinic Services LLC has since May 16, 2014 maintained a license to practice pharmacy in The State of New Jersey, New Jersey State Board of Pharmacy license #28RO00095200. **EXHIBIT C**. That license allows Empower to receive prescriptions from New Jersey physicians, sell pharmaceuticals to New Jersey patients and collect payments from New Jersey insurance plans (including payments from The State of New Jersey itself, which pays for prescription drugs via the state Medicaid plan). In return for these benefits, however, Empower Clinic Services LLC must *e.g.*, store certain records at The New Jersey State Board of Pharmacy (124 Halsey Street, Newark NJ 07102), and Empower authorizes The New Jersey State Board of Pharmacy to receive customer complaints on Empower's behalf, to

facilitate communications between prescribing physicians and Empower pharmacists, to facilitate communications between customers and Empower's owner, to inspect Empower's operations, and Empower consents to jurisdiction in this District to resolve alleged violations of New Jersey pharmacy regulations. *See e.g.*, N.J.A.C. 13:45C-1.3(a) and -1.6; 13:39-5.8, -7.6 and -7.7. Receiving customer complaints, storing records, facilitating communications with pharmacists and the owner, and enabling inspection are some of the functions of a regular and established place of business. In maintaining a license as a New Jersey pharmacy, Empower Clinic Services LLC has expressly consented to venue in this District and has authorized The New Jersey State Board of Pharmacy, 124 Halsey Street, Newark NJ 07102, to act as Empower's "regular and established place of business" in New Jersey.

FACTUAL BACKGROUND

The '935 Patent Claims Avanafil

14. Avanafil is a prescription pharmaceutical. *See* **EXHIBIT F**. Avanafil has the following structural formula:



See **EXHIBIT F** at § 11.

15. One of the systemic names for avanafil is "(S)-2-(2-hydroxy methyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinyl methyl)carbamoyl]pyrimidine." *See* **EXHIBIT N** at "OTHER NAMES".

16. Avanafil is claimed by United States letters patent no. 6656935 ("the '935 patent"), claims 1-16. For example, patent claim 16 claims "(S)-2-(2-hydroxy methyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinyl methyl)carbamoyl] pyrimidine." *See* **EXHIBIT A** at claim 16.

17. Similarly, patent claims 19 covers avanafil pharmaceutical compositions (*e.g.*, tablets and troches). *See* **EXHIBIT A** at claim 19.

18. Similarly, patent claim 20 covers using avanafil to treat penile erectile dysfunction. *See* **EXHIBIT A** at claim 20.

19. The '935 patent claims avanafil. The United States Food & Drug Administration accordingly provides public notice that the '935 patent covers avanafil *per se*, and avanafil pharmaceutical compositions (*e.g.*, tablets and troches), and the medical use of avanafil to treat penile erectile dysfunction. The FDA provides this notice in its publication, *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the "Orange Book." **EXHIBIT G**.

20. Because avanafil is patented, the FDA *Orange Book* says that Metuchen is *the only* legal source of avanafil products in The United States of America. *See id*.

21. Pharmacy regulations require Empower to have a copy of the *Orange Book*. *See* N.J.A.C. § 13:39-5.8(a)(12). The *Orange Book* provides clear and unambiguous notice of the patent. *See* **EXHIBIT G**. We may thus presume that Empower knew of the '935 patent, and knew that it covers avanafil.

22. Empower's marketing materials expressly refer to the STENDRA® package insert. *See e.g.*, **EXHIBIT H** at footnotes 1 and 3. The STENDRA® package insert, however, provides a patent marking notice. **EXHIBIT F** at page

25. We can presume that Empower had actual knowledge of the '935 patent from the STENDRA® avanafil package insert.

23. Empower's marketing materials illegitimately copy much of the STENDRA® package insert. *See* **EXHIBIT I**. The STENDRA® package insert, however, provides a patent marking notice. **EXHIBIT F** at page 25. We can presume that Empower had actual knowledge of the '935 patent because Empower copied the STENDRA® avanafil package insert.

Defendants' Avanafil Infringes the '935 Patent

24. Empower sells avanafil orally disintegrating tablets ("ODTs"), **EXHIBIT H**, and troches, **EXHIBIT J**. Avanafil, however, is claimed by the '935 patent. *See* **EXHIBIT A** claims 1-16. Empower's making, using, offering for sale and selling avanafil products directly and literally infringes the '935 patent claim 1-16. *See* 35 U.S.C. § 271(a).

25. On information and belief, Empower is a pharmacy, not a chemical manufacturing plant. It thus does not possess the personnel and facilities required to make avanafil active pharmaceutical ingredient. Rather, on information and belief Empower purchases bulk avanafil active pharmaceutical ingredient from abroad (*e.g.*, from China or India) and covertly imports it into The United States without notifying the US FDA. Empower's covert

importation of avanafil infringes the '935 patent claims 1-16. *See* 35 U.S.C. § 271(a).

26. Empower's avanafil orally disintegrating tablets ("ODTs"), **EXHIBIT H**, and troches, **EXHIBIT J**, infringe the '935 patent claim 19.

27. Empower promotes its products as an "Anti-erectile dysfunction agent." *See* **EXHIBIT H** at *e.g.*, page 1. This use infringes the '935 patent claim 20.

Defendants' Infringement is Willful

28. Empower had actual knowledge of the '935 patent. Yet sells infringing products anyway. In so doing, Empower infringes the '935 patent *willfully*.

29. On June 1, 2018 Metuchen provided Defendants a copy of the '935 patent and asked that Defendants cease and desist from infringing. *See* **EXHIBIT K**. Defendants flatly refuse to respond. In refusing to even respond to Metuchen's request, Empower continued to infringe the '935 patent *willfully*.

30. This would be quite troubling were it a stand-alone instance. Unfortunately, it is not. Rather, this is but the latest instance of Defendants' willful disregard of third-party intellectual property rights. For example, Vivus Inc. (not a party to this proceeding) markets QSYMIA® (phentermine and topiramate). *See* **EXHIBIT L**. QSYMIA®, like avanafil, is patented. *Id*. at page 43. QSYMIA® is also subject to a risk evaluation and mitigation strategy

(REMS) required by the FDA to inform prescribers and patients of an increased risk of congenital malformations in infants exposed to QSYMIA® during the first trimester of pregnancy and the importance of pregnancy prevention for females of reproductive potential receiving QSYMIA®. Empower ignored both the patents and the REMS and marketed knock-off QSYMIA® without providing patients with information about the risk for fetal harm. *See* **EXHIBIT M**. Mr. Noorian thus, in his rush to make a quick buck, both infringed the QSYMIA® patents and potentially exposed unborn fetuses to the risk of birth defects.

31. Mr. Noorian's repeated disregard for third-party patent rights in the past indicates that in the instant case, his infringement is willful. This, and his cavalier disregard for the patient safety, calls for piercing the corporate veil and holding him personally responsible for his misdeeds.

Defendants' Marketing Materials Infringe Metuchen's Copyright

32. The STENDRA® avanafil package insert is copyrighted. *See* **EXHIBIT F** at page 25. Defendants nonetheless copied it, using that pirated copy to push their knock-off products. For example, Empower's promotional material for its avanafil tablet is largely copied from the STENDRA® package insert. This can be readily seen in **EXHIBIT I**. That exhibit is a copy of a page of promotional material for Empower's avanafil tablet; the highlighted text was

copied from the STENDRA® package insert (**EXHIBIT F**). Defendants' marketing materials infringe Metuchen's copyright.

33. The STENDRA® package insert provides a copyright notice. *See* **EXHIBIT F** at page 25. Defendants thus had actual knowledge of the copyright. Yet copied nonetheless. Defendants' copyright infringement is therefore willful.

Defendants' Marketing Materials Infringe Metuchen's Trademark

34. STENDRA® is a Federally-registered trademark. **EXHIBIT Q**. Empower's marketing materials use the STENDRA® trademark. *See e.g.*, EXHIBIT H at footnotes 1 and 3. Further, on information and belief Empower financially sponsors a website which refers to Empower's products as "AVANAFIL (Stendra)." *See* **EXHIBIT O**. In so doing, Empower falsely implies that its product is STENDRA® avanafil. Empower's efforts to confuse consumers has succeeded: customers are now confused about *who* sells *what*. *See id*.; **EXHIBIT P**. In fostering consumer confusion, Empower infringes Metuchen's trademark rights and deceives consumers. *See* 15 U.S.C. §§ 1114 (trademark infringement); 1125(a)(1)(A) (Lanham Act false designation of origin).

Defendants' Knock-Off Products Damage Metuchen's Reputation

35. Empower represents that its avanafil products are equivalent to STENDRA® avanafil. For example, Metuchen markets STENDRA® avanafil as "a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of erectile dysfunction." *See* **EXHIBIT F** at §1. Empower copies this marketing claim, saying that its products are an "Anti-erectile dysfunction agent, phosphodiesterase type 5 (PDE5) inhibitor." *See* **EXHIBIT H** at *e.g.*, page 1.

36. Similarly, Empower's marketing materials provide the results of clinical trials. *See id.* at *e.g.*, pages 7-9. Those clinical trials, however, were not done with Empower's products. To the contrary, those clinical trials were done with *Plaintiffs'* active pharmaceutical ingredient - an ingredient which FDA inspected and approved, and which was manufactured in a process which FDA inspected and approved. Empower, however, uses an active pharmaceutical ingredient which has not been approved by, nor even inspected by, the FDA. In using *Plaintiffs'* clinical trials to promote *Empower's* products, Empower falsely represents that its products are equivalent to STENDRA® avanafil.

37. This is troubling because Empower's products appear to be defective. Patients complain Empower's products provide only "mixed success," because "[e]ffectiveness seems to wax and wane." *See* **EXHIBIT P**. Patients complain of "seeing essentially zero results" with Empower's knock-

offs. *Id*. Patients complain of "regretting dropping a wad of cash on this stash, only to find that they're not working at all :/" *Id*.

38. Defendants market defective, potentially-contaminated products, yet promote them by citing clinical trial results obtained using *Plaintiffs'* FDA-inspected avanafil. Defendants falsely imply their products are equivalent to STENDRA® avanafil. This deceives patients. *See* 15 U.S.C. § 1125(a)(1)(B) (False Advertising). This also damages the reputation of both STENDRA® avanafil and Metuchen Pharmaceuticals. *See* N.J.S.A. § 56:4-1 *et seq*. (unfair competition, trademark infringement, and false advertising under the New Jersey Fair Trade Act).

Defendants' Knock-Off Name Damages Consumers and Metuchen

39. Empower sells a defective product, passing it off as equivalent to genuine STENDRA® avanafil. *See supra*. This obfuscation damages New Jersey consumers. This obfuscation also damages the reputation of both STENDRA® avanafil and Metuchen Pharmaceuticals. *See* N.J.S.A. § 56:4-1 *et seq*. (unfair competition, trademark infringement, and false advertising under the New Jersey Fair Trade Act).

Defendants' Products Violate New Jersey Pharmacy Regulations

41. The United States Food & Drug Administration restricts use of avanafil, listing its *only* legitimate use as use in Metuchen's STENDRA®

product. **EXHIBIT G**. New Jersey Board of Pharmacy regulations incorporate this restriction, and say that even "compounded" pharmaceuticals must follow FDA use restrictions. *See* NJAC 13:39-7.5(c). Empower's knock-off products violate the FDA restriction because the knock-offs allow avanafil to be used in products which are not genuine STENDRA® avanafil. Empower's products thus violate NJAC 13:39-7.5(c).

COUNT I
(Patent Infringement)

42. Metuchen repeats the foregoing allegations as if set forth herein at length.

43. Defendants' importation of avanafil active pharmaceutical ingredient infringes the '935 patent. *See* 35 U.S.C. § 271(a).

44. Defendants' manufacture, offering for sale, and sale of avanafil-containing tablets and troches infringes the '935 patent. *See* 35 U.S.C. § 271(a).

45. Defendants infringe despite having actual knowledge of the '935 patent. Furthermore, Defendants' infringement here is but another example of a pattern of repeated, habitual infringement. Defendants' infringement is therefore willful. The Court should accordingly treble the actual damages shown, 35 U.S.C. § 284, and award Plaintiffs their attorneys fees, 35 U.S.C. § 285.

COUNT II
(Copyright Infringement)

46. Metuchen repeats the foregoing allegations as if set forth herein at length.

47. Defendants' copying of the STENDRA® avanafil package insert infringes Metuchen's copyright. *See* 17 U.S.C. §§ 106, 501(a). The Court should accordingly award Metuchen the greater of: (1) Metuchen's actual damages plus Defendants' profits made from that copying, and (2) statutory damages. *See* 17 U.S.C. § 504(a).

48. Defendants had actual knowledge of Metuchen's copyright. Furthermore, Defendants' infringement here is but another example of a pattern of repeated, habitual infringement of third-party intellectual property rights. Defendants' infringement is therefore willful. The Court should accordingly increase statutory damages, *see* 17 U.S.C. § 504(c)(2), and award Plaintiffs their costs and attorneys fees, 17 U.S.C. § 505.

COUNT III
(Federal Trademark Infringement)

49. Metuchen repeats the foregoing allegations as if set forth herein at length.

50. Empower's misuse of Metuchen's STENDRA® trademark infringes that trademark. *See* 15 U.S.C. §§ 1114.

COUNT IV
(Lanham Act False Designation of Origin)

51. Metuchen repeats the foregoing allegations as if set forth herein at length.

52. Empower's misuse of the STENDRA® trademark and misrepresentation of the clinical studies done with Plaintiffs' avanafil deceive consumers about the true origin of and quality of Defendants' goods. This violates the Lanham Act. *See* 15 U.S.C. § 1125(a)(1)(A).

COUNT V
(Lanham Act False Advertising)

53. Metuchen repeats the foregoing allegations as if set forth herein at length.

54. Defendants market defective, apparently contaminated products, yet say they that are equivalent to STENDRA® avanafil. This consumer deception violates the Lanham Act. *See* 15 U.S.C. § 1125(a)(1)(B).

COUNT VI
(New Jersey Unfair Competition)

55. Metuchen repeats the foregoing allegations as if set forth herein at length.

56. Defendants market defective products, yet say they are equivalent to STENDRA® avanafil. This damages the reputation of both STENDRA® avanafil and Plaintiffs. This constitutes unfair competition, trademark

infringement and false advertising under the New Jersey Fair Trade Act. *See* N.J.S.A. § 56:4-1 *et seq*.

57. In falsely presenting their products as equivalent to STENDRA® avanafil, Defendants create the risk that patients using their knock-off drugs may sue *Plaintiffs* for the resulting product-liability claims. Defendants should indemnify Plaintiffs for that risk.

COUNT VII
(New Jersey Unfair Competition)

58. Metuchen repeats the foregoing allegations as if set forth herein at length.

59. Defendants intentionally misappropriate an unrelated pharmacy's name in a transparent attempt to mislead New Jersey consumers and make it more difficult for them to find Defendants and hold them accountable as merchants of defective drugs. This obfuscation constitutes unfair competition, trademark infringement, and false advertising under the New Jersey Fair Trade Act. *See* N.J.S.A. § 56:4-1 *et seq*.

COUNT VIII
(Violation of New Jersey Pharmacy Board regulations)

60. Metuchen repeats the foregoing allegations as if set forth herein at length.

61. Empower knowingly and willfully fails to restrict the use of avanafil to FDA-approved avanafil, and fails to restrict the use of avanafil to

Metuchen's STENDRA® product. Empower's products thus violate NJAC 13:39-7.5(c).

WHEREFORE, Plaintiffs respectfully ask the Court to Order Defendants to:

I. Cease importing, making, offering for sale or selling any product containing avanafil until the expiration of United States letters patent no. 6656935.

II. Turn over to Plaintiffs all of Defendants' inventory of avanafil (both as Active Pharmaceutical Ingredient ("API") and compounded into finished dosage form).

III. Provide an accounting of Defendants' sales of avanafil products, and identify the vendor of the avanafil active pharmaceutical ingredient and the prescribing practitioners,

IV. Reimburse Plaintiffs for the profits which they lost due to Defendants' sales of patent-infringing avanafil, and pay Plaintiffs triple the lost profits damages because of Defendants' willfulness in their patent infringement.

V. Reimburse Plaintiffs their attorneys' fees, because Defendants' patent infringement is exceptional.

VI. Reimburse Plaintiffs the greater of: (1) Plaintiffs' actual damages due to copyright infringement plus Defendants' illicit profits due to copyright infringement, and (2) statutory damages for copyright infringement, increased pursuant to 17 U.S.C. § 504(c)(2), and award Plaintiffs their costs and attorneys fees, 17 U.S.C. § 505.

VII. Reimburse Plaintiffs for the reputational and financial damage incurred due to: Empower's misuse of / infringement of Metuchen's Federally-registered STENDRA® trademark, Empower's false designation of the origin of its goods, Empower's false advertising, and Empower's unfair competition.

VII. Reimburse Plaintiffs for the reputational and financial damage incurred due to Empower's knowing and willful failure to restrict its use of avanafil to FDA-approved avanafil, and to restrict the use of avanafil to Metuchen's STENDRA® product.

VIII. Require Defendants to notify each patient who has obtained its knock-off avanafil that Defendants' product is not made by nor authorized by Plaintiffs. Require Defendants to purchase a product liability insurance policy naming Plaintiffs as beneficiary, indemnifying Plaintiffs for any product liability claims (including attorneys fees) made against the Plaintiffs which are based on the use of Defendants' products.

IX. Grant Plaintiffs a first priority security interest in all of Defendants' property, both real and personal, to assure prompt compliance with the Court's order.

and for such other relief as the court deems just.

PHARMACEUTICAL PATENT ATTORNEYS, LLC
Attorneys For Plaintiffs Mitsubishi Tanabe Pharma Corporation And Metuchen Pharmaceuticals, LLC

By ___/mark pohl/_____
J. Mark Pohl, Esq.

Dated: August 16, 2018

CERTIFICATION

I hereby certify that the matter in controversy is not the subject of any other court, arbitration or administrative proceeding.

__/mark pohl/_____
J. Mark Pohl, Esq.

EXHIBIT A

United States letters patent no. 6656935

US006656935B2

(12) **United States Patent**
Yamada et al.

(10) **Patent No.: US 6,656,935 B2**
(45) **Date of Patent: Dec. 2, 2003**

(54) **AROMATIC NITROGEN-CONTAINING 6-MEMBERED CYCLIC COMPOUNDS**

(75) Inventors: **Koichiro Yamada**, Saitama-ken (JP); **Kenji Matsuki**, Saitama-ken (JP); **Kenji Omori**, Saitama (JP); **Kohei Kikkawa**, Kawaguchi (JP)

(73) Assignee: **Tanabe Seiyaku Co., Ltd.**, Osaka (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/925,892**

(22) Filed: **Aug. 10, 2001**

(65) **Prior Publication Data**

US 2003/0032647 A1 Feb. 13, 2003

Related U.S. Application Data

(63) Continuation of application No. PCT/JP00/06258, filed on Sep. 13, 2000.

(30) **Foreign Application Priority Data**

Sep. 16, 1999 (JP) 11-261852
Apr. 28, 2000 (JP) 2000-130371

(51) **Int. Cl.**[7] **C07D 239/48**; C07D 403/04; C07D 401/04; A61K 31/506; A61P 15/10

(52) **U.S. Cl.** **514/230.5**; 514/231.5; 514/252.01; 514/275; 544/323; 544/325; 544/105; 544/114; 544/238

(58) **Field of Search** 544/323, 325, 544/105, 114, 238; 514/275, 230.5, 231.5, 252.01

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Primary Examiner—Richard L. Raymond
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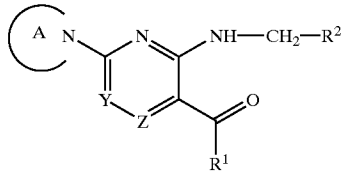
(57) **ABSTRACT**

An aromatic nitrogen-containing 6-membered cyclic compound of the formula (I):

(I)



wherein Ring A is a substituted or unsubstituted nitrogen-containing heterocyclic group; R^1 is a substituted or unsubstituted lower alkyl group, —NH—Q—R^3 (R^3 is a substituted or unsubstituted nitrogen containing heterocyclic group, and Q is a lower alkylene group or a single bond), or —NH—R^4 (R^4 is a substituted or unsubstituted cycloalkyl group); R^2 is a substituted or unsubstituted aryl group; one of Y and Z is =CH—, and the other is =N—, or a pharmaceutically acceptable salt thereof, these compounds exhibiting excellent selective PDE V inhibitory activities, and hence, being useful in the prophylaxis or treatment of penile erectile dysfunction, etc.

22 Claims, No Drawings

AROMATIC NITROGEN-CONTAINING 6-MEMBERED CYCLIC COMPOUNDS

This application is a continuation application of PCT international application No. PCT/JP00/06258 which has an international filing date of Sep. 13, 2000 which designated the United States, the entire contents of which are incorporated by reference.

TECHNICAL FIELD

The present invention relates to a novel aromatic nitrogen-containing 6-membered cyclic compound exhibiting a cGMP specific phosphodiesterase (PDE) inhibitory activity (PDE V inhibitory activity) and being useful as a medicament, and a process for preparing the same.

BACKGROUND ART

In general, it is known that cGMP, which is an intracellular second messenger, is decomposed and inactivated by phosphodiesterase which widely distributes in many cell types and tissues of the living body, and when said PDE activity is inactivated, the level of cGMP in cells is increased, and as a result, various pharmacological activities, for example, relaxation of vascular smooth muscle, relaxation of bronchial smooth muscle, and inhibition of platelet aggregation are exhibited.

Moreover, it has been reported that such cGMP specific PDE inhibitors (i.e., PDE V inhibitors) are useful in the treatment of diseases caused by a functional disorder of cGMP-signaling, including hypertension, angina pectoris, myocardial infarction, chronic or acute heart failure, pulmonary hypertension, etc. (cf., PCT Patent Publication WO 96/05176, etc.), and prostatic hyperplasia (Australian Patent Publication No. 9955977). It has also been reported that PDE V inhibitors may be useful in the treatment of female sexual dysfunction (Vemulapalli et al., Life Sciences, 67, 23–29 (2000)), diabetic gastroparesis (Watkins et al., J. Clin. Invest. 106: 373–384 (2000)), achalasia (Bortolotti et al., Gastroenterology; 118: 253–257 (2000)), diarrhea (Mule et al., Br. J. Pharmacol., 127, 514–520 (1999)), constipation (Bakre et al., J. Cell. Biochem. 77: 159–167 (2000)) and asthma (Turner et al., Br. J. Pharmacol., 111, 1198–1204 (1994)).

Furthermore, it has been also reported that 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-phenylsulfonyl]-4-methylpiperazine [general name: Sildenafil] having PDE V inhibitory activity is useful in the treatment of diseases such as penile erectile dysfunction (copulative impotence), etc. (cf., Boolell et al., The Journal of Urology, Supplement, vol. 155, no. 5, p. 495A739 (1996); Terrett et al., Bioorganic & Medicinal Chemistry Letters, vol. 6, no. 15, p. 1819 (1996); and Ballard et al., British Journal of Pharmacology, Proceeding Supplement, vol. 118, p. 153 (1996)).

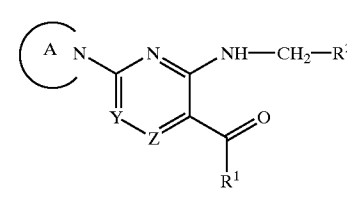
However, sildenafil has been reported to have side effects such as headache, facial suffusion, gut disorder, rhinitis, color sense disorder, penile erectile continuance, etc. (Irwin et al., The New England Journal of Medicine, vol. 338, no. 20, p. 1397–1404 (1998); Morales et al., International Journal of Impotence Research, vol. 10, no. 2, p. 69–73 (1998); and Goldenberg, Clinical Therapeutics, vol. 20, no. 6, p. 1033–1048 (1998)).

In addition, sildenafil has also been reported that the effects of sildenafil on light response of retina tissues and its PDE VI inhibitory activity correlate each other in the experiments on dogs (Morales et al., International Journal of Impotence Research, vol. 10, no. 2, p. 69–73 (1998)), while it has been reported that PDE VI on retina plays an importance role in the sensation of light (Morrales et al., International Journal of Impotence Research, vol. 10, no. 2, p. 69–73 (1998); Estrade et al., European Journal of Pharmacology, vol. 352, p. 157–163 (1998)).

DISCLOSURE OF INVENTION

An object of the present invention is to provide a novel aromatic nitrogen-containing 6-membered cyclic compound showing an excellent phosphodiesterase V (PDE V) inhibitory activity, and being useful as a remedy for the prophylaxis or treatment of penile erectile dysfunction with few side effects. Another object of the present invention is to provide a process for preparing such a novel aromatic nitrogen-containing 6-membered cyclic compound.

The present invention relates to an aromatic nitrogen-containing 6-membered cyclic compound of the formula (I):



(I)

wherein Ring A is a substituted or unsubstituted nitrogen-containing heterocyclic group; R^1 is a substituted or unsubstituted lower alkyl group, a group of the formula: —NH—Q—R^3 (in which R^3 is a substituted or unsubstituted nitrogen-containing heterocyclic group, and Q is a lower alkylene group or a single bond), or a group of the formula: —NH—R^4 (in which R^4 is a substituted or unsubstituted cycloalkyl group); R^2 is a substituted or unsubstituted aryl group; one of Y and Z is a group of the formula: =CH—, and the other is a group of the formula: =N—, or a pharmaceutically acceptable salt thereof, and a process for preparing the same.

Among the compounds (I) of the present invention, the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- to 10-membered monocyclic or bicyclic nitrogen-containing heterocyclic group, more particularly, a 5- or 6-membered nitrogen-containing heteromonocyclic group and a 8- to 10-membered nitrogen-containing heterobicyclic group, and most particularly, a 5- or 6-membered non-aromatic nitrogen-containing heteromonocyclic group such as pyrrolidinyl group, piperazinyl group, piperidyl group, morpholino group, etc., a 5- or 6-membered aromatic nitrogen-containing heteromonocyclic group such as imidazolyl group, pyrrolyl group, etc., and a nitrogen-containing heterobicyclic group such as 6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl group, 5,6,7,8-tetrahydroimidazo[1,2-a]-pyrazin-7-yl group, 5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl group, 1,2,3,4-tetrahydro-2-isoquinolinyl group, 1H-2,3,4,5,6,7-hexahydropyrazolo[4,3-c]pyridin-5-yl group, 4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-6-yl group, 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-6-yl group, 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridin-3-yl group, etc.

The nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for R^3 is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, for example, a 5- or 6-membered non-aromatic nitrogen-containing heteromono-

cyclic group such as morpholinyl group, piperazinyl group, piperidyl group, thiadiazolyl group, dihydropyrimidinyl group, dihydropyrazolyl group, a 5- or 6-membered aromatic nitrogen-containing heteromonocyclic group such as pyrimidinyl group, pyridazinyl group, pyridyl group, pyrazolyl group, imidazolyl group, oxazolyl group, thiazolyl group, pyrazinyl group, and a 8- to 10-membered nitrogen-containing heterobicyclic group such as benzothiazolyl group, quinolyl group, dihydrobenzoxazolyl group, etc.

The substituent of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A and R^3 is, for example, (1) a lower alkyl group, (2) a hydroxy-substituted lower alkyl group, (3) a formyl group, (4) an oxo group, (5) an amino group, (6) a di-(lower alkyl)amino group, (7) a hydroxy group, (8) a lower alkoxy group, (9) a lower alkoxycarbonyl group, (10) a lower alkoxy-substituted lower alkanoyl group, (11) a lower alkanoyl group, (12) a cyano-substituted lower alkyl group, and (13) a pyrimidinyl group substituted by (i) a benzylamino group substituted by a halogen atom and a lower alkoxy group and (ii) a cycloalkylcarbamoyl group substituted by a hydroxy group, etc.

The aryl group of the "substituted or unsubstituted aryl group" for R^2 is, for example, a 5- to 10-membered monocyclic or bicyclic aromatic hydrocarbon group such as phenyl group, naphthyl group, etc.

The substituent of the "substituted or unsubstituted aryl group" for R^2 is, for example, a lower alkoxy group, a halogen atom, a cyano group, a nitro group, a hydroxy group, a lower alkyl group, etc.

The substituent of the "substituted or unsubstituted lower alkyl group" for R^1 and the substituent of the "substituted or unsubstituted cycloalkyl group" for R^4 are, for example, a lower alkoxy group, a hydroxy group, a morpholinyl group, a lower alkylsulfonyl group, a di-(lower alkyl)phosphino group, a di-(lower alkyl)amino group, a pyrimidinyl-substituted lower alkylamino group, a pyridyl group, a pyridylamino group, a lower alkyl-substituted piperazinyl group, a pyrimidinyloxy group, etc.

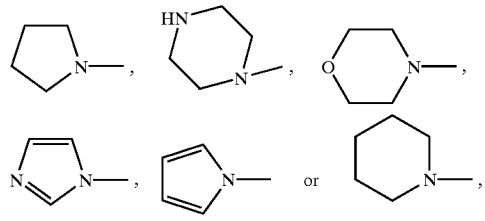
Throughout the present description and the claims, the "lower alkyl group" means a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, etc. The "lower alkoxy group" means a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms, such as methoxy, ethoxy, propoxy, isopropyloxy, butyloxy, isobutyloxy, tert-butyloxy, etc.

The "cycloalkyl group" means a cycloalkyl having 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc. The "lower alkylene group" means a straight chain or branched chain alkylene group having 1 to 6 carbon atoms, such as methylene, ethylene, trimethylene, etc.

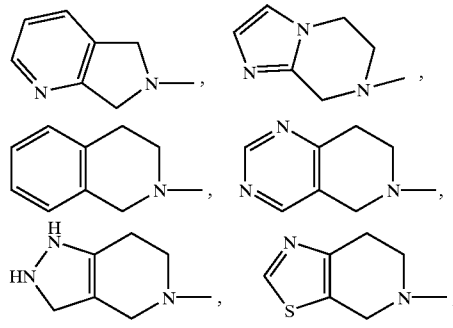
The "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom, or an iodine atom.

Among the compounds (I) of the present invention, preferable compounds are compounds of the formula (I) wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, and the substituent of the above "substituted or unsubstituted nitrogen-containing heterocyclic group" is selected from the group consisting of (1) a lower alkyl group, (2) a hydroxy-substituted lower alkyl group, (3) a formyl group, (4) an oxo group, (5) an amino group, (6) a hydroxy group, (7) a lower alkoxycarbonyl group, and (8) a pyrimidinyl group substituted by (i) a benzylamino group substituted by a halogen atom and a lower alkoxy group and (ii) a cycloalkylcarbamoyl group substituted by a hydroxy group, R^1 is a lower alkyl group which may optionally be substituted by a group selected from the group consisting of a lower alkoxy group, a hydroxy group, a morpholinyl group, a lower alkylsulfonyl group, a di-(lower alkyl)phosphino group, a di-(lower alkyl) amino group, a pyrimidinyl-substituted lower alkylamino group, a pyridyl group, a pyridylamino group, and a lower alkyl-substituted piperazinyl group, a group of the formula: —NH—Q—R^3, or a group of the formula: —NH—R^4, the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for R^3 is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, and the substituent of the above "substituted or unsubstituted nitrogen-containing heterocyclic group" is selected from the group consisting of a lower alkyl group, a hydroxy-substituted lower alkyl group, an oxo group, an amino group, a di-(lower alkyl)amino group, a lower alkanoyl group and a cyano-substituted lower alkyl group, R^4 is a cycloalkyl group being substituted by a group selected from the group consisting of hydroxy group, a lower alkoxy group and a pyrimidinyloxy group, R^2 is a phenyl group being substituted by a group selected from the group consisting of a lower alkoxy group, a halogen atom, a cyano group, a nitro group, a hydroxy group and a lower alkyl group.

More particularly, preferable compounds of the present invention are compounds of the formula (I), wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered nitrogen-containing heteromonocyclic group of the formula:



or a nitrogen-containing heterobicyclic group of the following formula wherein the above-mentioned 5- or 6-membered nitrogen-containing heteromonocyclic group and a 5- or 6-membered cyclic group are fused:



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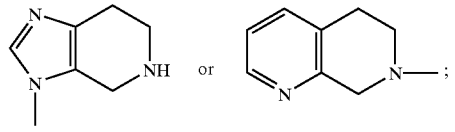
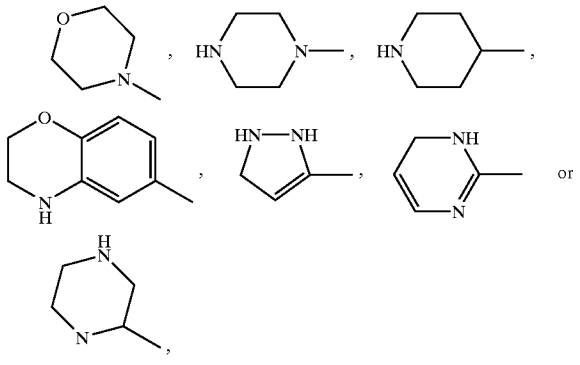
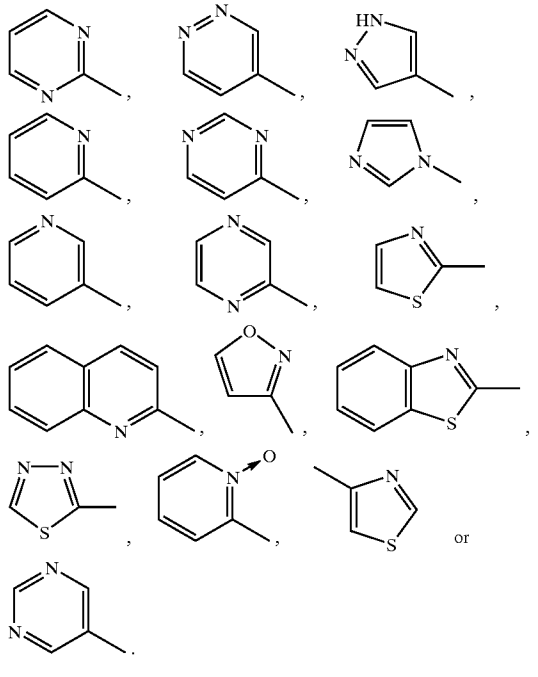


and the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for R^3 is a non-aromatic nitrogen-containing heteromonocyclic group of the formula:



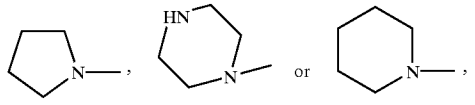
or an aromatic nitrogen-containing heterocyclic group of the formula:



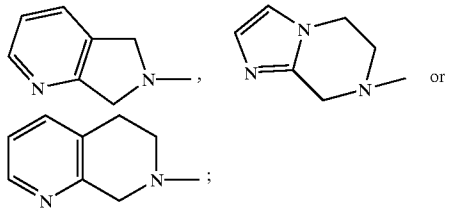
Among the compounds (I) of the present invention, other preferable compounds are compounds of the formula (I) wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, and the substituent of the above "substituted or unsubstituted nitrogen-containing heterocyclic group" is selected from the group consisting of a lower alkyl group, a hydroxy-substituted lower alkyl group, a formyl group and an oxo group, R^1 is

a lower alkyl group which may optionally be substituted by a group selected from the group consisting of a lower alkoxy group and a morpholinyl group, a group of the formula: —NH—Q—R^3, or a group of the formula: —NH—R^4, the "substituted or unsubstituted nitrogen-containing heterocyclic group" for R^3 is a 5- or 6-membered nitrogen-containing heteromonocyclic group which may optionally be substituted by a lower alkyl group, R^4 is a cycloalkyl group being substituted by a group selected from the group consisting of hydroxy group and a lower alkoxy group, R^2 is a phenyl group being substituted by a group selected from the group consisting of a lower alkoxy group, a halogen atom and a cyano group.

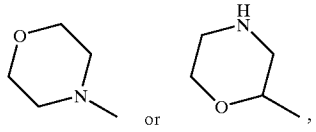
More particularly, preferable compounds of the present invention are compounds of the formula (I) wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered non-aromatic nitrogen-containing heteromonocyclic group of the formula:



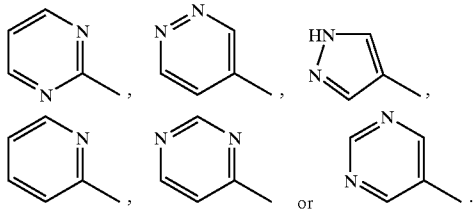
or a nitrogen-containing heterobicyclic group of the following formula wherein the above-mentioned 5- or 6-membered non-aromatic nitrogen-containing heteromonocyclic group and a 5- or 6-membered aromatic nitrogen-containing heteromonocyclic group are fused:



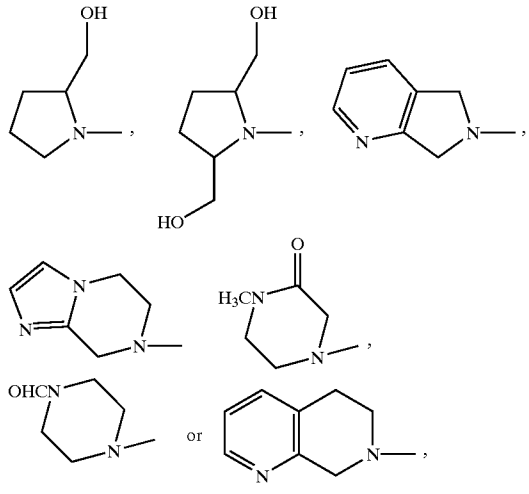
and the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for R^3 is a non-aromatic nitrogen-containing heteromonocyclic group of the formula:



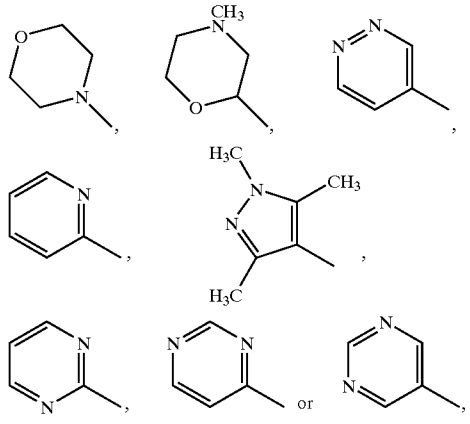
or an aromatic nitrogen-containing heteromonocyclic group of the formula:



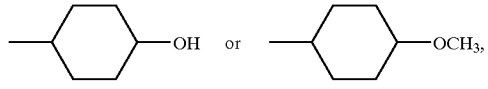
More particularly, preferable compounds of the present invention are compounds of the formula (I) wherein Ring A is a group of the formula:



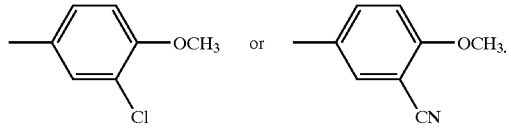
R^1 is a lower alkyl group, a lower alkoxy-substituted lower alkyl group, a morpholinyl-substituted lower alkyl group, a group of the formula: —NH—Q—R^3, or a group of the formula: —NH—R^4, R^3 is a group of the formula:



R^4 is a group of the formula:

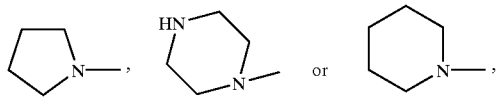


and R^2 is a group of the formula:

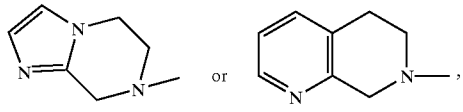


Among the compounds (I) of the present invention, more preferable compounds are compounds of the formula (I) wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, and the substituent of the above "substituted or unsubstituted nitrogen-containing heterocyclic group" is a group selected from the group consisting of a lower alkyl group, a hydroxy-substituted lower alkyl group, a formyl group and an oxo group, R^1 is a lower alkoxy-substituted lower alkyl group, a group of the formula: —NH—Q—R^3, or a group of the formula: —NH—R^4, the "substituted or unsubstituted nitrogen-containing heterocyclic group" for R^3 is a 5- or 6-membered nitrogen-containing heteromonocyclic group which may optionally be substituted by a lower alkyl group, R^4 is a hydroxy-substituted cycloalkyl group, and R^2 is a phenyl group being substituted by a group selected from the group consisting of a lower alkoxy group and a halogen atom.

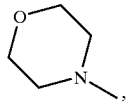
More particularly, more preferable compounds of the present invention are compounds of the formula (I) wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered non-aromatic nitrogen-containing heteromonocyclic group of the formula:



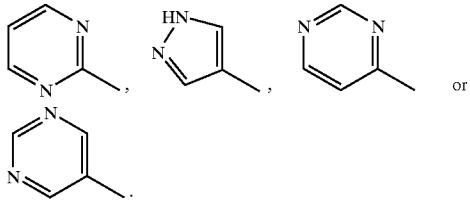
or a group of the formula:



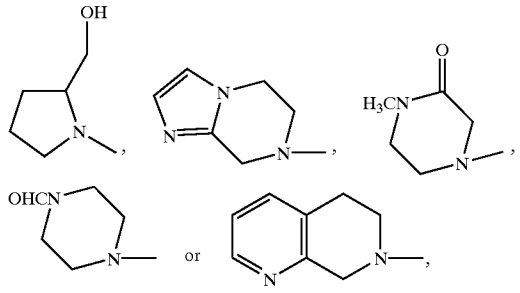
the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for R^3 is a non-aromatic nitrogen-containing heteromonocyclic group of the formula:



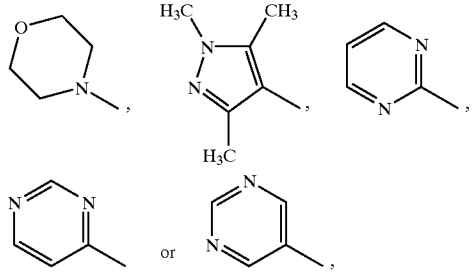
or an aromatic nitrogen-containing heteromonocyclic group of the formula:



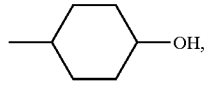
More particularly, more preferable compounds of the present compounds are compounds of the formula (I) wherein Ring A is a group of the formula:



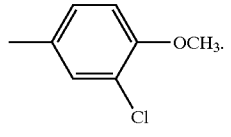
R^1 is a lower alkoxy-substituted lower alkyl group, a group of the formula: —NH—Q—R^3, or a group of the formula: —NH—R^4, R^3 is a group of the formula:



R^1 is a group of the formula:

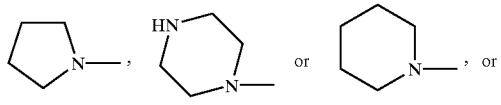


and R^2 is a group of the formula:

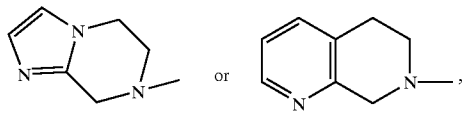


Among the compounds (I) of the present invention, further preferable compounds are compounds of the formula (I) wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, and the substituent of the above "substituted or unsubstituted nitrogen-containing heterocyclic group" is a hydroxy-substituted lower alkyl group, R^1 is a group of the formula: —NH—Q—R^3, the "substituted or unsubstituted nitrogen-containing heterocyclic group" for R^1 is a 5- or 6-membered nitrogen-containing heteromonocyclic group which may optionally be substituted by a lower alkyl group, and R^2 is a phenyl group being substituted by a group selected from the group consisting of a lower alkoxy group and a halogen atom.

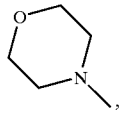
More particularly, the more preferable compounds of the present invention are compounds of the formula (I) wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered non-aromatic nitrogen-containing heteromonocyclic group of the formula:



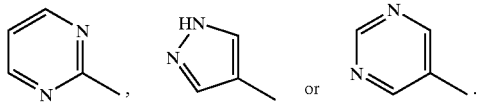
or a group of the formula:



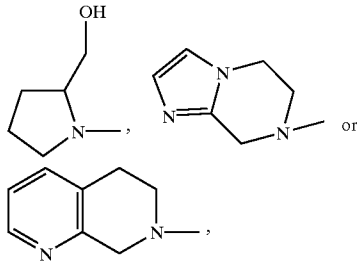
the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for R^3 is a non-aromatic nitrogen-containing heteromonocyclic group of the formula:



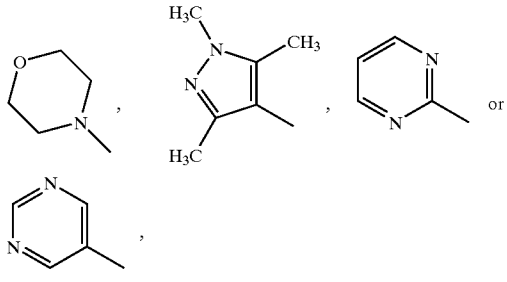
or an aromatic nitrogen-containing heteromonocyclic group of the formula:



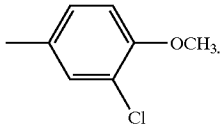
More particularly, the preferable compounds of the present invention are compounds of the formula (I), wherein Ring A is a group of the formula:



R^1 is a group of the formula: —NH—Q—R^3, R^3 is a group of the formula:



and R^2 is a group of the formula:



Among the compounds (I) of the present invention, the most preferable compounds are compounds of the formula (I) wherein Y is a group of the formula: ═N—, and Z is a group of the formula: ═CH—.

Among the compounds (I) of the present invention, pharmaceutically preferable compounds are compounds selected from the following group or a pharmaceutically acceptable salt thereof.

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidine;

2-(6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl)-4-(3-cyano-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-methoxycyclohexyl)carbamoyl]-pyrimidine;

2-(6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl)-4-(3-cyano-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]-pyrimidine;

2-(6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl)-4-(3-cyano-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine;

2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxybenzylamino)-5-[N-[[(2R)-4-methyl-2-morpholinyl]methyl]carbamoyl]-pyrimidine;

2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxybenzylamino)-5-[N-[[(2S)-4-methyl-2-morpholinyl]methyl]carbamoyl]-pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(4-pyrimidinylmethyl) carbamoyl]pyrimidine;

2-(4-methyl-3-oxo-1-piperazinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;

2-(4-formyl-1-piperazinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]-pyrimidine;

2-[cis-2,5-bis(hydroxymethyl)-1-pyrrolidinyl]-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-acethylpyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(4-pyridazinylmethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyrimidinylmethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyridylmethyl) carbamoyl]pyrimidine;

(S)-2-[N-(2-pyrimidinylmethyl)carbamoyl]-3-(3-chloro-4-methoxybenzylamino)-5-[2-hydroxymethyl-1-pyrrolidinyl]pyrazine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-morpholinoethyl) carbonyl] pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-[(4-methyl-2-morpholinyl) methyl]-carbamoyl]pyrimidine;

(S)-2-[N-(2-morpholinoethyl)carbamoyl]-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)pyrazine;

2-[N-(2-pyrimidinylmethyl)carbamoyl]-3-(3-chloro-4-methoxybenzylamino)-5-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)pyrazine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-methoxyethyl)carbonyl] pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine, or a pharmaceutically acceptable salt thereof.

Among the compounds (I) of the present invention, pharmaceutically more preferable compounds are compounds selected from the following group or a pharmaceutically acceptable salt thereof.

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(4-pyrimidinylmethyl) carbamoyl]pyrimidine;

2-(4-methyl-3-oxo-1-piperazinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;

2-(4-formyl-1-piperazinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyrimidinylmethyl) carbamoyl]pyrimidine;

(S)-2-[N-(2-pyrimidinylmethyl)carbamoyl]-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)pyrazine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-methoxyethyl)carbonyl] pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine, or a pharmaceutically acceptable salt thereof.

Among the compounds (I) of the present invention, pharmaceutically preferable other compounds are compounds

selected from the following group or a pharmaceutically acceptable salt thereof.

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyrimidinylmethyl)carbamoyl]pyrimidine;

(S)-2-[N-(2-pyrimidinylmethyl)carbamoyl]-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)pyrazine;

(S)-2-[N-(2-morpholinoethyl)carbamoyl]-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)pyrazine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine, or a pharmaceutically acceptable salt thereof.

Among the compounds (I) of the present invention, especially pharmaceutically preferable compounds are compounds selected from the following group or a pharmaceutically acceptable salt thereof.

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine, or a pharmaceutically acceptable salt thereof, 2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine, or a pharmaceutically acceptable salt thereof; and further (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine, or a pharmaceutically acceptable salt thereof.

When the compound (I) of the present invention or a pharmaceutically acceptable salt thereof has an asymmetric carbon atom at Ring A, R^1 and/or R^2, it may exist in the form of an optically active isomer thereof owing to said asymmetric carbon atom thereof, and the present invention also includes these optical isomers and a mixture thereof.

The compound (I) of the present invention or a pharmaceutically acceptable salt thereof exhibits an excellent selective PDE V inhibitory activity but substantially shows few side effects such as color sense disorder, and hence, it can be used in the prophylaxis or treatment of penile erectile dysfunction.

The present compound (I) can clinically be used either in the free form or in the form of a pharmaceutically acceptable salt thereof. The pharmaceutically acceptable salt of the compound (I) includes a salt with an inorganic acid such as hydrochloride, sulfate, nitrate or hydrobromide, or a salt with an organic acid such as acetate, fumarate, oxalate, citrate, methanesulfonate, benzenesulfonate, tosylate, or maleate.

The present compound (I) or a salt thereof includes either intramolecular salt or an additive thereof, and solvates or hydrates thereof.

The present compound (I) or a pharmaceutically acceptable salt thereof can be administered either orally or parenterally, and can be formulated into a conventional pharmaceutical preparation such as tablets, granules, fine granules, pills, capsules, powders, injections, inhalants, buccal preparation, sublingual tablets, syrups, dry syrups, jellys, suppositories, ointments, elixirs, liniments, lotions, drinks, nasal drops, percutaneous preparations, and rapidly-disintegrating tablets in oral cavity, etc. These pharmaceutical preparations may be prepared by formulating with a pharmaceutically acceptable additive such as excipient, binder, wetting agent, disintegrator, thickening agent, etc., by a conventional method.

The dose of the compound (I) of the present invention or a pharmaceutically acceptable salt thereof may vary in accordance with the administration routes, and the ages, weights and conditions of the patients. For example, when administered in an injection preparation, it is usually in the range of about 0.001–100 mg/kg/day, preferably in the range of about 0.1–10 mg/kg/day. When administered in an oral preparation, it is usually in the range of about 0.1–200 mg/kg/day, preferably in the range of about 0.1–80 mg/kg/day.

Concomitantly, since the compound (I) of the present invention or a pharmaceutically acceptable salt thereof exhibits an excellent selective PDE V inhibitory activity, it also may be useful in the prophylaxis or treatment of diseases caused by a functional disorder of cGMP-signaling, such as pulmonary hypertension, diabetic gastroparesis, hypertension, angina pectoris, myocardial infarction, chronic or acute heart failure, female sexual dysfunction, prostatic hyperplasia, asthma, diarrhea, constipation and achalasia in addition to the above-mentioned erectile dysfunction.

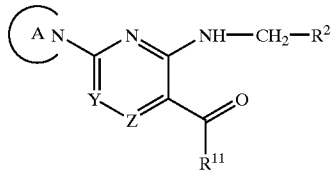
BEST MODE FOR CARRYING OUT THE INVENTION

The compounds (I) of the present invention may be prepared by the following Processes A to F.

Process A

Among the compounds (I) of the present invention, the compound of the formula (I) wherein R^1 is a group of the formula: —NH—Q—R^3 or —NH—R^4, i.e., the compound of the formula (I-a):

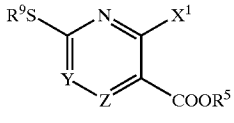
(I-a)



(wherein R^{11} is a group of the formula: —NH—Q—R^3 or —NH—R^4, and the other symbols are as defined above) can be prepared by

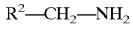
reacting a compound of the formula (II):

(II)



wherein X^1 is a halogen atom, R^5 is a protecting group for carboxyl group, R^9 is substituted or unsubstituted lower alkyl group or a substituted or unsubstituted aryl group, and the other symbols are as defined above,

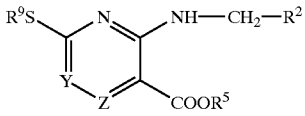
with a compound of the formula (III):



(III)

wherein the symbols are as defined above,

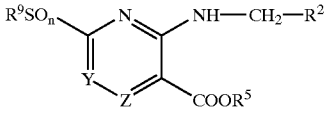
oxidizing the resulting compound of the formula (IV):



(IV)

wherein the symbols are as defined above,

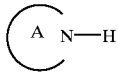
to give a sulfonyl (or sulfinyl) compound of the formula (V):



(V)

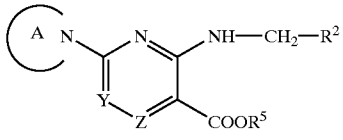
wherein n is 1 or 2, and the other symbols are as defined above,

reacting the compound (V) with a compound of the formula (VI):



(VI)

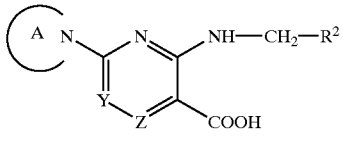
wherein the symbol is as defined above, or a salt thereof, to give a compound of the formula (VII):



(VII)

wherein the symbols are as defined above,

removing a protecting group R^5 for a carboxyl group of the compound (VII) to give a compound of the formula (VIII):



(VIII)

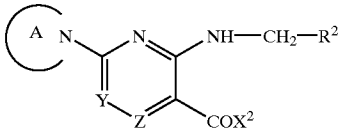
wherein the symbols are as defined above, and

followed by reacting the compound (VIII) with a compound of the formula (IX-a):

(IX-a)

wherein the symbols are as defined above.

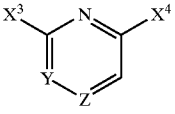
The compound (I-a) can also be prepared by subjecting the compound (VIII) to halogenation to give a compound of the formula (X):



(X)

wherein X^2 is a halogen atom, and the other symbols are as defined above, and followed by reacting the compound (X) with the compound (IX-a).

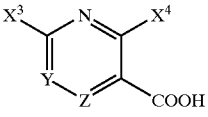
In addition, the above compound (VII) can also be prepared by treating a dihalogeno compound of the formula (XI):



(XI)

wherein X^3 and X^4 are a halogen atom, and the other symbols are as defined above, with carbon dioxide,

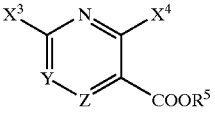
protecting the carboxyl group of the resulting compound of the formula (XII):



(XII)

wherein the symbols are as defined above,

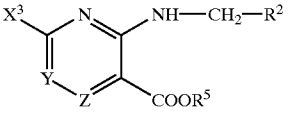
to give a compound of the formula (XIII):



(XIII)

wherein the symbols are as defined above,

reacting the compound (XIII) with the compound (III) to give a compound of the formula (XIV):



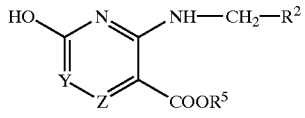
(XIV)

wherein the symbols are as defined above, and

followed by reacting the compound (XIV) with the compound (VI).

Further, the above compound (XIV) can also be prepared by subjecting the compound (V) to hydrolysis, followed by halogenating the resulting compound of the formula (XV):

(XV)

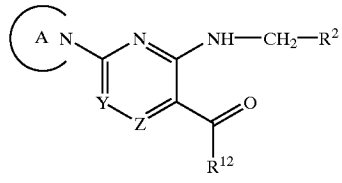


wherein the symbols are as defined above.

to Process B

Among the compounds (I) of the present invention, the compound of the formula (I) wherein R^1 is a substituted or unsubstituted lower alkyl group, i.e., the compound of the formula (I-b):

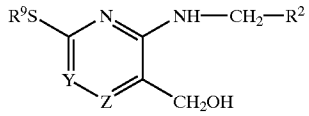
(I-b)



(wherein R^{12} is a substituted or unsubstituted lower alkyl group, and the other symbols are as defined above) can be prepared by

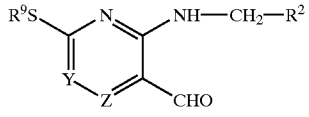
oxidizing a compound of the formula (XVI):

(XVI)



wherein the symbols are as defined above, which is obtained by reduction of the compound (IV), to give a compound of the formula (XVII):

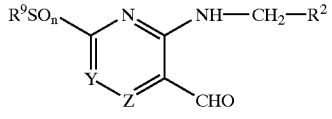
(XVII)



wherein the symbols are as defined above,

further oxidizing the compound (XVII) to give a compound of the formula (XVIII):

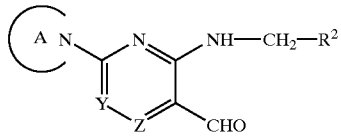
(XVIII)



wherein the symbols are as defined above,

reacting the compound (XVIII) with the compound (VI) to give a compound of the formula (XIX):

(XIX)



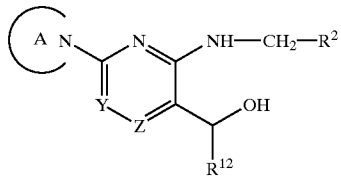
wherein the symbols are as defined above,

reacting the compound (XIX) with a metal salt of a compound of the formula (IX-b):

$$R^{12}—H \qquad \text{(IX-b)}$$

wherein R^{12} is as defined above, to give a compound of the formula (XX):

(XX)

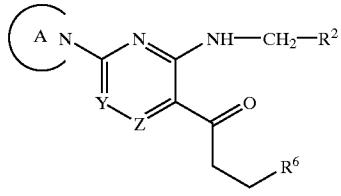


wherein the symbols are as defined above,

followed by oxidizing the compound (XX).

In addition, among the compounds (I) of the present invention, the compound of the formula (I) wherein a group R^1 is a lower alkoxy-substituted ethyl group, a morpholino-substituted ethyl group, a 4-lower alkylpiperazinyl group-substituted ethyl group, a 3-pyridylamino-substituted ethyl group, a 2-pyridyl-lower alkylamino group-substituted ethyl group, a di-lower alkylaminoethyl group or a hydroxyethyl group, i.e., the compound of the formula (I-c):

(I-c)

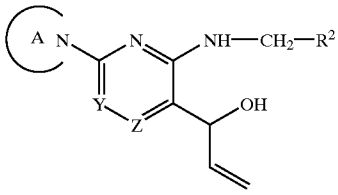


wherein R^6 is a lower alkoxy group, a morpholino group, a 4-lower alkylpiperazinyl group, a 3-pyridylamino group, a 2-pyrimidyl-lower alkylamino group, a di-lower alkylamino group or a hydroxy group, and the other symbols are as defined above,

can be prepared by reacting the compound (XIX) with a Grignard compound of the formula:

$$CH_2=CHMgBr \qquad \text{(XXI)}$$

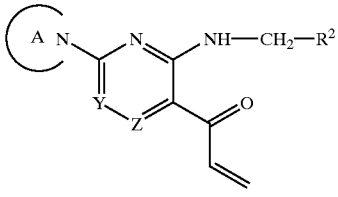
to give a compound of the formula (XXII):



(XXII)

wherein the symbols are as defined above,

oxidizing the compound (XXII) to give a compound of the formula (XXIII):



(XXIII)

wherein the symbols are as defined above,

followed by reacting the compound (XXIII) with a compound of the formula (XXIV):

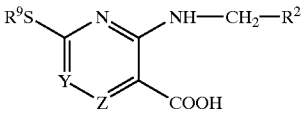
R^6—H (XXIV)

wherein R^6 is as defined above.

Process C

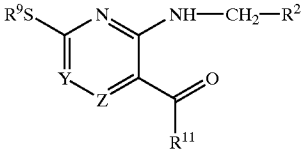
The compound (I-a) can be prepared by

reacting a compound of the formula (XXV):



(XXV)

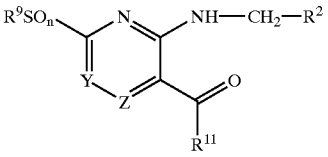
wherein the symbols are as defined above, which is obtained by removing the protecting group R^5 for a carboxyl group of the compound (IV), with the compound (IX-a) to give a compound of the formula (XXVI-a):



(XXVI-a)

wherein the symbols are as defined above,

oxidizing the compound (XXVI-a) to give a compound of the formula (XXVII-a):



(XXVII-a)

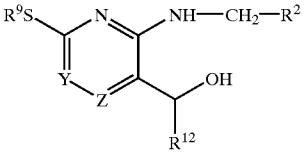
wherein the symbols are as defined above,

followed by reacting the compound (XXVII-a) with the compound (VI).

Process D

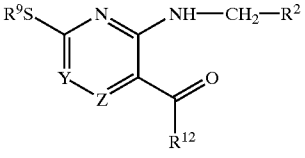
The compound (I-b) can be prepared by

oxidizing a compound of the formula (XXVIII):



(XXVIII)

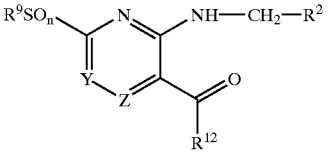
wherein the symbols are as defined above, which is obtained by reacting the compound (XVII) with a metal salt of the compound (IX-b), to give a compound of the formula (XXVI-b):



(XXVI-b)

wherein the symbols are as defined above,

further oxidizing the compound (XXVI-b) to give a compound of the formula (XX)VII-b):



(XXVII-b)

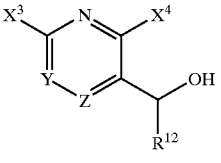
wherein the symbols are as defined above,

followed by reacting the compound (XXVII-b) with the compound (VI).

Process E

The compound (I-b) can be prepared by

oxidizing a compound of the formula (XXX):



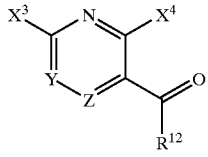
(XXX)

wherein the symbols are as defined above, which is obtained by reacting the dihalogeno compound (XI) with a compound of the formula (XXIX):

R^{12}—CHO (XXIX)

wherein R^{12} is as defined above, to give a compound of the formula (XXXI):

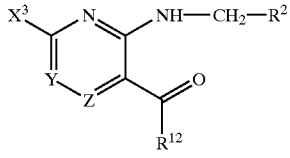
(XXXI)



wherein the symbols are as defined above,

reacting the compound (XXXI) with the compound (III) to give a compound of the formula (XXXII):

(XXXII)

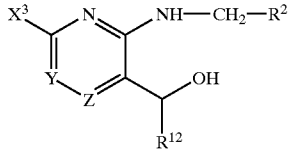


wherein the symbols are as defined above,

followed by reacting the compound (XXXII) with the compound (VI).

The above compound (XXXII) can also be prepared by reacting the compound (XXX) with the compound (III) to give a compound of the formula (XXXIII):

(XXXIII)



wherein the symbols are as defined above,

followed by oxidizing the compound (XXXIII).

Process F

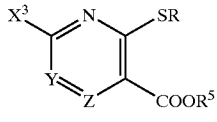
The compound (I-a) can be prepared by

reacting the compound (XIII) with a compound of the formula (XXXIV):

RSH (XXXIV)

wherein R is a substituted or unsubstituted lower alkyl group or a substituted or unsubstituted aryl group, to give a compound of the formula (XXXV):

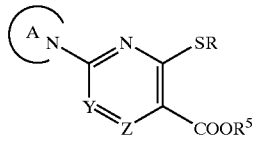
(XXXV)



wherein the symbols are as defined above,

reacting the compound (XXXV) with the compound (VI) or a salt thereof to give a compound of the formula (XXXVI):

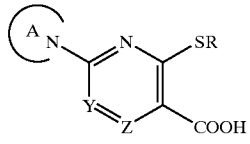
(XXXVI)



wherein the symbols are as defined above,

removing the protecting group R^5 for a carboxyl group of the compound (XXXVI) to give a compound of the formula (XXXVII):

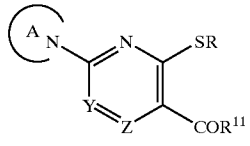
(XXXVII)



wherein the symbols are as defined above,

reacting the compound (XXXVII) with the compound (IX-a) to give a compound of the formula (XXXIX):

(XXXIX)



wherein the symbols are as defined above,

subjecting the compound (XXXIX) to oxidation to give a sulfonyl or sulfinyl compound,

followed by reacting the resultant with the compound (III).

The above Processes A to F can be carried out as follows.

Process A

The reaction of the compound (II) with the compound (III) is carried out in the presence or absence of an acid scavenger in a solvent. The acid scavenger includes, for example, an organic base such as N,N-diisopropylethylamine, N-methylmorpholine, triethylamine, pyridine, etc., and an inorganic base such as sodium hydride, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, etc. The solvent may be any solvents which do not disturb the reaction, for example, dimethylsulfoxide, tetrahydrofuran, toluene, ethyl acetate, chloroform, dimethoxyethane, xylene, N,N-dimethylformamide, etc. The reaction is carried out at a temperature of from −10° C. to room temperature, preferably at a temperature of from 0° C. to room temperature.

The reaction of oxidizing the compound (IV) to give the sulfonyl (or sulfinyl) compound (V) is carried out in the presence of an oxidizing agent in a solvent. The oxidizing agent includes, for example, peracids such as m-chloroperbenzoic acid, peracetic acid, etc., and an inorganic oxidizing agent such as manganese dioxide, sodium periodate, hydrogen peroxide, dinitrogen tetroxide, halogen, hydroperoxide, iodobenzene acetate, t-butyl hypochlorite, sulfuryl chloride, potassium peroxymonosulfate, etc. The solvent may be any solvent which does not disturb the reaction, for example, chloroform, methylene chloride, dichloroethane, acetic acid, etc. The reaction is carried out at a temperature of from −78° C. to 50° C., preferably at a temperature of from −10° C. to 10° C.

The reaction of the compound (V) with the compound (VI) or a salt thereof can be carried out in the presence or absence of an acid scavenger in a solvent. The acid scavenger includes, for example, an organic base such as N,N-diisopropylethylamine, N-methylmorpholine, triethylamine, pyridine, etc., and an inorganic base such as sodium hydride, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, etc. The salt of the compound (VI) is preferably an alkali metal salt such as sodium salt, potassium salt, etc. The solvent may be any solvent which does not disturb the reaction, for example, N,N-dimethylformamide, tetrahydrofuran, dimethoxyethane, dimethylsulfoxide, etc. The reaction is carried out at a temperature of from 0° C. to 150° C., preferably at a temperature of from room temperature to 60° C.

The reaction of removing the protecting group R^5 for a carboxyl group of the compound (VII) to give the compound (VIII) can be carried out by a conventional method such as hydrolysis, catalytic reduction, etc. which is selected according to the types of the protecting group for a carboxyl group to be removed. When a protecting group for a carboxyl group is removed by hydrolysis, the hydrolysis is carried out, for example, in the presence of a base in a solvent. The base is preferably, for example, an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide, lithium hydroxide, etc., or an alkali metal carbonate such as sodium carbonate, potassium carbonate, etc. The solvent may be water or a mixture of water and methanol, ethanol, tetrahydrofuran, dioxane, N,N-dimethyformamide, dimethylsulfoxide, etc. The reaction is carried out at a temperature of from 0 to 80° C., preferably at a temperature of from 5° C. to 60° C. The protecting group for a carboxyl group represented by R^5 may be any conventional protecting group for a carboxyl group, such as a lower alkyl group, benzyl group, etc.

The reaction of the compound (VIII) with the compound (IX-a) can be carried out in the presence or absence of a condensing agent, a base or an activating agent in a suitable solvent. The condensing agent includes, for example, dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, diphenylphosphoryl azide, diethylcyanophosphonate, etc., which is usually used in the peptide synthesis. The base includes, for example, an organic base such as triethylamine, N-methymorpholine, etc., and the activating agent includes, for example, 1-hydroxybenzotriazole, etc. The solvent may be any solvent which does not disturb the reaction, for example, methylene chloride, tetrahydrofuran, N,N-dimethylformamide, acetonitrile, N,N-dimethylacetamide, ethyl acetate, etc. The reaction is carried out at a temperature of from −30° C. to 50° C., preferably at a temperature of from −10° C. to 10° C.

The alternative process of converting the compound (VIII) into the compound (X), which is further reacted with the compound (IX-a) can be carried out by firstly reacting the compound (VIII) with a halogenating agent in the presence or absence of an activating agent by a conventional method, and reacting the resulting compound (X) with the compound (IX-a). The reaction of the compound (VIII) with a halogenating agent is carried out in a solvent. The halogenating agent is preferably thionyl chloride, oxalyl chloride, phosphorus pentachloride, etc. The activating agent is preferably an amide compound such as N,N-dimethylformamide, etc. The solvent may be any solvent which does not disturb the reaction, for example, methylene chloride, chloroform, tetrahydrofuran, benzene, toluene, dioxane, etc. The reaction is carried out at a temperature of from −30° C. to 100° C., preferably at a temperature of from −5° C. to 10° C.

The subsequent reaction with the compound (IX-a) is carried out in the presence of an acid scavenger in a solvent. The acid scavenger includes, for example, an organic base such as N,N-diisopropylethylamine, N-methylmorpholine, triethylamine, pyridine, dimethylaminopyridine, etc., and an inorganic base such as sodium hydride, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, etc. The solvent may be any solvent which does not disturb the reaction, for example, tetrahydrofuran, methylene chloride, chloroform, toluene, benzene, dioxane, ethyl acetate, etc. The reaction is carried out at a temperature of from −30° C. to 100° C., preferably at a temperature of from −5° C. to 10° C.

The reaction of treating the dihalogeno compound (XI) with carbon dioxide to give the compound (XII) can be carried out in the presence of a base in a solvent. The base includes, for example, an alkali metal salt of an organic base such as lithium diisopropylamide, lithium 2,2,6,6-tetramethylpiperidide, etc. The solvent may be any to solvent which does not disturb the reaction, for example, tetrahydrofuran, 1,2-dimethoxyethane, diethyl ether, etc. The reaction is carried out at a temperature of from −100° C. to −30° C., preferably at a temperature of from −100° C. to −70° C.

The reaction of protecting the carboxyl group of the compound (XII) to give the compound (XIII) can be carried out by a conventional method, for example, by reacting with an alkylating agent in the presence of a base in a solvent, when the protecting group is a lower alkyl group. The alkylating agent is preferably a lower alkyl halide such as methyl iodide. The base is preferably an alkali metal hydrogen carbonate such as sodium hydrogen carbonate, and the solvent may be any solvent which does not disturb the reaction, for example, N,N-dimethylformamide, tetrahydrofuran, etc. The reaction is carried out at a temperature of from 0° C. to 100° C., preferably at a temperature of from room temperature to 70° C.

The reaction of the compound (XIII) with the compound (III) to give the compound (XIV) can be carried out in the same manner as in the reaction of the compound (II) with the compound (III).

The reaction of the compound (XIV) with the compound (VI) to give the compound (VII) can be carried out in the same manner as in the reaction of the compound (V) with the compound (VI).

The hydrolysis reaction of the compound (V) to give the compound (XV) can be carried out in the presence of a base in a solvent. The base includes, for example, an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide, lithium hydroxide, etc., and an alkali metal carbonate such as sodium carbonate, potassium carbonate, etc. The solvent is preferably water, or a mixture of water and methanol, ethanol, tetrahydrofuran, dioxane, N,N-dimethylformamide, dimethylsulfoxide, etc. The reaction is carried out at a temperature of from −20° C. to 80° C., preferably at a temperature of from −5° C. to 60° C.

The reaction of halogenating the compound (XV) to give the compound (XIV) can be carried out in the same manner as in the reaction of obtaining the compound (X) by halogenating the compound (XIII) by a halogenating agent.

Process B

The reduction reaction of the compound (IV) to give the compound (XVI) can be carried out in the presence of a reducing agent in a suitable solvent. The reducing agent is preferably an alkali metal aluminum hydride such as lithium

aluminum hydride, and an alkali metal borohydride such as lithium borohydride, etc. The solvent may be any solvent which does not disturb the reaction, for example, tetrahydrofuran, dioxane, diethyl ether, dimethoxyethane, etc. The reaction is carried out at a temperature of from −78° C. to a boiling point of the solvent to be used, preferably at a temperature of from −10° C. to room temperature.

The oxidation reaction of the compound (XVI) to give the compound (XVII) can be carried out in the presence of an oxidizing agent in a solvent. The oxidizing agent may be any one which can convert an alcohol into a carbonyl compound, for example, manganese dioxide, barium permanganate, potassium permanganate, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, pyridinium chlorochromate, pyridinium dichloromate, etc. The solvent may be any solvent which does not disturb the reaction, for example, chloroform, toluene, ethyl acetate, 1,2-dichloroethane, methylene chloride, tetrahydrofuran, etc. The reaction is carried out at a temperature of from 0° C. to 100° C., preferably at a temperature of from room temperature to 70° C.

The oxidation reaction of the compound (XVII) to give the compound (XVIII) is carried out in the same manner as in the reaction of obtaining the compound (V) by oxidizing the compound (IV).

The reaction of the compound (XVIII) with the compound (VI) to give the compound (XIX) is carried out in the same manner as in the reaction of the compound (V) with the compound (IV).

The reaction of the compound (XIX) with a metal salt of the compound (IX-b) to give the compound (XX) may be carried out in a suitable solvent. The metal salt of the compound (IX-b) is preferably lithium salt, etc. The solvent may be any solvent which does not disturb the reaction, for example, tetrahydrofuran, dioxane, diethyl ether, dimethoxyethane, etc. The reaction may preferably proceed at a temperature of from −78° C. to room temperature.

The oxidation reaction of the compound (XX) to give the compound (I-b) may be carried out in the same manner as in the reaction of obtaining (XVII) by oxidizing the compound (XVI).

The reaction of the compound (XIX) with the Grignard compound can be carried out in a suitable solvent. The solvent is preferably tetrahydrofuran, dioxane, diethyl ether, etc. The reaction may preferably proceed at a temperature of from −78° C. to 60° C., preferably at a temperature of from −78° C. to room temperature.

The oxidation reaction of the compound (XXII) to give the compound (XXIII) is carried out in the same manner as in the reaction of obtaining the compound (XVII) by oxidizing the compound (XVI).

The reaction of the compound (XXIII) with the compound (XXIV) wherein R^6 is a morpholino group, a 4-lower alkylpiperazinyl group, a 3-pyridylamino group, a 2-pyrimidyl-lower alkylamino group, or a di-lower alkylamino group to give the compound (I-c) wherein R^6 is a morpholino group, a 4-lower alkylpiperazinyl group, a 3-pyridylamino group, a 2-pyrimidinyl-lower alkylamino group, or a di-lower alkylamino group can be carried out in the presence or absence of a base in a suitable solvent. The base includes, for example, an organic base such as N,N-diisopropylethylamine, N-methylmorpholine, triethylamine, pyridine, etc., and an inorganic base such as sodium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, etc. The solvent may preferably be ethanol, N,N-dimethylformamide, tetrahydrofuran, dimethoxyethane, dimethylsulfoxide, etc. The reaction may preferably proceed at a temperature of from 0° C. to 150° C., preferably at a temperature of from room temperature to 60° C.

On the other hand, the reaction of the compound (XXIII) with the compound (XXIV) wherein R^6 is a hydroxy group or a lower alkoxy group to give the compound (XXI) wherein R^6 is a hydroxy group or a lower alkoxy group can be carried in the presence of an acid in a solvent or without a solvent. The acid includes, for example, an inorganic acid such as sulfuric acid, etc., or an organic acid such as methanesulfonic acid, camphorsulfonic acid, toluenesulfonic acid, benzenesulfonic acid, etc. The solvent may preferably be diethyl ether, toluene, benzene, N,N-dimethylformamide, dimethoxyethane, dimethylsulfoxide, etc. The reaction may preferably proceed at a temperature of from 0° C. to 150° C., preferably at a temperature of from room temperature to 60° C.

Process C

The reaction of removing the protecting group R^5 for a carboxyl group of the compound (IV) to give the compound (XXV) can be carried out in the same manner as in the reaction of obtaining the compound (VIII) by removing the protecting group R^5 for a carboxyl group of the compound (VII).

The reaction of the compound (XXV) with the compound (IX-a) to give the compound (XXVI-a) can be carried out in the same manner as in the reaction of the compound (VIII) with the compound (IX-a).

The reaction of oxidizing the compound (XXVI-a) to give the compound (XXVII-1) can be carried out in the same manner as in the reaction of obtaining the compound (V) by oxidizing the above compound (IV).

The reaction of the compound (XXVII-a) with the compound (VI) to give the compound (I-a) of the present invention can be carried out in the same manner as in the reaction of the compound (V) with the compound (VI).

Process D

The reaction of the compound (XVII) with a metal salt of the compound (IX-b) to give the compound (XXVIII) can be carried out in the same manner as in the reaction of the compound (XIX) with a metal salt of the compound (IX-b).

The reaction of oxidizing the compound (XXVIII) to give the it compound (XXVI-b) can be carried out in the same manner as in the reaction of obtaining the compound (XVII) by oxidizing the compound (XVI).

The process wherein the compound (XXVI-b) is oxidized to give the compound (XXVII-b) which is further converted into the compound (I-b) of the present invention can be carried out in the same manner as in the process wherein the compound (XXVI-a) is oxidized to give the compound (XXVII-a) which is further converted into the compound (I-a) of the present invention.

Process E

The reaction of the compound (XI) with the compound (XXIX) to give the compound (XXX) is carried out in the presence of a base in a suitable solvent. The base includes, for example, an alkali metal salt of an organic base such as lithium diisopropylamide, lithium 2,2,6,6-tetramethylpiperidide, etc. The solvent may be any solvent which does not disturb the reaction, for example, tetrahydrofuran, 1,2-dimethoxyethane, diethyl ether, etc. The reaction is carried out at a temperature of from −100° C. to −30° C., preferably at a temperature of from −100° C. to −70° C.

The reaction of oxidizing the compound (XXX) to give the compound (XXXI) can be carried out in the same manner as in the reaction of oxidizing the compound (XVI) to give the compound (XVII).

The reaction of the compound (XXXI) with the compound (III) to give the compound (XXXII) can be carried out

in the same manner as in the reaction of the compound (II) with the compound (III).

The reaction of the compound (XXXII) with the compound (VI) or a salt thereof to give the compound (I-b) of the present invention can be carried out in the same manner as in the reaction of the compound (V) with the compound (VI).

The reaction of the compound (XXX) with the compound (III) to give the compound (XXXIII) can be carried out in the same manner as in the reaction of the compound (II) with the compound (III). Besides, the reaction of oxidizing the compound (XXXIII) to give the compound (XXXII) can be carried out in the same manner as in the reaction of oxidizing the compound (XVI) to give the compound (XVII).

Process F

The reaction of the compound (XIII) with the compound (XXXIV) can be carried out in the presence or absence of an acid scavenger in a solvent. The acid scavenger includes, for example, an organic base such as N,N-diisopropylethylamine, N-methylmorpholine, triethylamine, pyridine, etc., or an inorganic base such as sodium hydride, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, etc. The solvent may be any solvent which does not disturb the reaction, for example, N,N-dimethylformamide, tetrahydrofuran, toluene, ethyl acetate, chloroform, dimethoxyethane, xylene, dimethylformamide, etc. The reaction is carried out at a temperature of from −10° C. to room temperature, preferably at a temperature of from 0° C. to room temperature.

The reaction of the compound (XXXV) with the compound (VI) or a salt thereof can be carried out in the same manner as in the reaction of the compound (V) with the compound (VI).

The reaction of removing the protecting group R^5 for a carboxyl group of the compound (XXXVI) to give the compound (XXXVII) can be carried out in the same manner as in the reaction of removing the protecting group R^5 for a carboxyl group of the compound (VII) to give the compound (VIII).

The reaction of the compound (XXXVII) with the compound (IX-a) can be carried out in the same manner as in the reaction of the compound (VIII) with the compound (IX-a).

The oxidation reaction of the compound (XXXIX) can be carried out in the same manner as the reaction of the compound (IV) to give the compound (V). The oxidating agent is preferably m-chloroperbenzoic acid, etc. The solvent may be any solvent which does not disturb the reaction, for example, chloroform, methylene chloride, dichloroethane, acetic acid, etc. The reaction is carried out at a temperature of from −78° C. to 50° C., preferably at a temperature of from −10° C. to 10° C.

The subsequent reaction with the compound (III) can be carried out in the same manner as in the reaction of the compound (II) and the compound (III).

The compound (I) thus obtained can be converted into a pharmaceutically acceptable salt thereof.

The starting compound (II) can be prepared, for example, according to the method disclosed in Journal of American Chemical Society, p. 350, vol. 65, 1943.

Examples of the compound (I) of the present invention which can be prepared by the above exemplified methods are illustrated below, but the present invention should not be construed to be limited thereto.

EXAMPLE 1

(1) To a solution of 4-chloro-5-ethoxycarbonyl-2-methylthiopyrimidine (25.33 g) in N,N-dimethylformamide (85 ml) are added a solution of 3-chloro-4-methoxybenzylamine (19.62 g) in N,N-dimethylformamide (15 ml) and triethylamine (16.7 ml) under ice-cooling. The mixture is stirred at room temperature for 20 minutes, and thereto is added 3-chloro-4-methoxybenzylamine (940 mg), and the mixture is further stirred for 15 minutes. To the mixture is further added said amine (940 mg), and the mixture is stirred for 15 minutes. The reaction mixture is poured into a mixture of ice water and citric acid, and the mixture is extracted with ethyl acetate. The extract is washed successively with a 10% aqueous citric acid solution, water and brine, and dried over anhydrous sodium sulfate. The solvent is evaporated under reduced pressure, and the residue is washed with n-hexane to give 4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonyl-2-methylthiopyrimidine (38.34 g), m.p. 86° C.

(2) To a solution of the compound (5.00 g) obtained in the above (1) in chloroform (50 ml) is added a solution of m-chloroperbenzoic acid (4.00 g) in chloroform (50 ml) under ice-cooling, and the mixture is stirred for 2 hours. The reaction mixture is washed with a saturated aqueous sodium hydrogen carbonate solution and brine, and the organic layer is dried over anhydrous sodium sulfate, and the solvent is evaporated under reduced pressure to give crude 4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonyl-2-methylsulfinylpyrimidine, MS (m/z): 447 (MH^+).

(3) The crude product obtained in the above (2) is dissolved in tetrahydrofuran (40 ml), and thereto is added a solution of L-prolinol (1.50 g) and triethylamine (1.60 g) in tetrahydrofuran (10 ml) at room temperature. The mixture is stirred overnight, and the reaction mixture is diluted with ethyl acetate, and washed with aqueous sodium hydrogen carbonate solution and brine. The organic layer is dried over anhydrous sodium sulfate, and the solvent is evaporated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; chloroform) and crystallized from a mixture of ether and n-hexane to give (S)-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonyl-2-(2-hydroxymethyl-1-pyrrolidinyl)pyrimidine (4.72 g), m.p. 88–90° C., MS (m/z): 421 (MH^+).

(4) A mixture of the compound (3.4 g) obtained in the above (3), a 10% aqueous sodium hydroxide solution (23 ml), and dimethylsulfoxide (34 ml) is stirred at room temperature for 15 hours. The reaction mixture is poured into a 10% aqueous citric acid solution, and the precipitates are crystallized from a mixture of tetrahydrofuran and ether to give (S)-4-(3-chloro-4-methoxybenzylamino)-5-carboxy-2-(2-hydroxymethyl-1-pyrrolidinyl)pyrimidine (2.52 g), m.p. 205–208° C., MS (m/z): 391 $(M-H)^-$.

(5) A mixture of the compound (600 mg) obtained in the above (4), 2-aminomethylpyrimidine (217 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (323 mg), 1-hydroxybenzotriazole monohydrate (227 mg) and N,N-dimethylformamide (12 ml) is stirred at room temperature for 8 hours, and the reaction mixture is poured into aqueous sodium hydrogen carbonate solution. The mixture is extracted with ethyl acetate, washed with brine, and dried over anhydrous sodium sulfate. The solvent is evaporated under reduced pressure, and the residue is purified by silica gel column chromatography (solvent; chloroform:methanol=50:1) to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidylmethyl) carbamoyl]pyrimidine (610 mg), m.p. 160–163° C.

EXAMPLE 2

(1) To a suspension of lithium aluminum hydride (4.15 g) in tetrahydrofuran (150 ml) is added a solution of 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (38.32 g) in tetrahydrofuran (100 ml) under ice-cooling at 5° C. to 10° C. over a period of one hour. After the addition, the ice bath is removed, and the reaction mixture is stirred at room temperature for one hour. To the reaction mixture is added water (4.15 ml) under ice-cooling, and thereto is further added 3N aqueous sodium hydroxide solution (4.15 ml). To the mixture is added water (4.15 ml) three times, and the mixture is stirred at room temperature for one hour. The reaction mixture is treated with magnesium sulfate, and the solid precipitates obtained are filtered. The precipitates are washed with tetrahydrofuran. The filtrate and the washings are combined, and concentrated under reduced pressure, and triturated with a mixture of ethyl acetate and isopropyl ether. The resulting crystals are collected by filtration, and washed well with isopropyl ether to give 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-hydroxymethylpyrimidine as pale yellow crystalline powder.

First production: yield; 25.10 g, m.p. 162–163° C.

Second production: yield; 2.32 g, m.p. 159–160° C.

In addition, the above solid precipitates are washed again with isopropyl ether, and the filtrate is concentrated under reduced pressure to give colorless crystals. The resulting solid is suspended in isopropyl ether, filtered, and the precipitates are washed well with isopropyl ether and hexane to give 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-hydroxymethylpyrimidine (4.26 g) as colorless crystals, m.p. 161–162° C.

(2) To a suspension of 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-hydroxymethylpyrimidine (25.10 g) obtained in the above (1) in chloroform (150 ml) is added manganese dioxide powder (37.6 g), and the mixture is vigorously stirred at room temperature for one day. To the mixture is further added manganese dioxide powder (12.6 g, 0.5 time amount of the starting compound), and the mixture is stirred for three days. The insoluble materials are quickly removed by filtration on celite, and the filtrate is concentrated under reduced pressure. The residue is suspended in a mixture of ethyl acetate and isopropyl ether. The precipitates are filtered, and washed successively with isopropyl ether and hexane to give 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-formylpyrimidine (22.43 g) as colorless crystals, m.p. 124–125° C.

(3) A solution of 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-formylpyrimidine (2.057 g) in chloroform (20 ml) is treated with m-chloroperbenzoic acid (80%, 1.468 g) at 0° C. for 30 minutes. To the reaction mixture are is added L-prolinol (0.901 g), and then triethylamine (1.33 ml), and the mixture is reacted at 0° C. for one hour. The reaction mixture is warmed to room temperature, and diluted with ethyl acetate. The mixture is washed successively with a saturated aqueous sodium hydrogen carbonate solution, water and a saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The precipitates are removed by filtration through a silica plug. The filtrate is concentrated under reduced pressure to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-formylpyrimidine (1.9990 g) as colorless amorphous, MS (m/z): 377 (MH^+).

(4) To a solution of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-formylpyrimidine (91.0 mg) in tetrahydrofuran (20 ml) is added 1.10 M solution of methyl lithium in ether (1.1 ml) at −78° C., and the mixture is reacted for 10 minutes, and thereto is added aqueous sodium hydrogen carbonate solution. The reaction mixture is extracted with ethyl acetate to give crude (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-(1-hydroxyethyl)pyrimidine, MS (m/z): 393 (MH^+).

(5) The crude product obtained in the above (4) is treated with manganese dioxide (0.5 g) at room temperature, and the mixture is stirred overnight. The reaction mixture is heated under reflux for 5 hours, and the insoluble materials are removed by filtration. The filtrate is concentrated under reduced pressure, and purified by silica gel column chromatography (solvent; chloroform:ethyl acetate=3:1) to give (S)-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-acetylpyrimidine (56.7 mg) as colorless oil, MS (m/z): 391 (MH^+).

EXAMPLE 3

(1) To a solution of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-formylpyrimidine (84 mg) in tetrahydrofuran (about 1 ml) is added dropwise a 1.0M solution of vinyl magnesium bromide in tetrahydrofuran in a dry ice-acetone bath. The reaction mixture is stirred at −78° C. for 10 minutes, and stirred at room temperature for 10 minutes. The reaction mixture is poured into a mixture of ice and a saturated aqueous sodium hydrogen carbonate solution, and the mixture is extracted with ethyl acetate. The organic layer is washed successively with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure.

The obtained crude product is subjected to preparative thin layer chromatography (solvent; ethyl acetate:methanol=20:1) to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-(1-hydroxy-2-propen-1-yl)pyrimidine (30 mg) as colorless oil, MS (m/z): 405 (MH^+).

(2) To a solution of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-(1-hydroxy-2-propen-1-yl)pyrimidine (144 mg) in chloroform (2.5 ml) is added manganese dioxide (432 mg), and the mixture is vigorously stirred at room temperature for three days. The insoluble materials are removed by filtration on celite, and the filtrate is concentrated under reduced pressure to give pale yellow oil (124 mg). The resulting crude product is purified by silica gel column chromatography (silica gel 20 g, solvent; chloroform:ethyl acetate=2:1) to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-(acryloyl)pyrimidine (90 mg) as colorless crystals, m.p. 113–115° C., MS (m/z): 403 (MH^+).

(3) To a solution of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-(acryloyl) pyrimidine (72 mg) in ethanol (2 ml) is added morpholine (78 μl) at room temperature, and the mixture is stirred at room temperature for 40 minutes. The reaction mixture is concentrated under reduced pressure, and the residue is poured into water, and the mixture is extracted with ethyl acetate. The organic layer is washed successively with water and brine, dried over anhydrous magnesium sulfate, and concentrated to dryness under reduced pressure to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-morpholinoethyl) carbonyl]-pyrimidine (91 mg).

The obtained crude product is dissolved in ethyl acetate (10 ml), and the solution is treated with a saturated solution

of hydrochloric acid in methanol (5 ml), and concentrated under reduced pressure. To the residue is added ethyl acetate, and the mixture is filtered. The resulting solid is washed well with hexane to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-morpholinoethyl)carbonyl]pyrimidine dihydrochloride (65 mg), MS (m/z): 490 (MH^+).

EXAMPLE 4

(1) To a solution of 4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonyl-2-methylthiopyrimidine (972 mg) obtained in the above Example 1-(1) in chloroform (8 ml) is added a solution of m-chloroperbenzoic acid (80%, 598 mg) in chloroform (10 ml) under ice-cooling over a period of 30 minutes. The reaction mixture is stirred under ice-cooling for one hour. The reaction mixture is diluted with a saturated aqueous sodium hydrogen carbonate solution, and the chloroform layer is collected, washed successively with a saturated aqueous sodium hydrogen carbonate solution, water and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to quantitatively give 2-methylsulfinyl-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine as colorless caramels, MS (m/z): 384 (MH^+).

(2) To a solution of 2-methylsulfinyl-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (whole amount) obtained in the above (1) in tetrahydrofuran (6 ml) is added dropwise a 2N aqueous sodium hydroxide solution (1.32 ml) under ice-cooling over a period of 2 minutes. The reaction mixture is stirred under ice-cooling for 30 minutes, and thereto are added tetrahydrofuran (8 ml) and N,N-dimethylacetamide (6 ml). The reaction mixture is stirred under ice-cooling for 30 minutes, and thereto are added water (5 ml) and N,N-dimethylacetamide (2 ml), and stirred under ice-cooling for one hour. The reaction mixture is acidified with a 10% aqueous citric acid solution, diluted with water, and extracted twice with ethyl acetate. The extracts are combined, washed with water and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is separated by silica gel column chromatography (silica gel: 20 g, solvent; chloroform: ethyl acetate=5:1→chloroform:isopropanol=30:1) to give 2-hydroxy-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (618 mg) as slightly yellow crystalline powder, m.p. 195–197° C.

(3) A mixture of 2-hydroxy-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (500 mg) obtained in the above (2), diethylaminobenzene (2 ml) and phosphorus oxychloride (4 ml) is stirred at 80° C. for 30 minutes, and stirred at 100° C. for 5 hours. After cooling, the reaction solution is poured into ice-water, and the mixture is stirred at room temperature for 30 minutes. The resulting mixture is extracted with ethyl acetate, and the organic layer is washed with water and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (silica gel: 7 g, solvent; chloroform) to give 2-chloro-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (375 mg) as slightly yellow crystalline powder, m.p. 114–115°, MS (m/z): 356 (MH^+).

(4) A mixture of 2-chloro-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (285 mg) obtained in the above (3), 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine (197 mg), triethylamine (0.22 ml) and chloroform (3 ml) is stirred at room temperature for 2.5 hours, and stirred at 60° C. for 2.5 hours. The reaction mixture is diluted with ethyl acetate, and washed with water. The aqueous layer is extracted with ethyl acetate, and the organic layer is washed with water and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (silica gel: 10 g, solvent; chloroform:methanol=50:1), and concentrated under reduced pressure. The resultant is triturated with isopropyl ether to give 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (290 mg) as colorless crystalline powder, m.p. 179–182° C., MS (m/z): 443 (MH^+).

(5) A suspension of 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (290 mg) obtained in the above (4) and 2N aqueous sodium hydroxide solution (1.64 ml) in a mixture of dimethylsulfoxide (5 ml) and water (1 ml) is stirred at room temperature for one hour. To the mixture is added tetrahydrofuran (5 ml), and the mixture is stirred at room temperature for 13 hours. Tetrahydrofuran is evaporated under reduced pressure, and the resulting solution is diluted with water, and neutralized with a 10% aqueous citric acid solution. The precipitates are collected by filtration, washed with water, methanol and isopropyl ether to give 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-carboxypyrimidine (187 mg) as colorless crystalline powder, m.p. 223–226° C. (decomposed), MS (m/z): 413 $(M-H)^-$.

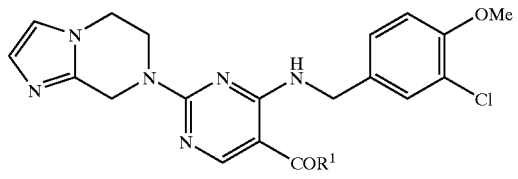
(6) A mixture of 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-carboxypyrimidine (60 mg), 4-methyl-2-aminomethylmorpholine (22.7 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (30.6 mg), 1-hydroxybenzotriazole (21.6 mg) and N,N-dimethylformamide (3 ml) is stirred at room temperature for 22 hours. Water is poured into the reaction mixture, and the mixture is extracted with ethyl acetate. The organic layer is washed successively with water, a saturated aqueous sodium hydrogen carbonate solution, water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the colorless crystals (70.0 mg), which are further recrystallized from a mixture of chloroform and hexane to give 2-(5,6,7,8-tetrahydroimidazo[1,2-a]-pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-[(4-methyl-2-morpholinyl)methyl]carbamoyl]pyrimidine (51.7 mg) as colorless needles, m.p. 132–134° C., MS (m/z): 527 (MH^+).

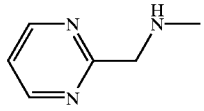
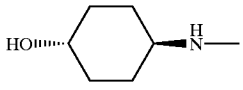
EXAMPLES 5–6

The corresponding starting materials are treated in a similar manner as in Example 4-(6) to give the compounds as listed in the following Table 1.

2.

TABLE 1

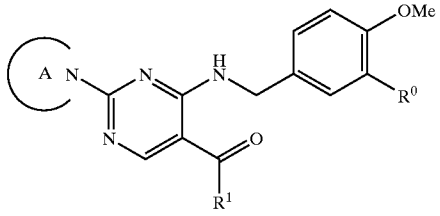


Ex. No.	R^1	Physiochemical properties
5		Powder MS(m/z):506 (MH^+)
6		Powder MS(m/z):512 (MH^+)

EXAMPLE 7–21

The corresponding starting materials are treated in a similar give the compounds as listed in the following Table

TABLE 2



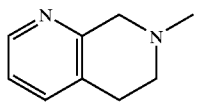
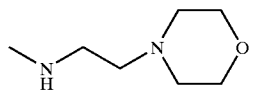
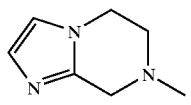
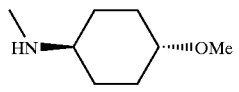
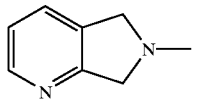
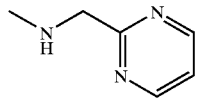
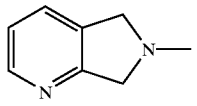
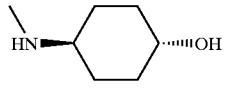
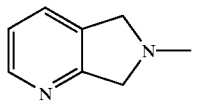
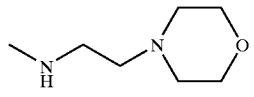
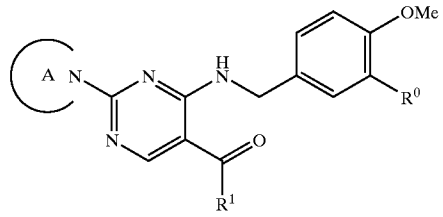
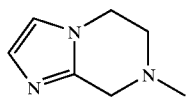
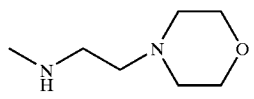
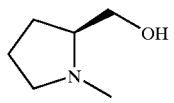
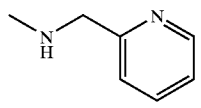
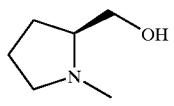
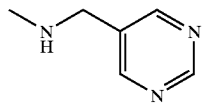
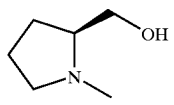
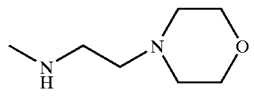
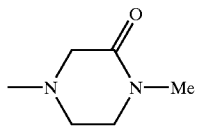
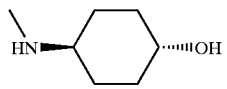
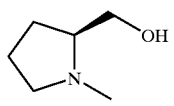
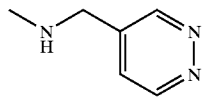
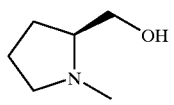
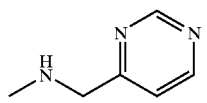
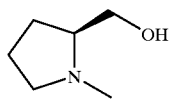
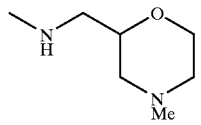
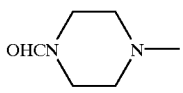
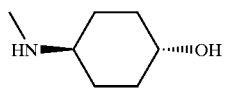
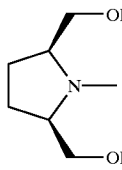
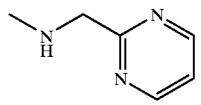
Ex. No.		R^0	R^1	Physiochemical properties
7		Cl		Amorphous MS(m/z):538 (MH^+)
8		Cl		Amorphous MS(m/z):526 (MH^+)
9		CN		M.p. 243–245° C.
10		CN		Amorphous MS(m/z):500 (MH^+)
11		CN		M.p. 129–132° C.

TABLE 2-continued



Ex. No.	A N—	R^0	R^1	Physiochemical properties
12		Cl		M.p. 150–152° C.
13		Cl		Powder (HCl) MS(m/z):483 (MH^+)
14		Cl		Amorphous MS(m/z):484 (MH^+)
15		Cl		Caramel MS(m/z):505 (MH^+)
16		Cl		Amorphous MS(m/z):503 (MH^+)
17		Cl		Amorphous MS(m/z):484 (MH^+)
18		Cl		Amorphous MS(m/z):484 (MH^+)
19		Cl		Amorphous MS(m/z):505 (MH^+)
20		Cl		Foam MS(m/z):503 (MH^+)
21		Cl		Amorphous MS(m/z):514 (MH^+)

EXAMPLE 22

To a solution of diisopropylamine (0.78 g) in tetrahydrofuran (40 ml) is added dropwise a 1.6M solution of n-butyl lithium in hexane (4.82 ml) in a dry ice-acetone bath over a period of 3 minutes. The mixture is stirred in the same bath for 30 minutes. To the mixture is added dropwise a solution of 2,6-dichloropyrazine (0.50 g) in tetrahydrofuran (5 ml) at the same temperature over a period of 15 minutes, and the mixture is stirred for one hour. The reaction mixture is poured into dry ice, and the mixture is stirred at room temperature for one hour. The reaction mixture is diluted with a 10% aqueous hydrochloric acid solution in order to adjust the pH value thereof to about 2, and then extracted with ethyl acetate. The combined organic layers are extracted with a saturated aqueous sodium hydrogen carbonate solution, and the aqueous extract is washed with ethyl acetate, acidified with a 10% aqueous hydrochloric acid, and extracted with ethyl acetate. The combined organic layer is washed with water and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is triturated with a mixture of chloroform and hexane (1:1) to give 2-carboxy-3,5-dichloropyrazine (234 mg) as a slightly brown crystalline powder, m.p. 139–141° C., MS (m/z): 191 $(M-H)^-$.

(2) A mixture of 2-carboxy-3,5-dichloropyrazine (226 mg) obtained in the above (1), sodium hydrogen carbonate (118 mg), methyl iodide (0.5 ml) and N,N-dimethylformamide (1.8 ml) is stirred at room temperature for 14 hours. The mixture is diluted with a 10% aqueous citric acid solution, and extracted with ethyl acetate. The combined organic layer is washed with water and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give 2-methoxycarbonyl-3,5-dichloropyrazine (245 mg) as pale brown crystalline powder, m.p. 60–63° C., MS (m/z): 206 (M^+).

(3) A mixture of 2-methoxycarbonyl-3,5-dichloropyrazine (234 mg) obtained in the above (2), 3-chloro-4-methoxybenzylamine (204 mg), triethylamine (0.17 ml) and dry toluene (3 ml) is stirred at room temperature for 7 hours. The reaction mixture is diluted with a 10% aqueous citric acid solution, and extracted with ethyl acetate. The extract is washed with water and a saturated aqueous sodium chloride solution, dried over sodium sulfate, and concentrated under reduced pressure. The residue is separated and purified by silica gel column chromatography (silica gel: 5 g, solvent; hexane:chloroform=1:1), and the desired fractions are concentrated under reduced pressure to give 2-methoxycarbonyl-3-(3-chloro-4-methoxybenzylamino)-5-chloropyrazine (102 mg) as pale yellow crystalline powder, m.p. 149–151° C., MS (m/z): 342 (MH^+).

(4) A mixture of 2-methoxycarbonyl-3-(3-chloro-4-methoxybenzylamino)-5-chloropyrazine (150 mg), 2-hydroxymethylpyrrolidine (88.6 mg), and triethylamine (0.12 ml) in tetrahydrofuran (5 ml) is stirred at room temperature for 4 hours, and the mixture is heated at 50° C. for 2 hours. To the mixture is added 2-hydroxymethylpyrrolidine (44.3 mg), and the mixture is stirred at 50° C. for one hour. After cooling, water is added to the reaction mixture, and the mixture is extracted with ethyl acetate. The extract is washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting yellow oil is purified by silica gel column chromatography (solvent; chloroform:hexane=1:1) to give (S)-2-methoxycarbonyl-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)-pyrazine (123 mg) as pale yellow powder, MS (m/z): 407 (MH^+).

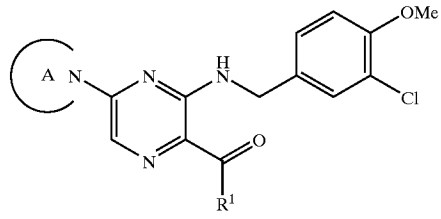
(5) To a solution of (S)-2-methoxycarbonyl-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)pyrazine (775 mg) obtained in the above (4) in ethanol (8 ml) is added a 4N aqueous sodium hydroxide solution (1.43 ml), and the mixture is stirred at room temperature for 24 hours. The reaction mixture is acidified with 10% aqueous hydrochloric acid solution, and extracted with ethyl acetate. The organic layer is washed with water and brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and washed with diisopropyl alcohol to give (S)-2-carboxy-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)pyrazine (537 mg) as yellow crystals, m.p. 169–171° C., MS (m/z): 391 $(M-H)^-$.

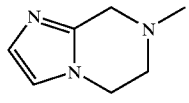
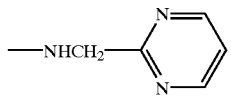
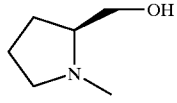
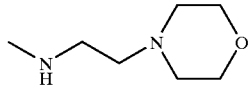
(6) A mixture of (S)-2-carboxy-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)pyrazine (80 mg) obtained in the above (5), 2-aminomethylpyrimidine (26.7 mg), 1,2-dichloroethane (43 mg), 1-hydroxybenzotriazole (30.3 mg) in N,N-dimethylformamide (3 ml) is stirred at room temperature for 18 hours. Water is poured into the reaction mixture, and extracted with ethyl acetate. The extract is washed with water, a saturated aqueous sodium hydrogen carbonate solution, and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; ethyl acetate) to give (S)-2-[N-(2-pyrimidinylmethyl)carbamoyl]-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)pyrazine (87.6 mg), MS (m/z): 484 (MH^+).

EXAMPLES 23–24

The corresponding starting materials are treated in a similar manner as in Example 22 to give the compounds as listed in the following Table 3.

TABLE 3



Ex. No.	A N—	R^1	Physiochemical properties
23			Amorphous MS(m/z):506 (MH^+)
24			Amorphous MS(m/z):505 (MH^+)

EXAMPLE 25

A mixture of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-(acryloyl)pyrimidine (31 mg), methanol (1 ml) and conc. sulfuric acid (one drop) is heated under reflux for 2 days. After the reaction is complete, the solvent is evaporated under reduced pressure, and the residue is separated by silica gel thin layer chromatography (solvent; chloroform:methanol=30:1) to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-methoxyethyl)carbonyl]pyrimidine (27 mg) as colorless oil, MS (m/z): 435 (MH^+).

EXAMPLE 26

A solution of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]-pyrimidine (82.48 g) and benzenesulfonic acid monohydrate (60.06 g) in methanol (1000 ml) is concentrated, and recrystallized from a mixture of methanol and acetone to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)-carbamoyl]pyrimidine dibenzenesulfonate (121.8 g) as colorless crystals, m.p. 158.5–161.5° C.

EXAMPLE 27

A mixture of (S)-4-(3-chloro-4-methoxybenzylamino)-5-carboxy-2-(2-hydroxymethyl-1-pyrrolidinyl)pyrimidine (100 mg) obtained in Example 1-(4), 4-amino-1,3,5-trimethylpyrazole (47.9 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (58.7 mg), 1-hydroxybenzotriazole monohydrate (41.3 mg), and N,N-dimethylformamide (3 ml) is stirred at room temperature for 8 hours, and poured into aqueous sodium hydrogen carbonate solution. The mixture is extracted with ethyl acetate, and the organic layer is washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent is evaporated under reduced pressure, and the residue is purified by silica gel column chromatography (solvent; chloroform:methanol=5:1) to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine (115 mg), MS (m/z): 500 (MH^+).

EXAMPLE 28

(1) A solution of 4-chloro-5-ethoxycarbonyl-2-methylthiopyrimidine (5.0 g) in sulfuryl chloride (20 ml) is heated at 50° C. for one hour. The reaction mixture is concentrated, and thereto is poured a saturated aqueous sodium hydrogen carbonate solution. The mixture is extracted with ethyl acetate, and the organic layer is washed with water and brine, dried over sodium sulfate, and concentrated. The residue is purified by silica gel flash column chromatography (solvent; ethyl acetate=hexane=1:10) to quantitatively give 2,4-dichloro-5-ethoxycarbonylpyrimidine (4.87 g) as yellow oil, MS (m/z): 220 (M^+).

(2) To a solution of 2,4-dichloro-5-ethoxycarbonylpyrimidine (4.2 g) obtained in the above (1) and mercaptobenzene (2.30 g) in toluene (40 ml) is added potassium carbonate (3.94 g) at 0° C., and the mixture is stirred at room temperature for one hour, stirred at 50° C. for one hour, and further stirred at 100° C. for 10 minutes. To the mixture is poured water, and the mixture is extracted with ethyl acetate. The organic layer is washed with brine, dried over sodium sulfate, and concentrated. The residue is purified by silica gel flash column chromatography (solvent; ethyl acetate:hexane=1:20→ethyl acetate:hexane=1:10) to give 2-chloro-4-phenylthio-5-ethoxycarbonylpyrimidine (4.16 g) as colorless crystals, MS (m/z): 295 (MH^+).

(3) To a solution of 2-chloro-4-phenylthio-5-ethoxycarbonylpyrimidine (4.05 g) obtained in the above (2) in tetrahydrofuran (40 ml) are added L-prolinol (1.66

g) and triethylamine (2.77 g), and the mixture is stirred at room temperature for 20 hours. Water is poured into the reaction mixture, and the mixture is extracted with ethyl acetate. The organic layer is washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel flash column chromatography (solvent; ethyl acetate:hexane=1:2) to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-phenylthio-5-ethoxycarbonylpyrimidine (4.16 g) as colorless viscous oil, MS (m/z): 360 (MH^+).

(4) To a solution of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-phenylthio-5-ethoxycarbonylpyrimidine (4.10 g) obtained in the above (3) in ethanol (50 ml) is added a 4N aqueous sodium hydroxide solution (8.6 ml), and the mixture is stirred at room temperature for 15 hours. To the reaction solution is added a 10% aqueous citric acid solution (30 ml) until the solution becomes weak acidic, and the mixture is extracted with ethyl acetate. The organic layer is washed with water and brine, dried over sodium sulfate, and concentrated to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-phenylthio-5-carboxypyrimidine (3.65 g) as colorless crystals, MS (m/z): 330 $(M-H)^-$.

(5) A mixture of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-phenylthio-5-carboxypyrimidine (2.55 g) obtained in the above (4), 2-aminomethylpyrimidine (1.09 g), 1,2-dichloroethane (1.77 g) and 1-hydroxybenzotriazole (1.25 g) in N,N-dimethylformamide (40 ml) is stirred at room temperature for 16 hours. To the mixture is poured water, and the mixture is extracted with ethyl acetate. The organic layer is washed with water, a saturated aqueous sodium hydrogen carbonate solution and brine, dried over sodium sulfate, and concentrated to give pale yellow crystals (4.05 g), which is further purified by silica gel flash column chromatography (solvent; ethyl acetate) to give 2-(2-hydroxymethyl-1-pyrrolidinyl)-4-phenylthio-5-[N-(2-pyrimidylmethyl)carbamoyl]pyrimidine (2.39 g) as colorless crystals, m.p., 154–156° C., IR (Nujol): 1633 cm^{-1}, MS (m/z): 423 (MH^+).

(6) To a solution of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-phenylthio-5-[N-(2-pyrimidylmethyl)carbamoyl] pyrimidine (100 mg) obtained in the above (5) in chloroform (3 ml) is added m-chloroperbenzoic acid (70.1 mg) at 0° C., and the mixture is stirred at 0° C. for 30 minutes. To the mixture are added 3-chlorobenzylamine (50.3 mg) and triethylamine (48.0 mg) at 0° C., and the mixture is stirred at room temperature for 17 hours. To the mixture is poured water, and the mixture is extracted with chloroform. The organic layer is washed with brine, dried over sodium sulfate, and concentrated under reduced pressure to give yellow oil (169 mg), which is purified by silica gel flash column chromatography (solvent; ethyl acetate), and triturated with a mixture of ethyl acetate and hexane to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chlorobenzylamino)-5-[N-(2-pyrimidylmethyl)-carbamoyl]pyrimidine (95.3 mg) as colorless powder, m.p. 153–156° C., IR (Nujol): 3241, 1637 cm^{-1}, MS (m/z): 454 (MH^+).

(7) To a solution of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-phenylthio-5-[N-(2-pyrimidylmethyl)carbamoyl] pyrimidine (100 mg) obtained in the above (5) in chloroform (3 ml) is added m-chloroperbenzoic acid (70%, 70.1 mg) at 0° C., and the mixture is stirred at 0° C. for 30 minutes. To the mixture are added 4-methoxybenzylamine (48.8 mg) and triethylamine (48.0 mg) at 0° C., and the mixture is stirred at room temperature for 20 minutes. To the mixture is poured water, and the mixture is extracted with chloroform, and the organic layer is washed with brine, dried over sodium sulfate, and concentrated to give a yellow oil (143 mg), which is purified by silica gel flash column chromatography (solvent; ethyl acetate) to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(4-methoxybenzylamino)-5-[N-(2-pyrimidylmethyl)-carbamoyl]pyrimidine (88.2 mg) as colorless powder, IR (Neat): 3296, 1633 cm^{-1}, MS (m/z): 450 (MH^+).

EXAMPLE 29

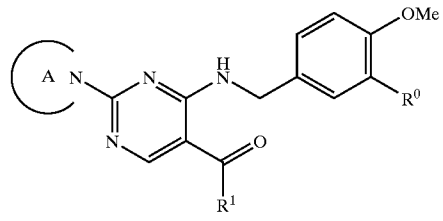
(1) A solution of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-formylpyrimidine (10.0 mg) in tetrahydrofuran (1.0 ml) obtained in Example 2 (3) is treated with a 1.6M solution of n-butyl lithium in hexane (83 μl) at −78° C. for 3 minutes, and thereto is added an aqueous sodium hydrogen carbonate solution. The reaction mixture is extracted with ethyl acetate to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-(1-hydroxypentyl) pyrimidine (13.7 mg) as oil.

(2) (S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-(1-hydroxypentyl)pyrimidine obtained in the above is treated with manganese dioxide (25 mg) at room temperature, and thereto is added gradually additional manganese dioxide (100 mg), and the mixture is stirred overnight. The reaction mixture is heated under reflux for 5 hours, and the insoluble materials are removed by filtration. The filtrate is concentrated under reduced pressure, and separated with preparative thin layer chromatography to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-pentanoylpyrimidine (5.8 mg) as colorless oil, MS (m/z): 433 (MH^+).

EXAMPLES 30–83

The corresponding starting compounds are treated in a similar manner to give the compounds as listed in the following Table 4.

TABLE 4



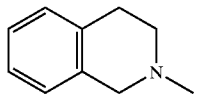
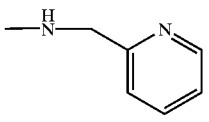
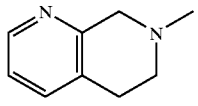
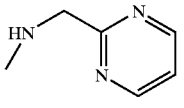
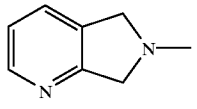
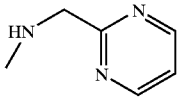
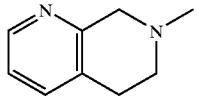
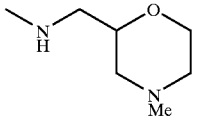
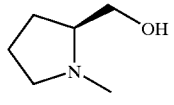
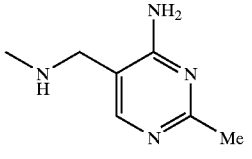
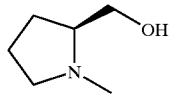
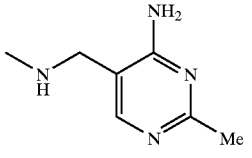
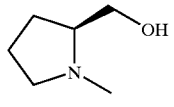
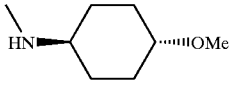
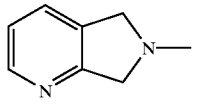
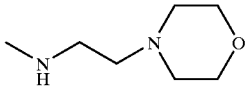
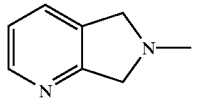
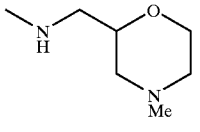
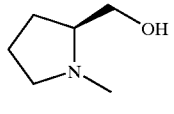
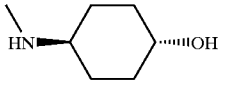
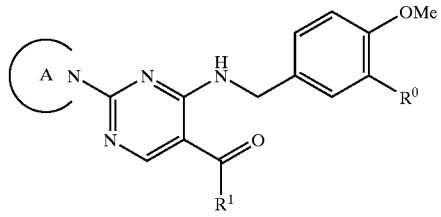
Ex. No.	A N—	R^0	R^1	Physiochemical properties
30		Cl		M.p. 210–214° C.
31		Cl		Amorphous MS(m/z):517 (MH^+)
32		Cl		Amorphous MS(m/z):503 (MH^+)
33		Cl		Amorphous MS(m/z):538 (MH^+)
34		Cl		HCl salt M.p. 223–226° C.
35		Cl		Amorphous MS(m/z):513 (MH^+)
36		Cl		Amorphous MS(m/z):504 (MH^+)
37		Cl		MS(m/z):524 (MH^+)
38		Cl		Amorphous MS(m/z):524 (MH^+)
39		Cl		Foam MS(m/z):490 (MH^+)

TABLE 4-continued



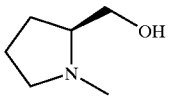
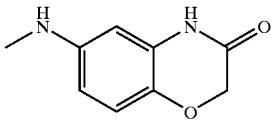
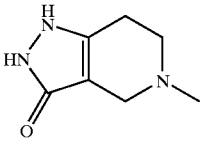
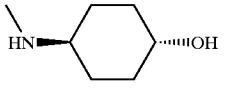
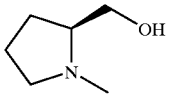
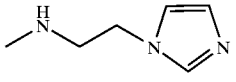
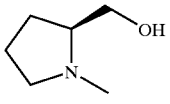
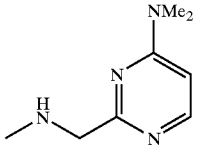
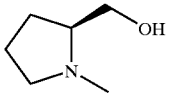
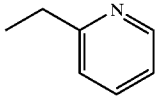
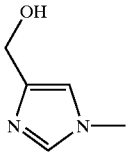
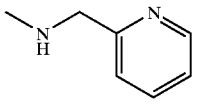
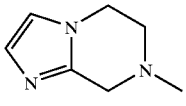
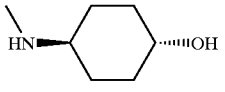
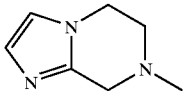
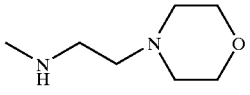
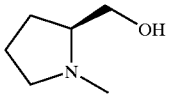
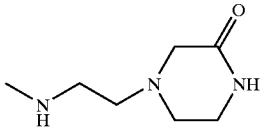
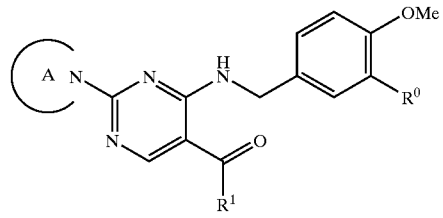
Ex. No.		R^0	R^1	Physiochemical properties
40		Cl		Amorphous MS(m/z):539 (MH^+)
41		Cl		Amorphous MS(m/z):528 (MH^+)
42		Cl		Amorphous MS(m/z):500 (MH^+)
43		Cl		Amorphous MS(m/z):527 (MH^+)
44		Cl		Amorphous MS(m/z):468 (MH^+)
45		Cl		M.p. 220–222° C.
46		NO_2		Amorphous MS(m/z):523 (MH^+)
47		NO_2		M.p. 188–190° C.
48		Cl		Amorphous MS(m/z):518 (MH^+)

TABLE 4-continued



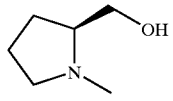
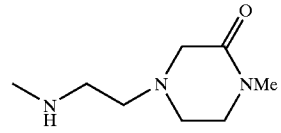
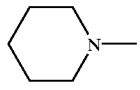
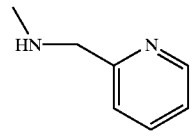
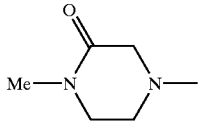
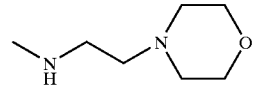
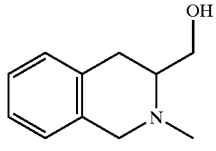
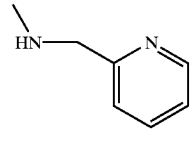
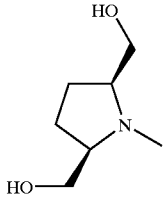
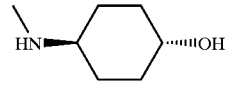
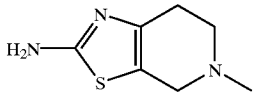
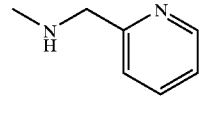
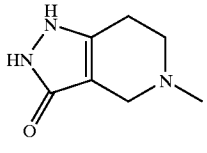
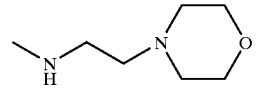
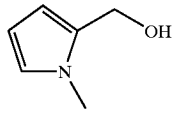
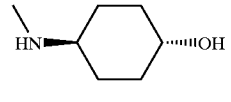
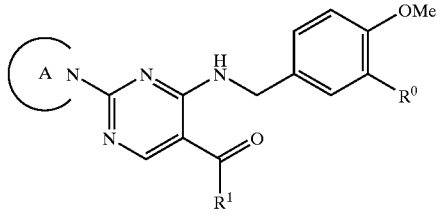
Ex. No.	A N—	R^0	R^1	Physiochemical properties
49		Cl		Amorphous MS(m/z):532 (MH^+)
50		Cl		M.p. 179–183° C.
51		Cl		Amorphous MS(m/z):518 (MH^+)
52		Cl		Powder (HCl) MS(m/z):545 (MH^+)
53		Cl		Amorphous MS(m/z):520 (MH^+)
54		Cl		Powder (HCl) MS(m/z):537 (MH^+)
55		Cl		Amorphous MS(m/z):543 (MH^+)
56		Cl		M.p. 181–183° C.

TABLE 4-continued



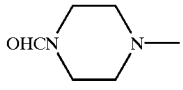
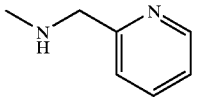
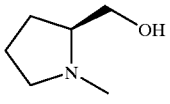
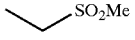
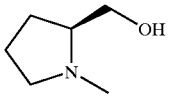
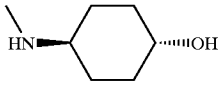
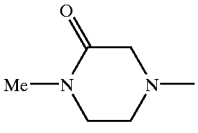
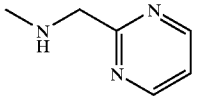
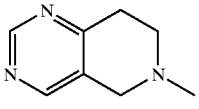
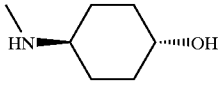
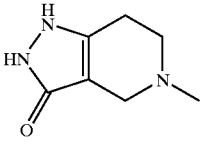
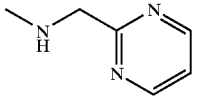
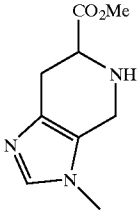
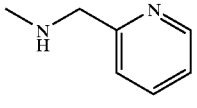
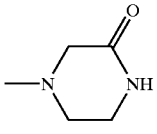
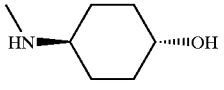
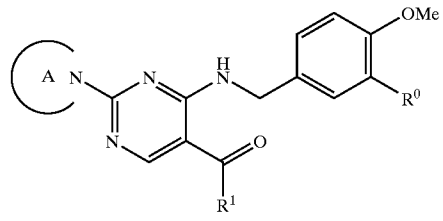
Ex. No.		R^0	R^1	Physiochemical properties
57		Cl		Powder (HCl) MS(m/z):496 (MH^+)
58		Cl		M.p. 199–200° C.
59		NO_2		M.p. 209.5–211.5° C.
60		Cl		M.p. 228–230.5° C.
61		Cl		Amorphous MS(m/z):524 (MH^+)
62		Cl		Amorphous MS(m/z):522 (MH^+)
63		Cl		Amorphous MS(m/z):563 (MH^+)
64		Cl		Amorphous MS(m/z):489 (MH^+)

TABLE 4-continued



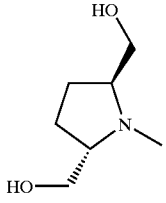
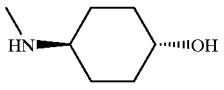
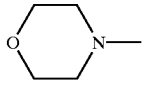
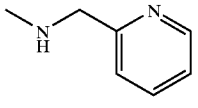
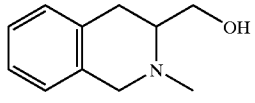
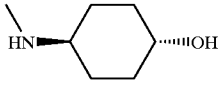
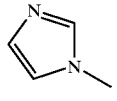
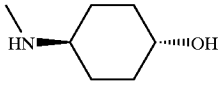
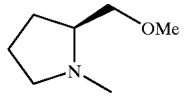
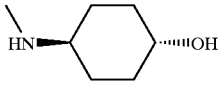
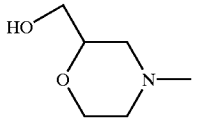
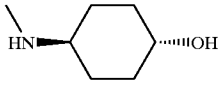
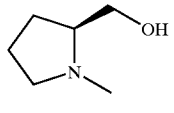
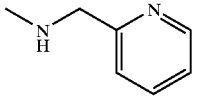
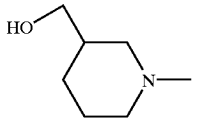
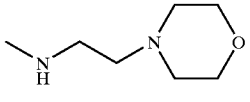
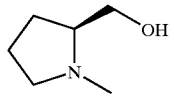
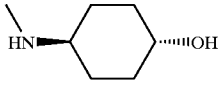
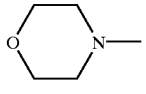
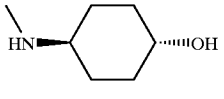
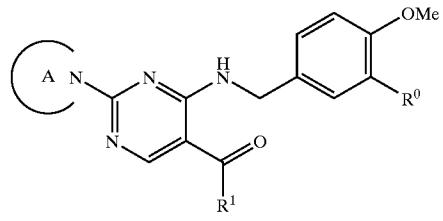
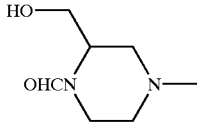
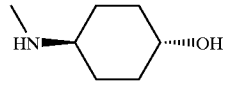
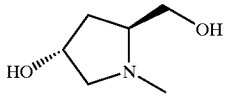
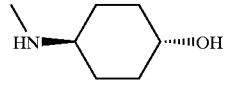
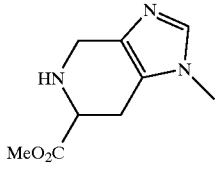
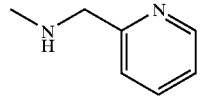
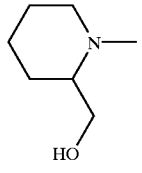
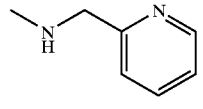
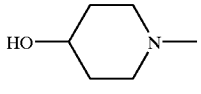
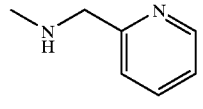
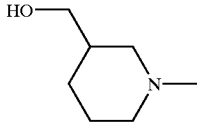
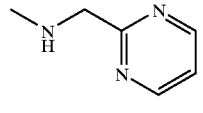
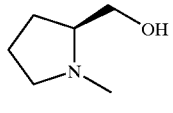
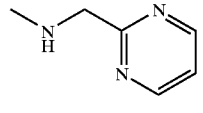
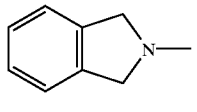
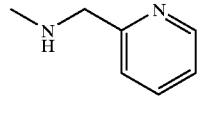
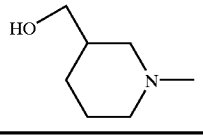
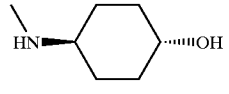
Ex. No.	A N—	R^0	R^1	Physiochemical properties
65		Cl		Amorphous MS(m/z):520 (MH^+)
66		Cl		M.p. 176–180° C.
67		CN		Powder (HCl) MS(m/z):543 (MH^+)
68		Cl		M.p. 143–145° C.
69		Cl		Powder (HCl) MS(m/z):504 (MH^+)
70		Cl		M.p. 130° C.
71		CN		Powder (HCl) MS(m/z):474 (MH^+)
72		Cl		Amorphous MS(m/z):519 (MH^+)
73		CN		Powder (HCl) MS(m/z):481 (MH^+)
74		Cl		M.p. 116–119° C.

TABLE 4-continued

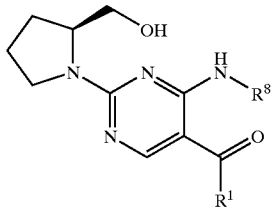


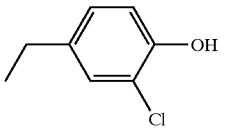
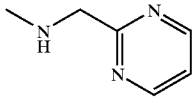
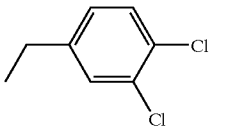
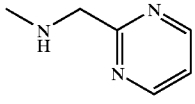
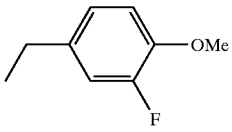
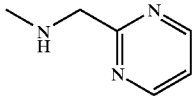
Ex. No.	A N—	R^0	R^1	Physiochemical properties
75		Cl		M.p. 159–161° C.
76		Cl		Powder (HCl) MS(m/z):506 (MH^+)
77		Cl		Amorphous MS(m/z):563 (MH^+)
78		Cl		Powder (HCl) MS(m/z):497 (MH^+)
79		Cl		M.p. 210–214° C.
80		Cl		M.p. 149–151.5° C.
81		NO_2		Amorphous MS(m/z):495 (MH^+)
82		Cl		M.p. 215° C.
83		Cl		M.p. 151–152° C.

EXAMPLE 84–86

The corresponding starting compounds are treated in a similar manner to give the compounds as listed in the following Table 5.

TABLE 5



Ex. No.	R^8	R^1	Physiochemical properties
84			Foam MS(m/z):470 (MH^+)
85			Powder MS(m/z):488 (MH^+)
86			Powder MS(m/z):468 (MH^+)

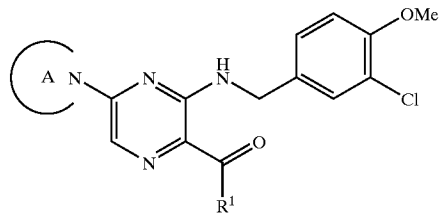
EXAMPLE 87

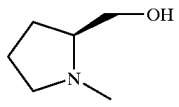
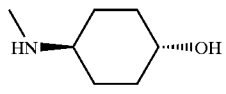
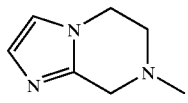
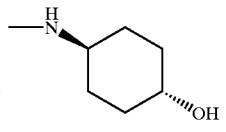
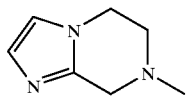
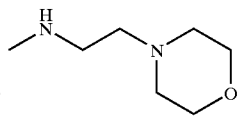
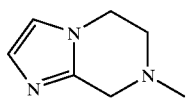
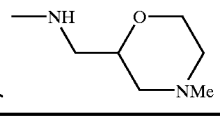
A mixture of (S)-2-carboxy-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl) pyrazine (80 mg) obtained in Example 22 (5), 2-aminomethyl-4-methylmorpholine (31.9 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (43 mg), 1-hydroxybenzotriazole (30.3 mg) in N,N-dimethylformamide (3 ml) is stirred at room temperature for 18 hours. To the reaction mixture is poured water, and the mixture is extracted with ethyl acetate. The extract is washed with water, a saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel flash column chromatography (solvent; ethyl acetate) to give (S)-2-[N-(4-methyl-2-morpholinyl) methylcarbamoyl]-3-(3-chloro-4-methoxybenzylamino)-5-(2-hydroxymethyl-1-pyrrolidinyl)pyrazine (80.5 mg), MS (m/z): 505 (MH^+), IR (Nujol): 3295, 1635 cm^{-1}.

EXAMPLES 88–91

The corresponding starting compounds are treated in a similar manner to give the compounds as listed in the following Table 6.

TABLE 6

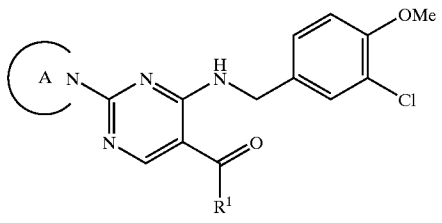


Ex. No.	A N—	R^1	Physiochemical properties
88			M.p. 177–179° C, MS(m/z):490 (MH^+)
89			M.p. 167–169° C. MS(m/z):512 (MH^+)
90			M.p. 140.5–141.5° C.
91			Amorphous MS(m/z):527 (MH^+)

EXAMPLES 92–145

The corresponding starting compounds are treated in a similar give the compounds as listed in the following Table 7.

TABLE 7



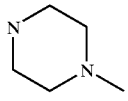
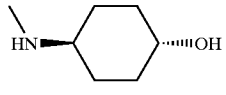
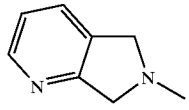
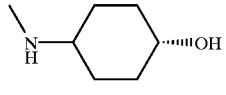
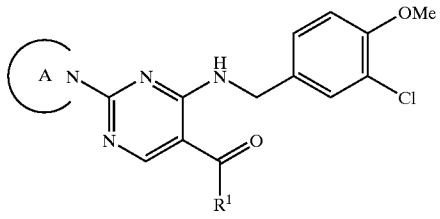
Ex. No.	A N—	R^1	Physiochemical properties
92			Powder MS(m/z):475 (MH^+)
93			Powder MS(m/z):509 (MH^+)

TABLE 7-continued



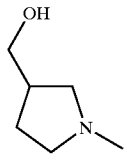
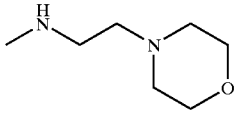
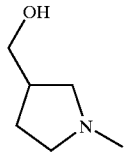
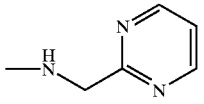
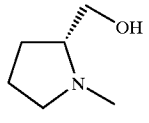
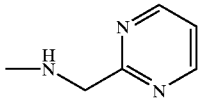
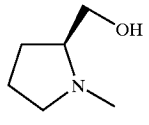
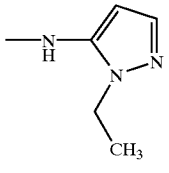
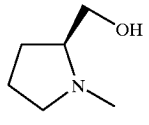
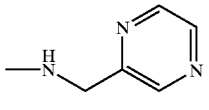
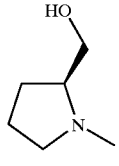
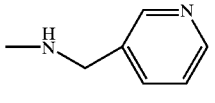
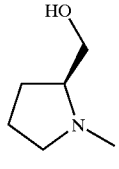
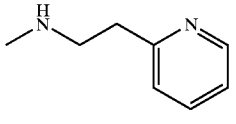
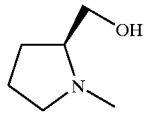
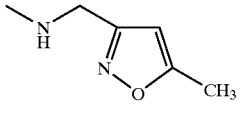
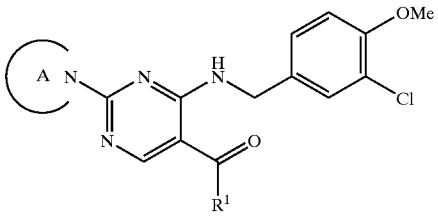
Ex. No.	A N—	R^1	Physiochemical properties
94			Amorphous MS(m/z):512 (MH^+)
95			M.p. 150–152° C.
96			M.p. 162–163° C.
97			Amorphous MS(m/z):486 (MH^+)
98			Amorphous MS(m/z):484 (MH^+)
99			Amorphous MS(m/z):483 (MH^+)
100			Amorphous MS(m/z):497 (MH^+)
101			M.p. 148–150° C.

TABLE 7-continued



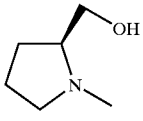
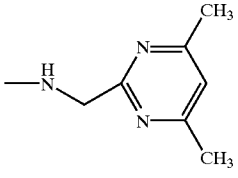
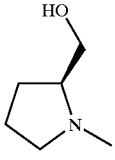
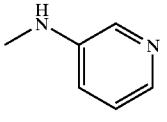
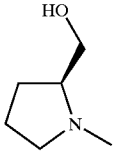
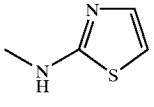
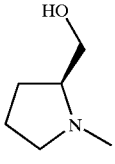
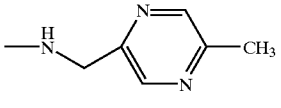
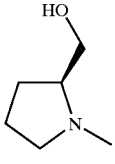
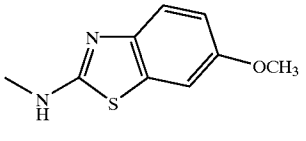
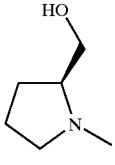
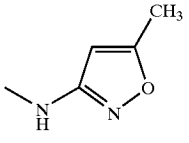
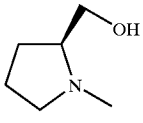
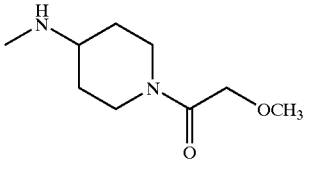
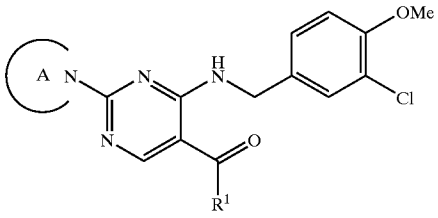
Ex. No.	A N—	R^1	Physiochemical properties
102			Amorphous MS(m/z):512 (MH^+)
103			M.p. 210–213° C.
104			M.p. 195–198° C.
105			Amorphous MS(m/z):498 (MH^+)
106			M.p. 232–235° C.
107			M.p. 207–208° C.
108			Amorphous MS(m/z):547 (MH^+)

TABLE 7-continued



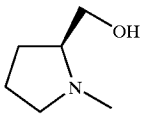
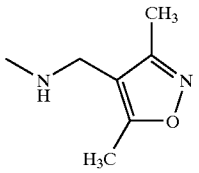
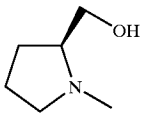
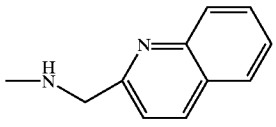
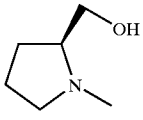
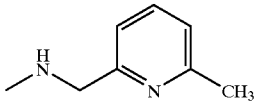
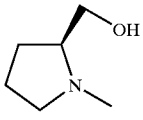
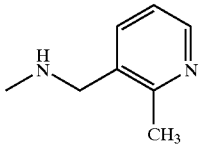
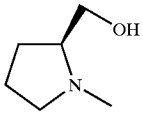
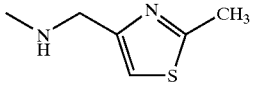
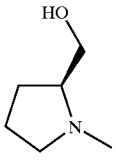
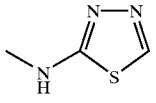
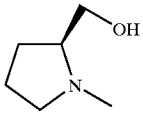
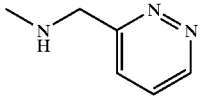
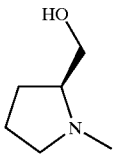
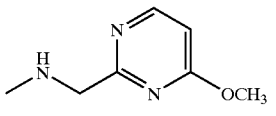
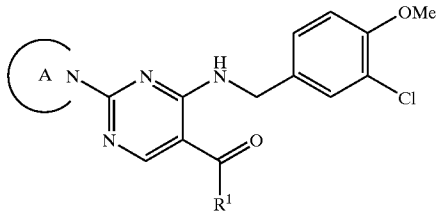
Ex. No.		R^1	Physiochemical properties
109			Amorphous MS(m/z):501 (MH^+)
110			M.p. 172–173° C.
111			M.p. 145–147° C.
112			Amorphous MS(m/z):497 (MH^+)
113			M.p. 148–150° C.
114			M.p. 217–219° C.
115			Amorphous MS(m/z):484 (MH^+)
116			Amorphous MS(m/z):514 (MH^+)

TABLE 7-continued



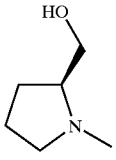
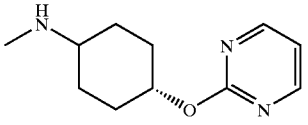
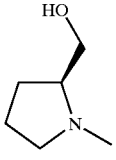
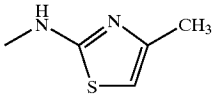
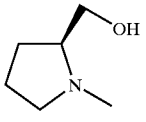
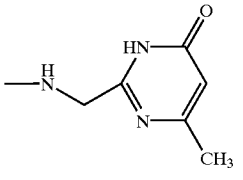
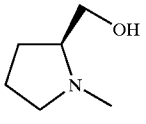
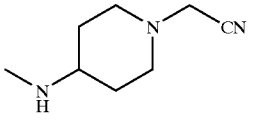
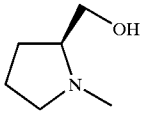
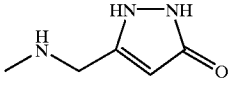
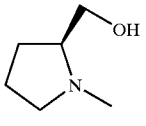
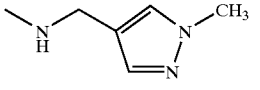
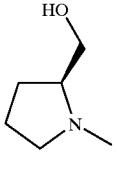
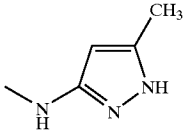
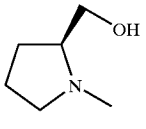
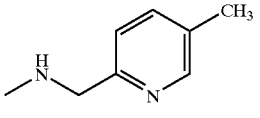
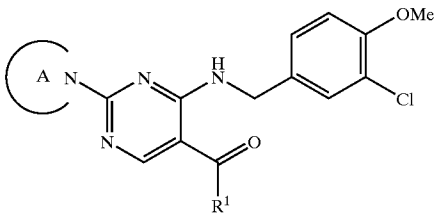
Ex. No.		R^1	Physiochemical properties
117			Amorphous MS(m/z):568 (MH^+)
118			M.p. 217–220° C.
119			M.p. 212–214° C.
120			Amorphous MS(m/z):514 (MH^+)
121			Amorphous MS(m/z):488 (MH^+)
122			M.p. 142–144° C.
123			Amorphous MS(m/z):472 (MH^+)
124			Amorphous MS(m/z):497 (MH^+)

TABLE 7-continued



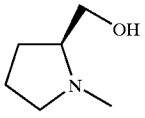
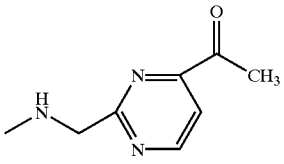
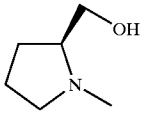
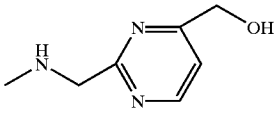
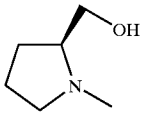
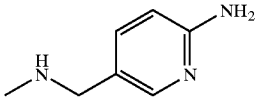
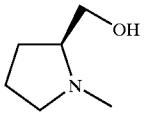
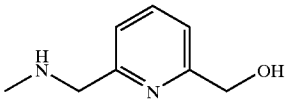
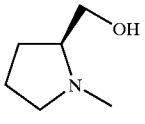
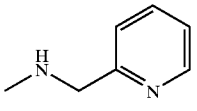
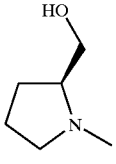
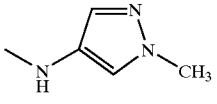
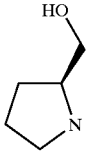
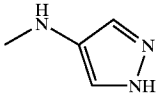
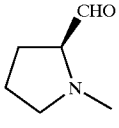
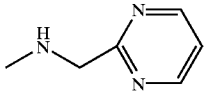
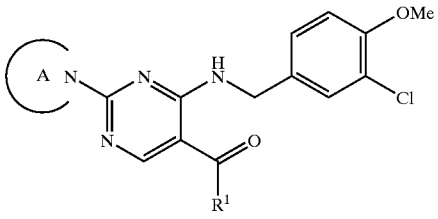
Ex. No.	A N—	R^1	Physiochemical properties
125			M.p. 143–146° C.
126			Amorphous MS(m/z):514 (MH^+)
127			Amorphous MS(m/z):498 (MH^+)
128			Amorphous MS(m/z):513 (MH^+)
129			M.p. 101–103° C.
130			M.p. 215–217° C.
131			M.p. 180–183° C.
132			Oil MS(m/z):482 (MH^+)

TABLE 7-continued



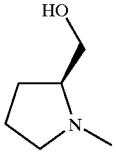
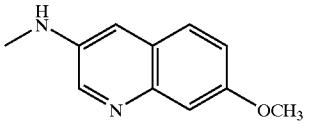
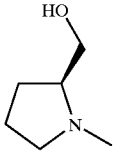
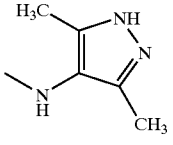
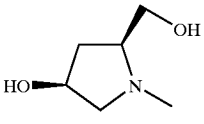
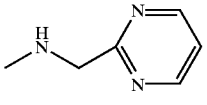
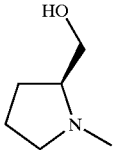
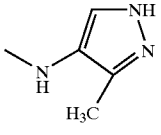
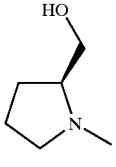
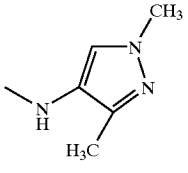
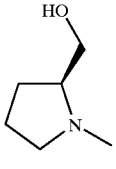
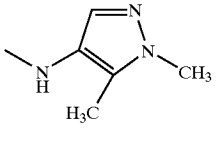
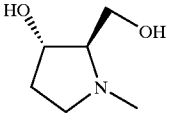
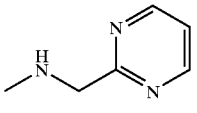
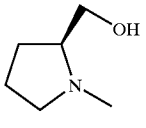
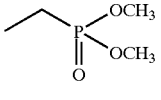
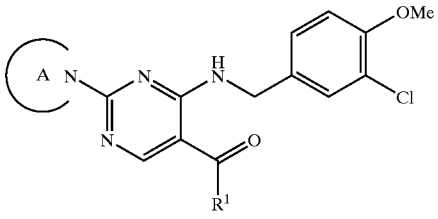
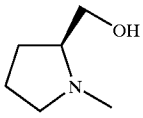
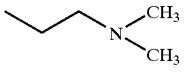
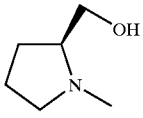
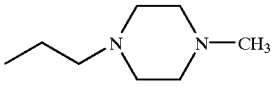
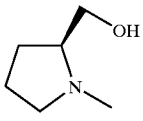
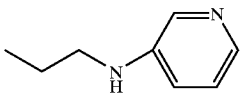
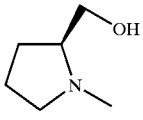
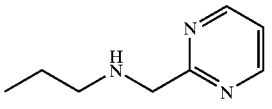
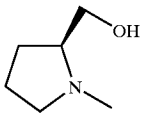
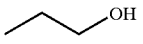
Ex. No.	A N—	R^1	Physiochemical properties
133			M.p. 176–179° C.
134			M.p. 224–227° C.
135			Amorphous MS(m/z):500 (MH^+)
136			M.p. 177–180° C.
137			Powder MS(m/z):486 (MH^+)
138			Powder MS(m/z):486 (MH^+)
139			Powder MS(m/z):500 (MH^+)
140			Amorphous MS(m/z):499 (MH^+)

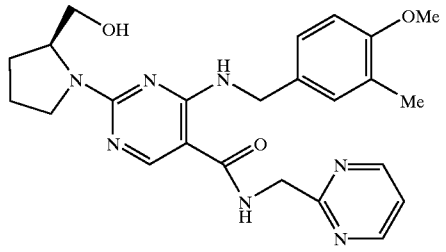
TABLE 7-continued



Ex. No.	A N—	R^1	Physiochemical properties
141			Amorphous MS(m/z):448 (MH^+)
142			Amorphous MS(m/z):503 (MH^+)
143			M.p. 112–114° C.
144			Amorphous MS(m/z):512 (MH^+)
145			M.p. 123–125° C.

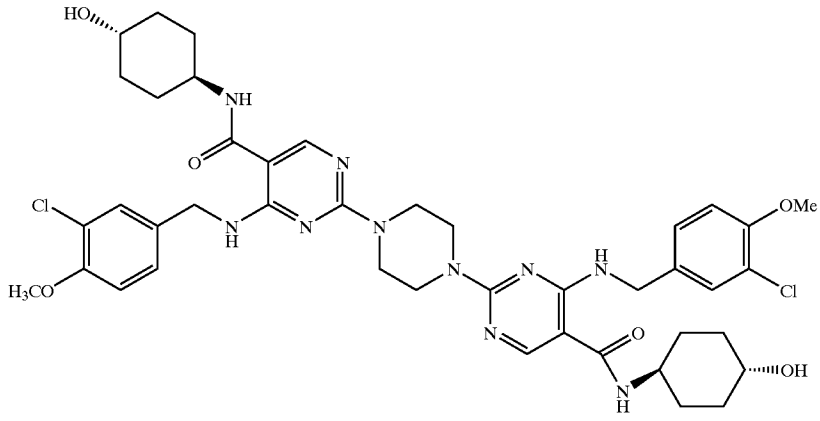
EXAMPLE 146

The corresponding starting compounds are treated in a similar manner to give the compound of the following formula as foam, MS (m/z): 464 (MH^+).



EXAMPLE 147

The corresponding starting compounds are treated in a similar manner to give the compound of the following formula, m.p. 140–144° C.



EXAMPLE 148

To a solution of (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidylmethyl)carbamoyl]-pyrimidine (307 mg) obtained in Example 1-(5) in methylene chloride (6 ml) is added dropwise boron bromide (300 μl) under ice-cooling. The reaction mixture is stirred at 0° C. for 4 hours, and thereto is added methanol, and then a saturated aqueous sodium hydrogen carbonate solution under ice-cooling. The mixture is extracted with a mixture of ethyl acetate and tetrahydrofuran, and the organic layer is washed successively with water and brine. The mixture is dried over sodium sulfate, and concentrated under reduced pressure to give a slightly brown amorphous (227 mg). The resultant is suspended in chloroform, and the resulting insoluble materials are removed by filtration. The filtrate is subjected to silica gel column chromatography, and further purified by NH-silica gel column chromatography to give (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-hydroxybenzylamino)-5-[N-(2-pyrimidylmethyl) carbamoyl]pyrimidine (129 mg) as a colorless foam, MS (m/z): 470 (MH^+), IR (Nujol): 3279, 1632, 1593, 1569, 1518, 1463 cm^{-1}.

EXAMPLE 149

(1) A suspension of 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-ethoxycarbonylpyrimidine (2.00 g) obtained in Example 1 (1) in dimethylsulfoxide (10 ml) is treated with 10% aqueous sodium hydroxide solution (10 ml) at room temperature. To the reaction mixture is added dimethylsulfoxide (5 ml), and the mixture is stirred at room temperature overnight. To the resulting colorless solution is added citric acid until the solution becomes acidic. To the solution is added an excess amount of water (about 50 ml), and the resulting precipitates are collected by filtration. The precipitates are washed with isopropyl alcohol and isopropyl ether successively, and dried under reduced pressure to give 2-methylthio-4-(3-chloro-4-methoxybenzylamino)-5-carboxypyrimidine (1.864 g) as pale yellow impalpable powder, m.p. 238–240° C. (dec.).

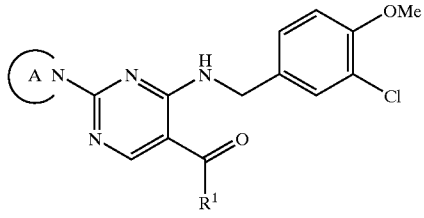
(2) To a suspension of 4-(3-chloro-4-methoxybenzylamino)-5-carboxy-2-methylthiopyrimidine (200 mg) in methylene chloride (5 ml) are added oxalyl chloride (150 mg) and N,N-dimethylformamide, and the mixture is stirred at room temperature for 30 minutes, and concentrated. To a suspension of the resulting acid chloride compound and 5-aminopyrimidine (84.0 mg) in methylene chloride (5 ml) is added dimethylaminopyridine (144 mg) at room temperature, and the mixture is stirred at room temperature. To the mixture is poured water, and the mixture is extracted with ethyl acetate. The extract is washed with a saturated aqueous sodium hydrogen carbonate solution, water and brine, dried over sodium sulfate, and concentrated. The residue is triturated with a mixture of ethyl acetate and n-hexane to give 4-(3-chloro-4-methoxybenzylamino)-5-(5-pyrimidinylaminocarbonyl)-2-methylthiopyrimidine (216 mg) as pale yellow needles, m.p. 238–240° C., IR (Nujol): 3251, 1666 cm^{-1}, MS (m/z): 416 (M^+).

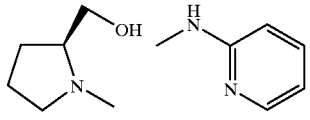
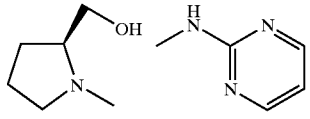
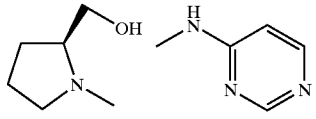
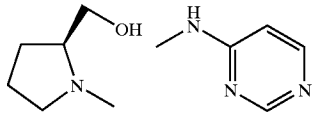
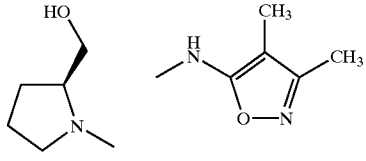
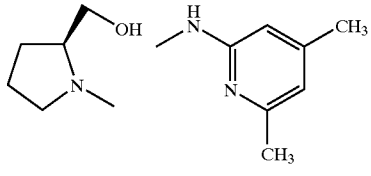
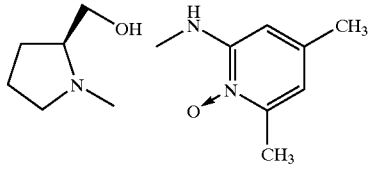
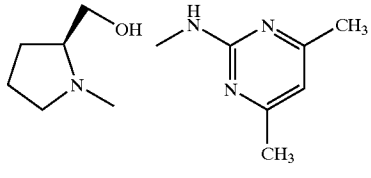
(3) To a suspension of the compound (150 mg) obtained in the above (2) in chloroform (10 ml) is added m-chloroperbenzoic acid (107 mg) at 0° C., and the mixture is stirred at 0° C. for one hour, and stirred at room temperature for one hour. To the mixture is added m-chloroperbenzoic acid (53 mg) at 0° C., and the mixture is stirred at 0° C. for 30 minutes. To the mixture are added L-prolinol (43.7 mg) and triethylamine (72.9 mg) at 0° C., and the mixture is stirred at room temperature for 20 hours. To the mixture is poured water, and the mixture is extracted with chloroform. The organic layer is washed with brine, dried over sodium sulfate, and concentrated under reduced pressure to give yellow viscous oil (201 mg), which is purified by NH-silica gel flash column chromatography (solvent; ethyl acetate), washed with a mixture of ethyl acetate and hexane to give (S)-4-(3-chloro-4-methoxybenzylamino)-5-(5-pyrimidinylaminocarbonyl)-2-(hydroxymethyl-1-pyrrolidinyl)pyrimidine (81 mg) as colorless needles, m.p. 192–195° C., IR (Nujol): 3279, 1669 cm^{-1}, MS (m/z): 470 (MH^+).

EXAMPLES 150–157

The corresponding starting compounds are treated in a similar manner as in Example 149 to give the compounds as listed in the following Table 8.

TABLE 8



Ex. No.	A N—	R^1	Physicochemical properties
150			Powder MS(m/z):469 (MH+)
151			Powder MS(m/z):470 (MH+)
152			M.p. 182–185° C.
153			M.p. 176–178° C.
154			Powder MS(m/z):487 (MH+)
155			M.p. 161–163° C.
156			Powder MS(m/z):513 (MH+)
157			Powder MS(m/z):498 (MH+)

EXAMPLE 158

(1) A suspension of 4-(3-chloro-4-methoxybenzylamino)-5-carboxy-2-methylthiopyrimidine (154.0 mg) obtained in Example 149 (1) in methylene chloride (5 ml) is treated with oxalyl chloride (119 μl) at room temperature, and thereto is added N,N-dimethylformamide. The mixture is stirred for one hour, and the solvent is evaporated under reduced pressure. The residue is treated with ether, and kept in a refrigerator overnight. The volatile materials are removed under reduced pressure, and the residue is treated with an excess amount of diazomethane at 0° C. and kept in a refrigerator overnight. The reaction is quenched with methanol, and the mixture is purified by silica gel chromatography (solvent; hexane:ethyl acetate=2:1) to give 4-(3-chloro-4-methoxybenzylamino)-5-(diazomethylcarbonyl)-2-methylthiopyrimidine (21.5 mg) as pale yellow solid, IR (Nujol): 3277, 2115, 1607, 1567, 1461, 1377, 1357, 1141 cm^{-1}, MS (m/z): 364 (MH^+), m.p. 162–165° C. (dec.).

(2) A suspension of the compound obtained in the above (1) (16.5 mg) in methanol (3 ml) is treated with toluenesulfonic acid monohydrate (16.5 mg) at room temperature. The solvent is evaporated under reduced pressure, and the residue is purified by preparative TLC (solvent; hexane:ethyl acetate=2:1) to give 4-(3-chloro-4-methoxybenzylamino)-5-(methoxymethylcarbonyl)-2-methylthiopyrimidine (11.0 mg) as colorless oil.

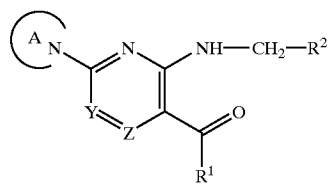
(3) A solution of the compound (11.0 mg) obtained in the above (2) in chloroform (1 ml) is treated with m-chloroperbenzoic acid (7.4 mg) at 0° C. The mixture is treated with triethylamine (8.3 μl) and L-prolinol (36 mg) at room temperature, and the reaction mixture is stirred overnight. The reaction mixture is diluted with ethyl acetate, washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium chloride solution, and dried over sodium sulfate. The residue is purified by preparative TLC (solvent; chloroform:ethyl acetate 1:1) to give (S)-4-(3-chloro-4-methoxybenzylamino)-5-(methoxymethylcarbonyl)-2-(2-hydroxymethyl-1-pyrrolidinyl)pyrimidine (8.5 mg) as colorless oil, MS (m/z): 421 (MH^+).

Industrial Applicability

The compound (I) of the present invention and a pharmaceutically acceptable salt thereof exhibit excellent PDE V inhibitory activities, and they are useful pharmaceutical compounds for the prophylaxis or treatment of penile erectile dysfunction, etc.

What is claimed is:

1. An aromatic nitrogen-containing 6-membered cyclic compound of the formula (I):



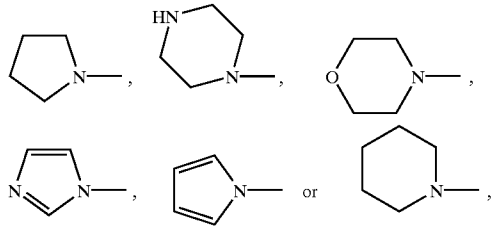
(I)

wherein Ring A is a substituted or unsubstituted nitrogen-containing heterocyclic group; R^1 is a substituted or unsubstituted lower alkyl group, a group of the formula: —NH—Q—R^3 (in which R^3 is a substituted or unsubstituted nitrogen containing heterocyclic group, and Q is a lower alkylene group or a single bond), or a group of the formula: —NH—R^4 (in which R^4 is a substituted or unsubstituted

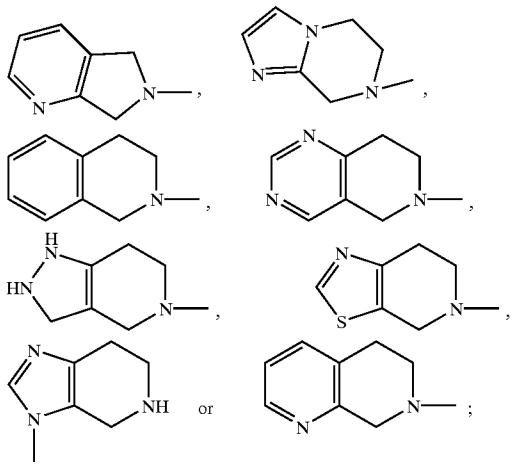
cycloalkyl group); R^2 is a substituted or unsubstituted aryl group; Z is a group of the formula: ═CH—, and Y is a group of the formula: ═N—, or a pharmaceutically acceptable salt thereof.

2. The compound according to claim **1**, wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, and the substituent of the above "substituted or unsubstituted nitrogen-containing heterocyclic group" is selected from the group consisting of (1) a lower alkyl group, (2) a hydroxy-substituted lower alkyl group, (3) a formyl group, (4) an oxo group, (5) an amino group, (6) a hydroxy group, (7) a lower alkoxycarbonyl group, and (8) a pyrimidinyl group substituted by (i) a benzylamino group substituted by a halogen atom and a lower alkoxy group, and (ii) a cycloalkylcarbamoyl group substituted by a hydroxy group, R^1 is a lower alkyl group which may optionally be substituted by a group selected from the group consisting of a lower alkoxy group, a hydroxy group, a morpholinyl group, a lower alkylsulfonyl group, a di-(lower alkyl)phosphino group, a di-(lower alkyl) amino group, a pyrimidinyl-substituted lower alkylamino group, a pyridyl group, a pyridylamino group and a lower alkyl-substituted piperazinyl group, a group of the formula: —NH—Q—R^3, or a group of the formula: —NH—R^4, the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for R^3 is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, and the substituent of the above "substituted or unsubstituted nitrogen-containing heterocyclic group" is selected from the group consisting of a lower alkyl group, a hydroxy-substituted lower alkyl group, an oxo group, an amino group, a di-(lower alkyl)amino group, a lower alkanoyl group and a cyano-substituted lower alkyl group, R^4 is a cycloalkyl group being substituted by a group selected from the group consisting of hydroxy group, a lower alkoxy group and a pyrimidinyloxy group, R^2 is a phenyl group being substituted by a group selected from the group consisting of a lower alkoxy group, a halogen atom, a cyano group, a nitro group, a hydroxy group and a lower alkyl group.

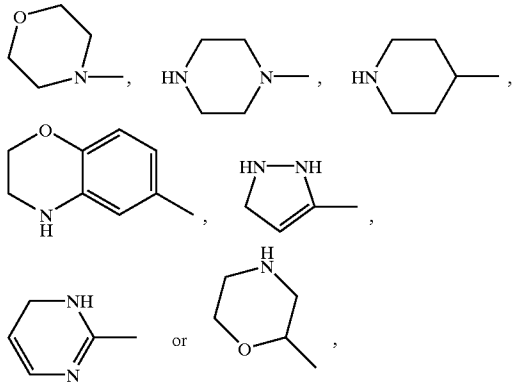
3. The compound according to claim **2**, wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered nitrogen-containing heteromonocyclic group of the formula:



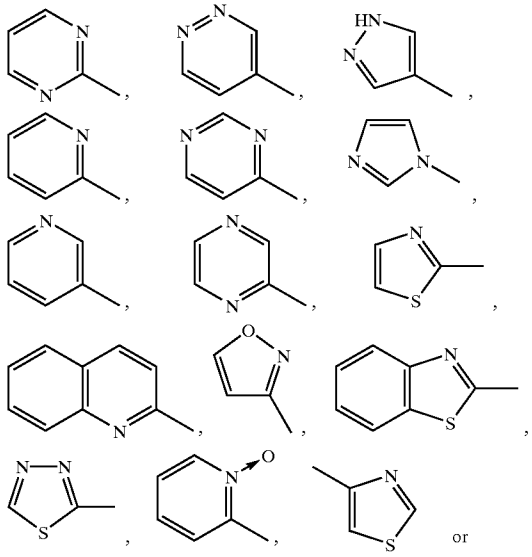
or a nitrogen-containing heterobicyclic group of the following formula wherein the above-mentioned 5- or 6-membered nitrogen-containing heteromonocyclic group and a 5- or 6-membered cyclic group are fused:



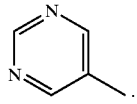
and the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for R^3 is a nonaromatic nitrogen-containing heteromonocyclic group of the formula:



or an aromatic nitrogen-containing heterocyclic group of the formula:



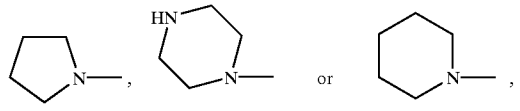
-continued



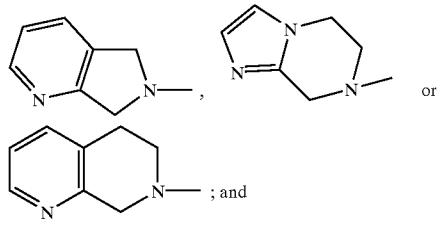
or a pharmaceutically acceptable salt thereof.

4. The compound according to claim **1**, wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, and the substituent of the above "substituted or unsubstituted nitrogen-containing heterocyclic group" is selected from the group consisting of a lower alkyl group, a hydroxy-substituted lower alkyl group, a formyl group and an oxo group, R^1 is a lower alkyl group which may optionally be substituted by a group selected from the group consisting of a lower alkoxy group and a morpholinyl group, a group of the formula: —NH—Q—R^3, or a group of the formula: —NH—R^4, the "substituted or unsubstituted nitrogen-containing heterocyclic group" for R^3 is a 5- or 6-membered nitrogen-containing heteromonocyclic group which may optionally be substituted by a lower alkyl group, R^4 is a cycloalkyl group being substituted by a group selected from the group consisting of hydroxy group and a lower alkoxy group, R^2 is a phenyl group being substituted by a group selected from the group consisting of a lower alkoxy group, a halogen atom and a cyano group.

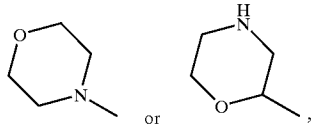
5. The compound according to claim **4**, wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered non-aromatic nitrogen-containing heteromonocyclic group of the formula:



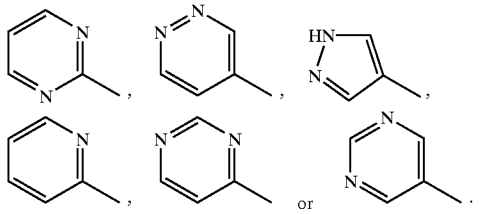
or a nitrogen-containing heterobicyclic group of the following formula wherein the above-mentioned 5- or 6-membered non-aromatic nitrogen-containing heteromonocyclic group and a 5- or 6-membered aromatic nitrogen-containing heteromonocyclic group are fused:



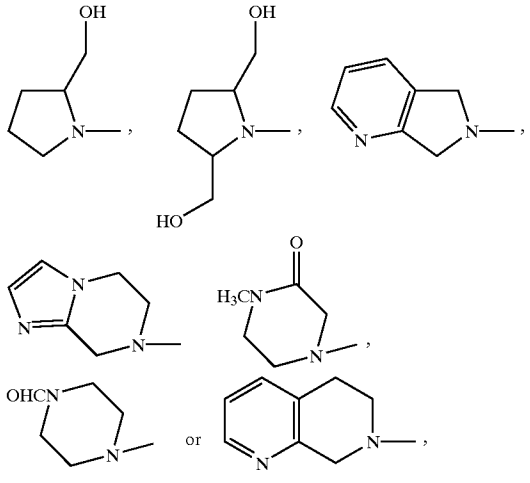
the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for R^3 is a non-aromatic nitrogen-containing heteromonocyclic group of the formula:



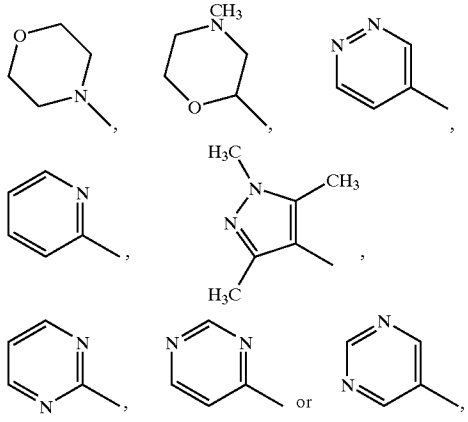
or an aromatic nitrogen-containing heteromonocyclic group of the formula:



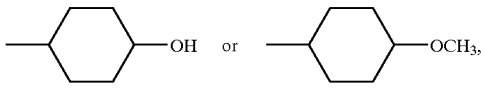
6. The compound according to claim **1**, wherein Ring A is a group of the formula:



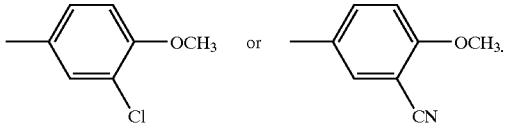
R^1 is a lower alkyl group, a lower alkoxy-substituted lower alkyl group, a morpholinyl-substituted lower alkyl group, a group of the formula: —NH—Q—R^3, or a group of the formula: —NH—R^4, R^3 is a group of the formula:



R^4 is a group of the formula:

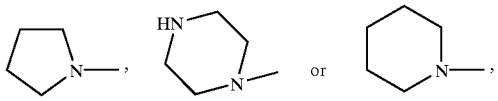


and R^2 is a group of the formula:

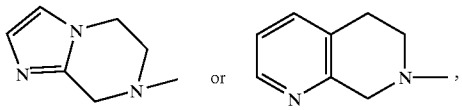


7. The compound according to claim **1**, wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, and the substituent of the above "substituted or unsubstituted nitrogen-containing heterocyclic group" is a group selected from the group consisting of a lower alkyl group, a hydroxy-substituted lower alkyl group, a formyl group and an oxo group, R^1 is a lower alkoxy-substituted lower alkyl group, a group of the formula: —NH—Q—R^3, or a group of the formula: —NH—R^4, the "substituted or unsubstituted nitrogen-containing heterocyclic group" for R^3 is a 5- or 6-membered nitrogen-containing heteromonocyclic group which may optionally be substituted by a lower alkyl group, R^4 is a hydroxy-substituted cycloalkyl group, and R^2 is a phenyl group being substituted by a group selected from the group consisting of a lower alkoxy group and a halogen atom.

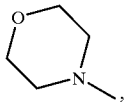
8. The compound according to claim **7**, wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered non-aromatic nitrogen-containing heteromonocyclic group of the formula:



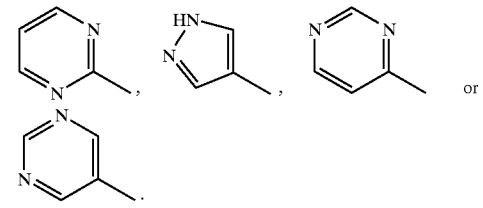
a group of the formula:



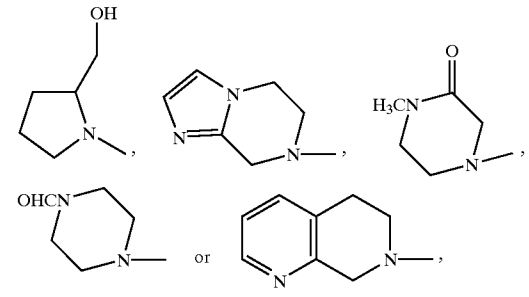
the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for R^3 is a non-aromatic nitrogen-containing heteromonocyclic group of the formula:



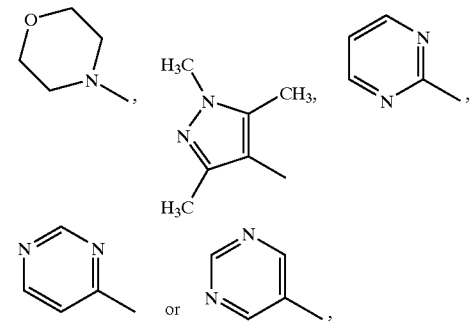
or an aromatic nitrogen-containing heteromonocyclic group of the formula:



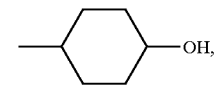
9. The compound according to claim **1**, wherein Ring A is a group of the formula:



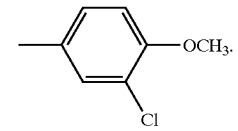
R^1 is a lower alkoxy-substituted lower alkyl group, a group of the formula: —NH—Q—R^3, or a group of the formula: —NH—R^4, R^3 is a group of the formula:



R^4 is a group of the formula:



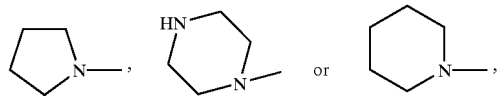
and R^2 is a group of the formula:



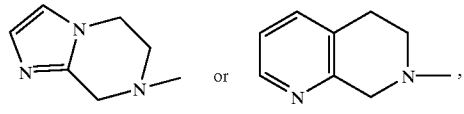
10. The compound according to claim **1**, wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered nitrogen-containing heteromonocyclic group or a 8- to 10-membered nitrogen-containing heterobicyclic group, and the substituent of the above "substituted or unsubstituted nitrogen-containing heterocyclic group" is a hydroxy-substituted lower alkyl group, R^1 is a group of the formula: —NH—Q—R^3, the "substi-

tuted or unsubstituted nitrogen-containing heterocyclic group" for R^3 is a 5- or 6-membered nitrogen-containing heteromonocyclic group which may optionally be substituted by a lower alkyl group, and R^2 is a phenyl group being substituted by a group selected from the group consisting of a lower alkoxy group and a halogen atom.

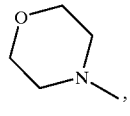
11. The compound according to claim **10**, wherein the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for Ring A is a 5- or 6-membered non-aromatic nitrogen-containing heteromonocyclic group of the formula:



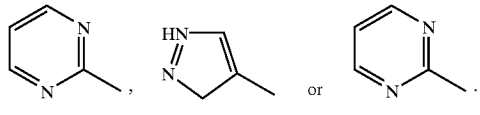
or a group of the formula:



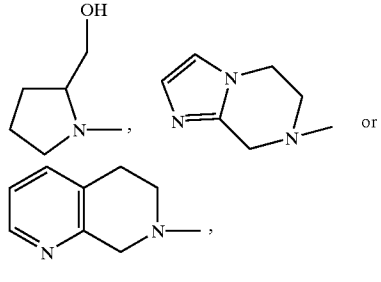
the nitrogen-containing heterocyclic group of the "substituted or unsubstituted nitrogen-containing heterocyclic group" for R^3 is a non-aromatic nitrogen-containing heteromonocyclic group of the formula:



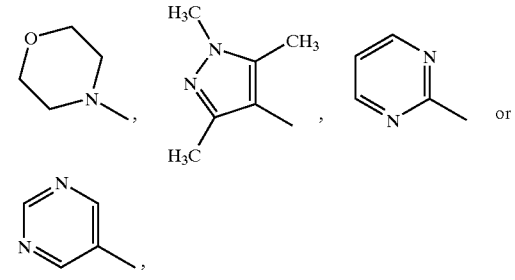
or an aromatic nitrogen-containing heteromonocyclic group of the formula:



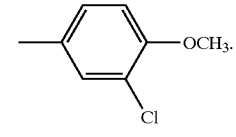
12. The compound according to claim **1**, wherein Ring A is a group of the formula:



R^1 is a group of the formula: —NH—Q—R^3, R^3 is a group of the formula:



and R^2 is a group of the formula:



13. The compound according to claim **1**, wherein said compound is selected from the group consisting of:

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidime;

2-(6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl)-4-(3-cyano-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-methoxycyclohexyl)carbamoyl]pyrimidine;

2-(6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl)-4-(3-cyano-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;

2-(6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-6-yl)-4-(3-cyano-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine;

2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxy-benzylamino)-5-[N-[[(2R)-4-methyl-2-morpholinyl]methyl]carbamoyl]pyrimidine;

2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxy-benzylamino)-5-[N-[[(2S)-4-methyl-2-morpholinyl]methyl]carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(4-pyrimidinylmethyl) carbamoyl]pyrimidine;

2-(4-methyl-3-oxo-I-piperazinyl)-4-(3-chloro-4-methoxybenzyl-amino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;

2-(4-formyl-1-piperazinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;

2-[cis-2,5-bis(hydroxymethyl)-1-pyrrolidinyl]-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine,

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-acethylpyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(4-pyridazinylmethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyridazinylmethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-[(4-methyl-2-morpholinyl)methyl]carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-methoxyethyl)carbonyl] pyrimidine; and

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine,

or a pharmaceutically acceptable salt thereof.

14. The compound according to claim **13**, wherein said compound is selected from the group consisting of:

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)5-[N-(4-pyrimidinylmethyl) carbamoyl]pyrimidine;

2-(4-methyl-3-oxo-1-piperazinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;

2-(4-formyl-1-piperazinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-pyrimidinylmethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-methoxyethyl)carbonyl] pyrimidine; and

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine,

or a pharmaceutically acceptable salt thereof.

15. The compound according to claim **13**, wherein said compound is selected from the group consisting of:

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;

2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine;

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5[N-(5-pyrimidinylmethyl) carbamoyl]pyrimidine; and

(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine,

or a pharmaceutically acceptable salt thereof.

16. The compound of claim **13**, wherein said compound is (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl) carbamoyl]pyrimidine, or a pharmaceutically acceptable salt thereof.

17. The compound of claim **13**, wherein said compound is 2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine, or a pharmaceutically acceptable salt thereof.

18. The compound of claim **13**, wherein said compound is (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl) carbamoyl]pyrimidine, or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition, which contains as an active ingredient the compound as set forth in any one of claims **1–12** and **13–18**, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor.

20. A method for treatment of penile erectile dysfunction, which comprises administering to a patient in need thereof an effective amount of the compound as set forth in any one of claims **1–12** and **13–18**, or a pharmaceutically acceptable salt thereof.

21. A method for treatment of pulmonary hypertension, which comprises administering to a patient in need thereof an effective amount of the compound as set forth in any one of claims **1–12** and **13–18**, or a pharmaceutically acceptable salt thereof.

22. A method for treatment of diabetic gastroparesis, which comprises administering to a patient in need thereof an effective amount of the compound as set forth in any one of claims **1–12** and **13–18**, or a pharmaceutically acceptable salt thereof.

* * * * *

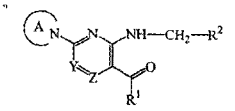
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,656,935 B2
DATED : December 2, 2003
INVENTOR(S) : Koichiro Yamada et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 76,
Lines 51-60, in the structure for formula (I):



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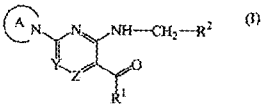
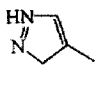


Column 79,
Line 5, after the structure

delete the period.

Column 81,
Line 47, before "a group", insert -- or --.

Column 83,
Lines 43-47,



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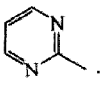

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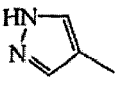

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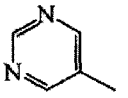

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Column 84,
Lines 24-26, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidime;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine; --.
Lines 40-42, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)4-(chloro-4-methoxy-benzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(hydroxymethyl-1-pyrrolidinyl)-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl) carbamoyl]pyrimidine; --.
Lines 43-45, "2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxy-benzylamino)-5-[N-[[(2R)-4-methyl-2-morpholinyl]methyl]carbamoyl]pyrimidine;" should read -- 2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxybenzylamino)-5-[N-[[(2R)-4-methyl-2-morpholinyl]methyl]carbamoyl] pyrimidine; --
Lines 46-48, "2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxy-benzylamino)-5-[N-[[(2S)-4-methyl-2-morpholinyl]methyl]carbamoyl]pyrimidine;" should read -- 2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxybenzylamino)-5-[N-[[(2S)-4-methyl-2-morpholinyl]methyl]carbamoyl] pyrimidine; --
Lines 49-51, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(pyrimidinylmethyl)carbamoyl]pyrimidine; --

UNITED STATES PATENT AND TRADEMARK OFFICE

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DATED : December 2, 2003
INVENTOR(S) : Koichiro Yamada et al.

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Line 64, replace the comma "," with a semicolon -- ; --.
Lines 65-67, "2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine; --.

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Lines 1-3, "2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-2-morpholinoethyl)carbamoyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-2-morpholinoethyl)carbamoyl]pyrimidine; --.
Lines 13-15, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyridazinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyrimidinylmethyl)carbamoyl]pyrimidine; --
Lines 16-18, "(S)-2-(hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbomoyl]pyrimidine;" should read -- (S)-2-(hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyridylmethyl)carbomoyl] pyrimidine; --.
Lines 19-21, "(S)-2-(2-hydroxymethyl-1-pyrrolidiny)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidiny)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-morpholinoethyl)carbonoy]pyrimidine; --.
Lines 22-24, "2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-[(4-methyl-2-morpholiny)methyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-[(4-methyl-2-morpholiny)methyl]pyrimidine; --
Lines 38-40, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino) 5-[N-(4-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(4-pyrimidinylmethyl)carbamoyl]pyrimidine; --.
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Column 86,
Lines 1-3, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine, --.
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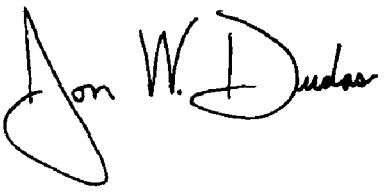
Signed and Sealed this

Twenty-eighth Day of September, 2004



JON W. DUDAS
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

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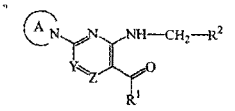

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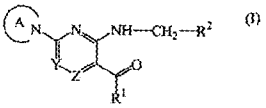

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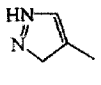

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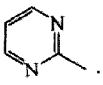
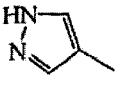


should read --



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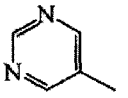

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

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DATED : December 2, 2003
INVENTOR(S) : Koichiro Yamada et al.

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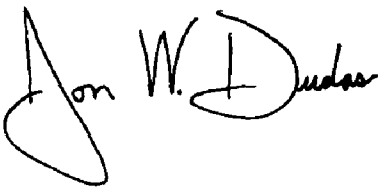
This certificate supersedes Certificate of Correction issued September 28, 2004.

Signed and Sealed this

Thirtieth Day of November, 2004



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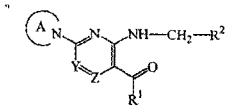
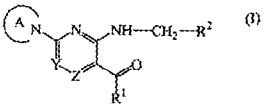


should read

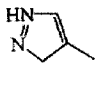


Column 79,
Line 5, after the structure

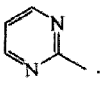
delete the period.

Column 81,
Line 47, before "a group", insert -- or --.

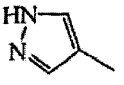
Column 83,
Lines 43-47,



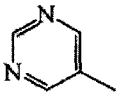
or



should read --



or



--.

Column 84,
Lines 24-26, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidime;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine; --.
Lines 40-42, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)4-(chloro-4-methoxy-benzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine; --.
Lines 43-45, "2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxy-benzylamino)-5-[N-[[(2R)-4-methyl-2-morpholinyl]methyl]carbamoyl]pyrimidine;" should read -- 2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxybenzylamino)-5-[N-[[(2R)-4-methyl-2-morpholinyl]methyl]carbamoyl] pyrimidine; --
Lines 46-48, "2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxy-benzylamino)-5-[N-[[(2S)-4-methyl-2-morpholinyl]methyl]carbamoyl]pyrimidine;" should read -- 2-[(2S)-2-hydroxymethyl-1-pyrrolidinyl]-4-(3-chloro-4-methoxybenzylamino)-5-[N-[[(2S)-4-methyl-2-morpholinyl]methyl]carbamoyl] pyrimidine; --
Lines 49-51, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(pyrimidinylmethyl)carbamoyl]pyrimidine; --

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,656,935 B2
DATED : December 2, 2003
INVENTOR(S) : Koichiro Yamada et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 84 (cont'd),
Lines 52-54, "2-(4methyl-3-oxo-I-piperazinyl)-4-(3-chloro-4-methoxybenzyl-amino)-5-[N-(trans-4-hydroxycyclohexyl)carbamoyl]pyrimidine;" should read -- 2-(4methyl-3-oxo-1-piperazinyl)-4-(3-chloro-4-methoxybenzyl-amino)-5-[N-(trans-4-hydroxycyclohexyl) carbamoyl]pyrimidine; --
Line 64, replace the comma "," with a semicolon -- ; --.
Lines 65-67, "2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine; --.

Column 85,
Lines 1-3, "2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-2-morpholinoethyl)carbamoyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-2-morpholinoethyl)carbamoyl]pyrimidine; --.
Lines 13-15, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyridazinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyrimidinylmethyl)carbamoyl]pyrimidine; --
Lines 16-18, "(S)-2-(hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbomoyl]pyrimidine;" should read -- (S)-2-(hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyridylmethyl)carbomoyl] pyrimidine; --.
Lines 19-21, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[(2-morpholinoethyl)carbonyl]pyrimidine; --.
Lines 22-24, "2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-[(4-methyl-2-morpholiny)methyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-[(4-methyl-2-morpholiny)methyl]pyrimidine; --
Lines 38-40, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino) 5-[N-(4-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(4-pyrimidinylmethyl)carbamoyl]pyrimidine; --.
Lines 48-50, "2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine; --.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,656,935 B2
DATED : December 2, 2003
INVENTOR(S) : Koichiro Yamada et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

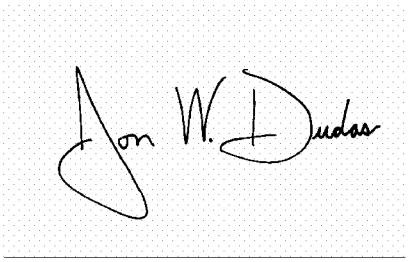
Column 85 (cont'd),
Lines 51-53, "2-(5,6,7,8-tetrahydroimidazo[1-2-a]pyrazine-7-yl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyridine;" should read -- 2-(5,6,7,8-tetrahydroimidazo[1-2-a]pyrazine-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyridine; --.
Lines 54-56, "2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine;" should read -- 2-(5,6,7,8-tetrahydro-1,7-naphthyridin-7-yl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(2-morpholinoethyl)carbamoyl]pyrimidine; --.
Lines 57-59, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-pyridinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyridinylmethyl)carbamoyl]pyrimidine; --.

Column 86,
Lines 1-3, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxy-benzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(1,3,5-trimethyl-4-pyrazolyl)carbamoyl]pyrimidine, --.
Lines 19-21, "(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5[N-(5-pyrimidinylmethyl)carbamoyl]pyrimidine;" should read -- (S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-[N-(5-pyrimidinylmethyl)carbamoyl]pyrimidine; --.

This certificate supersedes Certificate of Correction issued September 28, 2004 and November 30, 2004.

Signed and Sealed this

Third Day of May, 2005



JON W. DUDAS
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

(12) CERTIFICATE EXTENDING PATENT TERM UNDER 35 U.S.C. § 156

(68)	PATENT NO.	:	6,656,935
(45)	ISSUED	:	December 2, 2003
(75)	INVENTOR	:	Koichiro Yamada et al.
(73)	PATENT OWNER	:	Mitsubishi Tanabe Pharma Corp.
(95)	PRODUCT	:	STENDRA® (avanafil)

This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. 6,656,935 based upon the regulatory review of the product STENDRA® (avanafil) by the Food and Drug Administration. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) 1,687 days

from September 13, 2020, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156.

I have caused the seal of the United States Patent and Trademark Office to be affixed this 16th day of March 2016.

Michelle K. Lee

Michelle K. Lee
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

EXHIBIT B

Assignment records for the ‘935 patent

A 7687193

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

July 23, 2018

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF A DOCUMENT RECORDED ON JANUARY 14, 2002.

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

JOHN A BURSON
Certifying Officer

FORM PTO-1595
1-31-92

1/14/02

01-23-2002

101956473

U.S. Department of Commerce
Patent and Trademark Office
Attorney Docket No. 05273.0030
Attorney Customer Number: 22,852

To the Honorable Commissioner of P
Please record the attached original d

ATTN. BOX ASSIGNMENTS

OIPE JAN 1 4 2002 JC98 PATENT & TRADEMARK OFFICE

1. Name of conveying parties: **1) Koichiro YAMADA** **2) Kenji MATSUKI** **3) Kenji OMORI** **4) Kohei KIKKAWA**	2. Name and address of receiving party: Name: **TANABE SEIYAKU CO., LTD.**
Additional name of conveying party attached? ☐ Yes ☒ No	Internal Address: 2-10 Dosho-machi 3-chome Chuo-ku, Osaka, Japan
3. Nature of conveyance:	Street Address:
☒ Assignment ☐ Merger	City:
☐ Security Agreement ☐ Change of Name	State: Zip Code:
☐ Other:	Additional name & Address attached?
Execution Date: Inventors 1, 2, & 4: August 20, 2001; and Inventor 3: August 10, 2001	☐ Yes ☒ No

4. Application number or patent number: If this document is being filed together with a new application, the execution date of the application:

A. Patent Application Number: **09/925,892**	B. Patent Number:

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed: Name: Mr. Ernest F. Chapman	6. Total number of applications and registrations involved: 1 7. Total fee (37 CFR 3.41): $40 ☒ Enclosed (Please charge deficiency to deposit account) ☐ Authorized to be charged to deposit account
Internal Address: FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.	
Street Address: 1300 I Street, N.W.	
City: Washington, D.C.	
State: Zip: 20005-3315	8. Deposit Account No.: 06-0916

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Ernest F. Chapman [signature] JAN 1 4 2002
Signature Date

Registration No. 25,961

Total number of pages including cover sheet, attachments and documents: 3

01/18/2002 TDIAZ1 00000114 09925892
01 FC:581 40.00 OP

ATTORNEY DOCKET NO. 1-0570A(CIP2)
SOLE/JOINT INVENTION
(U.S. Rights Only)

A S S I G N M E N T

WHEREAS I/We, the below named inventor(s), [hereinafter referred to as Assignor(s)], have made an invention entitled:

AROMATIC NITROGEN-CONTAINING 6-MEMBERED CYCLIC COMPOUNDS

for which I/WE executed an application for United States Letters Patent concurrently herewith or on _____ or filed an application for United States Letters Patent on _____, 19____ (Serial No. _____); and

WHEREAS, TANABE SEIYAKU CO., LTD.
a corporation of Japan, whose post office address is 2-10 Dosho-machi 3-chome, Chuo-ku, Osaka, Japan (hereinafter referred to as Assignee), is desirous of securing the entire right, title, and interest in and to this invention, the application for United States Letters Patent on this invention and the Letters Patent to be issued upon this application;

NOW THEREFORE, be it known that, for good and valuable consideration the receipt of which from assignee is hereby acknowledged, I/WE, as assignor(s), have sold, assigned, transferred, and set over, and do hereby sell, assign, transfer, and set over unto the assignee, its lawful successors and assigns, my/our entire right, title, and interest in and to this invention and this application, and all divisions, and continuations thereof, and all Letters Patent of the United States which may be granted thereon, and all reissues thereof; and I/WE hereby authorize and request the Commissioner of Patents and Trademarks of the United States to issue all Letters Patent for this invention to assignee, its successors and assigns, in accordance with the terms of this Assignment;

AND, I/WE HEREBY further covenant and agree that I/We will, without further consideration, communicate with assignee, its successors and assigns, any facts known to me/us respecting this invention and testify in any legal proceeding, sign all lawful papers when called upon to do so, execute and deliver all papers that may be necessary or desirable to perfect the title to this invention in said assignee, its successors and assigns, execute all divisional, continuation, and reissue applications, make all rightful oaths and generally do everything possible to aid assignee, its successors and assigns, to obtain and enforce proper patent protection for this invention in the United States, it being understood that any expense incident to the execution of such papers shall be borne by the assignee, its successors and assigns.

AND, I/WE HEREBY authorize and request the attorneys I/we have empowered in the Declaration and Power of Attorney in this application, to insert here in parentheses (Application No. 09/925,892, filed August 10, 2001) the filing date and application number of said application when known.

IN TESTIMONY WHEREOF, I/We have hereunto set our hand(s).

1. Full Name of Sole or First Assignor	: Assignor's Signature	: Date
Koichiro YAMADA	: Koichiro Yamada	: August 20, 2001
Address 34-7, Shinshiraoka 3-chome, Shiraoka-machi, Minamisaitama-gun, Saitama-ken, Japan		: Citizenship : Japan
2. Full Name of Second Assignor	: Assignor's Signature	: Date
Kenji MATSUKI	: Kenji Matsuki	: August 20, 2001
Address 1093-5, Oazahaneo, Namegawa-machi, Hiki-gun, Saitama-ken, Japan		: Citizenship : Japan
3. Full Name of Third Assignor	: Assignor's Signature	: Date
Kenji OMORI	: Kenji Omori	: August 10, 2001
Address 16-6, Moto-machi 1-chome, Saitama-shi, Saitama-ken, Japan		: Citizenship : Japan

4. Full Name of Fourth Assignor Kohei KIKKAWA	: Assignor's Signature : *Kohei Kikkawa*	: Date : *August 20, 2001*
Address 22-4, Kitaharadai 2-chome, Kawaguchi-shi, Saitama-ken, Japan		: Citizenship : Japan
5. Full Name of Fifth Assignor	: Assignor's Signature :	: Date :
Address		: Citizenship :
6. Full Name of Sixth Assignor	: Assignor's Signature :	: Date :
Address		: Citizenship :
7. Full Name of Seventh Assignor	: Assignor's Signature :	: Date :
Address		: Citizenship :
8. Full Name of Eighth Assignor	: Assignor's Signature :	: Date :
Address		: Citizenship :
9. Full Name of Ninth Assignor	: Assignor's Signature :	: Date :
Address		: Citizenship :
10. Full Name of Tenth Assignor	: Assignor's Signature :	: Date :
Address		: Citizenship :
11. Full Name of Eleventh Assignor	: Assignor's Signature :	: Date :
Address		: Citizenship :
12. Full Name of Twelfth Assignor	: Assignor's Signature :	: Date :
Address		: Citizenship :

A 7687193

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

July 23, 2018

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF A DOCUMENT RECORDED ON MAY 2, 2012.

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

JOHN A BURSON
Certifying Officer

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	CHANGE OF NAME

CONVEYING PARTY DATA

Name	Execution Date
TANABE SEIYAKU CO., LTD.	10/01/2007

RECEIVING PARTY DATA

Name:	MITSUBISHI TANABE PHARMA CORPORATION
Street Address:	2-6-18, Kitahama, Chuo-ku
City:	Osaka-shi
State/Country:	JAPAN

PROPERTY NUMBERS Total: 1

Property Type	Number
Patent Number:	6656935

CORRESPONDENCE DATA

Fax Number: (202)408-4400
Phone: 2024084072
Email: charlene.woods@finnegan.com
Correspondence will be sent to the e-mail address first; if that is unsuccessful, it will be sent via US Mail.
Correspondent Name: Charles E. Van Horn
Address Line 1: 901 New York Avenue, N.W.
Address Line 4: Washington, DISTRICT OF COLUMBIA 20001-4413

CH $40.00 6656935

ATTORNEY DOCKET NUMBER:	05273.0030-00000
NAME OF SUBMITTER:	Charles E. Van Horn

Total Attachments: 10
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(Partial translation)

CERTIFICATE FOR ALL MATTERS AS RECORDED IN THE COMMERCIAL REGISTER

2-6-18, Kitahama, Chuo-ku, Osaka-shi
Mitsubishi Tanabe Pharma Corporation
Company/Corporation No. 1200-01-077463

Company Name	TANABE SEIYAKU CO., LTD.	
	Mitsubishi Tanabe Pharma Corporation	Changed on October 1, 2007 Registered on October 1, 2007
Head Office	2-10, Dosho-machi 3-chome, Chuo-ku, Osaka-shi	
	2-6-18, Kitahama, Chuo-ku, Osaka-shi	Changed on October 1, 2009 Registered on October 1, 2009
Method of Public Notice	By Electronic Public Notices http://www.mt-phama.co.jp/ In cases that the Electronic Public Notices cannot be possible from accidents or other unavoidable circumstances, the Public Notices shall be given in "The Nihon Keizai Shinbun".	Changed on October 1, 2007 Registered on October 1, 2007
Date of establishment of corporation	December 13, 1933	
(omitted)		
Matters concerning the registered record	Based on the provision of Paragraph 3 of the supplementary regulation of the 1989 Ministerial Ordinance No. 15 of the Ministry of Justice Transferred on April 20, 2000	

This is to certify that the above are all the matters that are recorded on the Register that have not been closed.
(Under the Jurisdiction of The Osaka Legal Affairs Bureau)

March 30, 2012

The Osaka Legal Affairs Bureau, Kita-subbranch
Registrar Yoshihiro SUGIMOTO (seal)

Docket No. 7 019567 *The Underline indicates deleted matters.

履歴事項全部証明書

大阪市中央区北浜二丁目６番１８号
田辺三菱製薬株式会社
会社法人等番号　１２００－０１－０７７４６３

商　号	田辺製薬株式会社	
	田辺三菱製薬株式会社	平成１９年１０月　１日変更 平成１９年１０月　１日登記
本　店	大阪市中央区道修町三丁目２番１０号	
	大阪市中央区北浜二丁目６番１８号	平成２１年１０月　１日移転 平成２１年１０月　１日登記
公告をする方法	電子公告とする。 ｈｔｔｐ：／／ｗｗｗ．ｍｔ－ｐｈａｒｍａ．ｃｏ．ｊｐ／ 事故その他やむを得ない事由によって電子公告による公告をすることができない場合は、日本経済新聞に掲載して行う。	平成１９年１０月　１日変更 平成１９年１０月　１日登記
会社成立の年月日	昭和８年１２月１３日	
目　的	１．医薬品、動物用医薬品、医薬部外品、化粧品、工業薬品、農薬、肥料、試薬、医療用機械器具および材料、各種化学製品の製造ならびに売買 ２．食品、食品添加物、調味料、香料、飲料品、酒精飲料、飼料、飼料添加物、計量器の製造ならびに売買 ３．前１，２号にかかげた物品に関連する機械、器具、装置および材料の製造ならびに売買 ４．衣料用繊維製品、寝装品、包装用材料および日用品雑貨の売買 ５．実験用動物の飼育ならびに売買 ６．薬用植物等の栽培ならびに売買 ７．前各号にかかげた物品の輸出ならびに輸入 ８．環境、衛生のための害鳥獣虫類、植物、微生物等防除の調査、施工および管理 ９．不動産の売買、賃貸借、仲介および管理 １０．建設業 １１．印刷業、出版業および翻訳業 １２．警備および労働者派遣事業 １３．医薬品、動物用医薬品、工業薬品等の各種化学製品に関する試験ならびに検査の受託 １４．コンピューターによる情報処理の受託、ソフトウェアの開発、売買および情報提供サービス業 １５．社員教育のための研修所の経営 １６．旅行業法に基づく旅行業者代理業 １７．広告宣伝業および市場調査業 １８．倉庫業ならびに貨物運送取扱業および運送代理店業 １９．損害保険代理店および生命保険の募集に関する業務	

整理番号　ヲ０１９５６７　　＊　下線のあるものは抹消事項であることを示す。　　１／９

大阪市中央区北浜二丁目６番１８号
田辺三菱製薬株式会社
会社法人等番号　１２００－０１－０７７４６３

	２０．前各号に付帯関連する諸般の事業ならびに関連ある事業に対する投融資 平成１９年１０月　１日変更　平成１９年１０月　１日登記	
単元株式数	１０００株	
	１００株	平成２２年１２月　１日変更 平成２２年１２月　１日登記
発行可能株式総数	２０億株	平成１９年１０月　１日変更 平成１９年１０月　１日登記
発行済株式の総数並びに種類及び数	発行済株式の総数 ５億６１４１万７９１６株	平成１９年１０月　１日変更 平成１９年１０月　１日登記
株券を発行する旨の定め	当会社の株式については、株券を発行する	平成１７年法律第８７号第１３６条の規定により平成１８年　５月１１日登記
	平成２１年　１月　５日廃止	平成２１年　１月　７日登記
資本金の額	金５００億円	平成１９年１０月　１日変更 平成１９年１０月　１日登記
株主名簿管理人の氏名又は名称及び住所並びに営業所	東京都千代田区丸の内一丁目４番５号 三菱ＵＦＪ信託銀行株式会社 大阪市北区堂島浜一丁目１番５号 三菱ＵＦＪ信託銀行株式会社大阪証券代行部 平成１９年　５月　７日変更	平成１９年　５月１８日登記
	東京都千代田区丸の内一丁目４番５号 三菱ＵＦＪ信託銀行株式会社 大阪市中央区伏見町三丁目６番３号 三菱ＵＦＪ信託銀行株式会社　大阪証券代行部 平成２１年１０月１３日変更	平成２１年１０月１３日登記

大阪市中央区北浜二丁目６番１８号
田辺三菱製薬株式会社
会社法人等番号　１２００－０１－０７７４６３

役員に関する事項	取締役　葉山夏樹	平成２０年　６月２４日重任 平成２０年　７月　２日登記
	取締役　葉山夏樹	平成２１年　６月１９日重任 平成２１年　６月２３日登記
		平成２２年　６月２２日退任 平成２２年　６月２５日登記
	取締役　土屋裕弘	平成２０年　６月２４日重任 平成２０年　７月　２日登記
	取締役　土屋裕弘	平成２１年　６月１９日重任 平成２１年　６月２３日登記
	取締役　土屋裕弘	平成２２年　６月２２日重任 平成２２年　６月２５日登記
	取締役　土屋裕弘	平成２３年　６月２２日重任 平成２３年　６月２４日登記
	取締役　柳澤憲一	平成２０年　６月２４日重任 平成２０年　７月　２日登記
	取締役　柳澤憲一	平成２１年　６月１９日重任 平成２１年　６月２３日登記
	取締役　柳澤憲一	平成２２年　６月２２日重任 平成２２年　６月２５日登記
	取締役　柳澤憲一	平成２３年　６月２２日重任 平成２３年　６月２４日登記
	取締役　浜岡純治	平成２０年　６月２４日重任 平成２０年　７月　２日登記
		平成２１年　６月１９日退任 平成２１年　６月２３日登記

整理番号　ヲ０１９５６７　　＊　下線のあるものは抹消事項であることを示す。　　３／９

大阪市中央区北浜二丁目６番１８号
田辺三菱製薬株式会社
会社法人等番号　１２００－０１－０７７４６３

	取締役　小峰健嗣	平成２０年　６月２４日重任
		平成２０年　７月　２日登記
	取締役　小峰健嗣	平成２１年　６月１９日重任
		平成２１年　６月２３日登記
		平成２２年　６月２２日退任
		平成２２年　６月２５日登記
	取締役　下宿邦彦	平成２０年　６月２４日重任
		平成２０年　７月　２日登記
	取締役　下宿邦彦	平成２１年　６月１９日重任
		平成２１年　６月２３日登記
		平成２２年　６月２２日退任
		平成２２年　６月２５日登記
	取締役　中島透	平成２０年　６月２４日就任
		平成２０年　７月　２日登記
		平成２１年　６月１９日退任
		平成２１年　６月２３日登記
	取締役　吉村章太郎	平成２０年　６月２４日就任
		平成２０年　７月　２日登記
		平成２１年　６月１９日退任
		平成２１年　６月２３日登記
	取締役　三津家正之	平成２１年　６月１９日就任
		平成２１年　６月２３日登記
	取締役　三津家正之	平成２２年　６月２２日重任
		平成２２年　６月２５日登記
	取締役　三津家正之	平成２３年　６月２２日重任
		平成２３年　６月２４日登記

整理番号　ヲ０１９５６７　　＊　下線のあるものは抹消事項であることを示す。　　

大阪市中央区北浜二丁目６番１８号
田辺三菱製薬株式会社
会社法人等番号　１２００－０１－０７７４６３

	取締役　子林孝司	平成２１年　６月１９日就任 平成２１年　６月２３日登記
	取締役　子林孝司	平成２２年　６月２２日重任 平成２２年　６月２５日登記
	取締役　子林孝司	平成２３年　６月２２日重任 平成２３年　６月２４日登記
	取締役　加賀邦明	平成２１年　６月１９日就任 平成２１年　６月２３日登記
	取締役　加賀邦明	平成２２年　６月２２日重任 平成２２年　６月２５日登記
	取締役　加賀邦明	平成２３年　６月２２日重任 平成２３年　６月２４日登記
	取締役　小酒井健吉	平成２２年　６月２２日就任 平成２２年　６月２５日登記
	取締役　小酒井健吉	平成２３年　６月２２日重任 平成２３年　６月２４日登記
	取締役　服部重彦 （社外取締役）	平成２３年　６月２２日就任 平成２３年　６月２４日登記
	取締役　吉岡征四郎 （社外取締役）	平成２３年　６月２２日就任 平成２３年　６月２４日登記
	岐阜県多治見市大畑町西仲根１番地の５４ 代表取締役　葉山夏樹	平成２０年　６月２４日重任 平成２０年　７月　２日登記 平成２１年　６月１９日退任 平成２１年　６月２３日登記

大阪市中央区北浜二丁目６番１８号
田辺三菱製薬株式会社
会社法人等番号　１２００－０１－０７７４６３

	大阪市浪速区湊町一丁目４番３６－１５０１号 代表取締役　小　峰　健　嗣	平成２０年　６月２４日重任 平成２０年　７月　２日登記 平成２１年　６月１９日退任 平成２１年　６月２３日登記
	兵庫県尼崎市武庫之荘西二丁目５３番１－９０４号 代表取締役　土　屋　裕　弘 兵庫県尼崎市武庫之荘西二丁目５３番１－９０４号 代表取締役　土　屋　裕　弘 兵庫県尼崎市武庫之荘西二丁目５３番１－９０４号 代表取締役　土　屋　裕　弘	平成２１年　６月１９日就任 平成２１年　６月２３日登記 平成２２年　６月２２日重任 平成２２年　６月２５日登記 平成２３年　６月２２日重任 平成２３年　６月２４日登記
	兵庫県芦屋市大原町９番１－８０３号 代表取締役　下　宿　邦　彦	平成２１年　６月１９日就任 平成２１年　６月２３日登記 平成２２年　６月２２日退任 平成２２年　６月２５日登記
	神奈川県川崎市高津区末長２２３番地８ 代表取締役　加　賀　邦　明 神奈川県川崎市高津区末長２２３番地８ 代表取締役　加　賀　邦　明	平成２２年　６月２２日就任 平成２２年　６月２５日登記 平成２３年　６月２２日重任 平成２３年　６月２４日登記
	監査役　家　近　正　直 社外監査役 監査役　家　近　正　直 （社外監査役）	平成１９年　６月２６日重任 平成１９年　７月　３日登記 平成２３年　６月２２日重任 平成２３年　６月２４日登記
	監査役　松　本　宏	平成１７年　６月２９日就任 平成１７年　７月　７日登記 平成２１年　６月１９日退任 平成２１年　６月２３日登記

整理番号　ヲ０１９５６７　　＊　下線のあるものは抹消事項であることを示す。　　６／９

大阪市中央区北浜二丁目６番１８号
田辺三菱製薬株式会社
会社法人等番号　１２００－０１－０７７４６３

	監査役　成松明博	平成１９年１０月　１日就任 平成１９年１０月　１日登記 平成２３年　６月２２日退任 平成２３年　６月２４日登記
	監査役　西田孝 （社外監査役）	平成１９年１０月　１日就任 平成１９年１０月　１日登記
	監査役　西田孝 （社外監査役）	平成２３年　６月２２日重任 平成２３年　６月２４日登記
	監査役　浜岡純治	平成２１年　６月１９日就任 平成２１年　６月２３日登記
	監査役　藤澤晃一	平成２３年　６月２２日就任 平成２３年　６月２４日登記
	会計監査人　新日本監査法人	平成２０年　６月２４日重任 平成２０年　７月　２日登記
	会計監査人　新日本有限責任監査法人	平成２０年　７月　１日新日本監査法人の名称変更 平成２０年　７月　２日登記
	会計監査人　新日本有限責任監査法人	平成２１年　６月１９日重任 平成２１年　６月２３日登記
	会計監査人　新日本有限責任監査法人	平成２２年　６月２２日重任 平成２２年　６月２５日登記
	会計監査人　新日本有限責任監査法人	平成２３年　６月２２日重任 平成２３年　６月２４日登記
取締役等の会社に対する責任の免除に関する規定	当会社は、会社法第４２６条第１項の規定により、取締役会の決議によって、同法第４２３条第１項の取締役（取締役であった者を含む。）の損害賠償責任を法令の限度において免除することができる。 当会社は、会社法第４２６条第１項の規定により、取締役会の決議によって、同法第４２３条第１項の監査役（監査役であった者を含む。）の損害賠償責任を法令の限度において免除することができる。	

整理番号　ヲ０１９５６７　　＊　下線のあるものは抹消事項であることを示す。　　

大阪市中央区北浜二丁目６番１８号
田辺三菱製薬株式会社
会社法人等番号　１２００－０１－０７７４６３

	平成２３年　６月２２日設定　平成２３年　６月２４日登記	
社外取締役等の会社に対する責任の制限に関する規定	当会社は、会社法第４２７条第１項の規定により、当社社外取締役との間に、同法第４２３条第１項の損害賠償責任を限定する契約を締結することができる。ただし、当該契約に基づく責任の限度額は、あらかじめ定めた額または法令が規定する最低責任限度額のいずれか高い額とする。 当会社は、会社法第４２７条第１項の規定により、当社社外監査役との間に、同法第４２３条第１項の損害賠償責任を限定する契約を締結することができる。ただし、当該契約に基づく責任の限度額は、あらかじめ定めた額または法令が規定する最低責任限度額のいずれか高い額とする。 平成２３年　６月２２日設定　平成２３年　６月２４日登記	
支　店	９ 東京都中央区日本橋本町二丁目２番６号	平成１９年１０月　１日設置 平成１９年１０月　１日登記
会社分割	平成２１年４月１日大阪市中央区平野町二丁目６番９号田辺三菱製薬工場株式会社に分割 平成２１年　４月　１日登記	
	平成２１年１０月１日大阪市中央区北浜二丁目６番１８号田辺三菱製薬工場株式会社に分割 平成２１年１０月　１日登記	
吸収合併	平成２１年４月１日大阪市中央区淡路町二丁目５番６号株式会社ウェルファイドサービスを合併 平成２１年　４月　１日登記	
取締役会設置会社に関する事項	取締役会設置会社 平成１７年法律第８７号第１３６条の規定により平成１８年　５月１１日登記	
監査役設置会社に関する事項	監査役設置会社 平成１７年法律第８７号第１３６条の規定により平成１８年　５月１１日登記	
監査役会設置会社に関する事項	監査役会設置会社 平成１８年　６月３０日登記	
会計監査人設置会社に関する事項	会計監査人設置会社 平成１８年　６月３０日登記	
登記記録に関する事項	平成元年法務省令第１５号附則第３項の規定により 平成１２年　４月２０日移記	

整理番号　ヲ０１９５６７　　＊　下線のあるものは抹消事項であることを示す。　　

大阪市中央区北浜二丁目６番１８号
田辺三菱製薬株式会社
会社法人等番号　１２００－０１－０７７４６３

これは登記簿に記録されている閉鎖されていない事項の全部であることを証明した書面である。
（大阪法務局管轄）

平成２４年　３月３０日
大阪法務局北出張所
登記官　　杉　本　好　弘

整理番号　ヲ０１９５６７　　＊　下線のあるものは抹消事項であることを示す。　　9／9

A 7687193

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

July 23, 2018

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF A DOCUMENT RECORDED ON DECEMBER 8, 2015.

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

JOHN A BURSON
Certifying Officer

PATENT ASSIGNMENT COVER SHEET

Electronic Version v1.1
Stylesheet Version v1.2

EPAS ID: PAT3648755

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	CHANGE OF ADDRESS

CONVEYING PARTY DATA

Name	Execution Date
MITSUBISHI TANABE PHARMA CORPORATION	04/01/2015

RECEIVING PARTY DATA

Name:	MITSUBISHI TANABE PHARMA CORPORATION
Street Address:	3-2-10, DOSHO-MACHI, CHUO-KU
City:	OSAKA-SHI, OSAKA
State/Country:	JAPAN
Postal Code:	541-8505

PROPERTY NUMBERS Total: 1

Property Type	Number
Patent Number:	6656935

CORRESPONDENCE DATA

Fax Number: (202)408-4400

Correspondence will be sent to the e-mail address first; if that is unsuccessful, it will be sent using a fax number, if provided; if that is unsuccessful, it will be sent via US Mail.

Email: charlene.woods@finnegan.com
Correspondent Name: JILL K. MACALPINE
Address Line 1: 901 NEW YORK AVENUE, N.W.
Address Line 4: WASHINGTON, D.C. 20001

ATTORNEY DOCKET NUMBER:	05273.0030
NAME OF SUBMITTER:	JILL MACALPINE
SIGNATURE:	/Jill K. MacAlpine/
DATE SIGNED:	12/08/2015

Total Attachments: 1
source=Change_of_Address_Document#page1.tif

MITSUBISHI TANABE PHARMA CORPORATION

Old Address:

2-6-18, Kitahama, Chuo-ku, Osaka-shi, Japan

MITSUBISHI TANABE PHARMA CORPORATION

New Address:

3-2-10, Dosho-machi, Chuo-ku, Osaka-shi, Osaka 541-8505 Japan

Respectfully submitted,

Jill K. MacAlpine
Reg. No. 60,475

PT 7687193

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

July 25, 2018

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE ASSIGNMENT RECORDS OF ALL DOCUMENTS FOUND OF RECORD AS OF THE DATE OF THIS CERTIFICATION FOR:

APPLICATION NUMBER: *09/925,892*
FILING DATE: *August 10, 2001*
PATENT NUMBER: *6,656,935*
ISSUE DATE: *December 02, 2003*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

P. SWAIN
Certifying Officer

Patent Assignment Abstract of Title

Total Assignments: 3

Application #: 09925892 **Filing Dt:** 08/10/2001 **Patent #:** 6656935 **Issue Dt:** 12/02/2003
PCT #: NONE **Intl Reg #:** **Publication #:** US20030032647 **Pub Dt:** 02/13/2003
Inventors: Koichiro Yamada, Kenji Matsuki, Kenji Omori, Kohei Kikkawa
Title: AROMATIC NITROGEN-CONTAINING 6-MEMBERED CYCLIC COMPOUNDS

Assignment: 1

Reel/Frame: 012476 / 0685 **Received:** 01/23/2002 **Recorded:** 01/14/2002 **Mailed:** 05/16/2002 **Pages:** 3
Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).
Assignors: YAMADA, KOICHIRO **Exec Dt:** 08/20/2001
MATSUKI, KENJI **Exec Dt:** 08/20/2001
OMORI, KENJI **Exec Dt:** 08/10/2001
KIKKAWA, KOHEI **Exec Dt:** 08/20/2001
Assignee: TANABE SEIYAKU CO., LTD.
2-10 DOSHO-MACHI 3-CHOME, CHUO-KU
OSAKA, JAPAN
Correspondent: FINNEGAN, HENDERSON, FARABOW, ET AL.
ERNEST F. CHAPMAN
1300 I STREET, N.W.
WASHINGTON, DC 20005-3315

Assignment: 2

Reel/Frame: 028142 / 0169 **Received:** 05/02/2012 **Recorded:** 05/02/2012 **Mailed:** 05/03/2012 **Pages:** 12
Conveyance: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).
Assignor: TANABE SEIYAKU CO., LTD. **Exec Dt:** 10/01/2007
Assignee: MITSUBISHI TANABE PHARMA CORPORATION
2-6-18, KITAHAMA, CHUO-KU
OSAKA-SHI, JAPAN
Correspondent: CHARLES E. VAN HORN
901 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20001-4413

Assignment: 3

Reel/Frame: 037244 / 0594 **Received:** 12/08/2015 **Recorded:** 12/08/2015 **Mailed:** 12/10/2015 **Pages:** 2
Conveyance: CHANGE OF ADDRESS
Assignor: MITSUBISHI TANABE PHARMA CORPORATION **Exec Dt:** 04/01/2015
Assignee: MITSUBISHI TANABE PHARMA CORPORATION
3-2-10, DOSHO-MACHI, CHUO-KU
OSAKA-SHI, OSAKA, JAPAN 541-8505
Correspondent: JILL K. MACALPINE
901 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20001

Search Results as of: 07/23/2018 12:01 PM

EXHIBIT C

Empower Clinic Services LLC d/b/a Empower Pharmacy

New Jersey Pharmacy License

EmpowerRx PHARMACY

6/24/2013

New Jersey Office of the Attorney General
Division of Consumer Affairs
Board of Pharmacy
124 Halsey Street, 6th Floor, PO Box 45013
Newark, NJ 07101

Re: Out of State Pharmacy Registration

Title: Owner/Officer
Name: Shaun Noorian
Business Address: 12123 Jones Rd Houston, TX 77070
Home Address:
Business Phone: (832) 678-4417
Home Phone:
Social Security Number:
Date of Birth:

Sincerely,

Shaun Noorian

New Jersey Office of the Attorney General
Division of Consumer Affairs
Board of Pharmacy
124 Halsey Street, 6th Floor, P.O. Box 45013
Newark, New Jersey 07101
(973) 504-6450

Application for an Out-of-State Pharmacy Registration

Check Appropriate Box(es):

☑ **New**	**$175**	☐ **Change of Name** Previous name:	**$175**
☐ **Change of Ownership** Date of proposed acquisition	**$175**	☐ **Change of Location** Date of Proposed Relocation:	**$175**

The required fees must accompany the application.
Make your check payable to the "New Jersey State Board of Pharmacy."
Do Not Send Cash.

Applicant - Please print or type in the information requested below. Provide the PIC's full name not his/her initials.

Name of Pharmacy: Empower Pharmacy		Area Code and Telephone Number: (832) 678-4417	
Street Address: 12123 Jones Rd		Area Code and Fax Number: (832) 678-4419	
City: Houston		State: Texas	ZIP Code: 77070
Resident State Pharmacy Permit Number: 26444	Toll-Free Telephone Number for Patient/Pharmacist Communication: (877) 562-8577	Area Code and Telephone Number (if different)	
Print Name of Pharmacist-in-Charge (PIC): Souchinda Nanthavongdouangsy	PIC's License Number: 42524	PIC's Weekly Hours of Employment: 40	

Please affix below a copy of your prescription label used to ship controlled and noncontrolled substances into New Jersey:

FOR ORAL USE ONLY
TAKE WITH FOOD

EmpowerRx PHARMACY
12123 Jones Rd Houston, TX 77070
Phone (877)562-8577 (832)678-4417
EmpowerRxPharmacy.com
Caution: Federal law prohibits transfer of this drug to any other person than patient for whom prescribed.

TEST DOCTOR

Rx 00195589 N
PATIENT TEST
1234 TEST TEST, TX 77450
IBUPROFEN 800 MG TABLET
1 TABS AMNEAL Lot# HL10311 Discard after 6/20/2014
TEST PRESCRIPTION. USE AS DIRECTED.

RPh SN No refills authorized 6/20/2013

THIS MEDICATION WAS SPECIFICALLY COMPOUNDED FOR YOU
FOR EXTERNAL USE ONLY!
STORE AT ROOM TEMPERATURE

EmpowerRx PHARMACY
12123 Jones Rd Houston, TX 77070
Phone (877)562-8577 (832)678-4417
EmpowerRxPharmacy.com
Caution: Federal law prohibits transfer of this drug to any other person than patient for whom prescribed.

TEST DOCTOR

RxC70002066 N
PATIENT TEST
1234 TEST TEST, TX 77450
TESTOSTERONE 200 MG/ML CREAM
1 ML Lot# 7891 Discard after 12/10/2013
TEST PRESCRIPTION. USE AS DIRECTED.

RPh SN No refills authorized 6/24/2013

JUL 02 2013

Ownership Type - check one: ☑ Corporation* ☐ Partnership ☐ Individual ☐ Other

On a separate sheet of paper, please provide the following information for each owner/officer, including professional designation (e.g. Pres. John Jones, M.D.):

- Name and title
- Address (business and home)
- Phone number (business and home)
- Social Security number
- Date of birth

* If the pharmacy is a corporation, please complete: Date of incorporation 12/12/2008

Name and address of the registered agent of the corporation: Shaun Noorian

12123 Jones Rd Houston, Tx 77070

Is the corporation's stock: ☐ Publicly traded; or ☑ Privately held?

Pharmacy Hours of Operation

Monday..... 8:30 A.M. to 5:30 P.M.
Tuesday..... 8:30 A.M. to 5:30 P.M.
Wednesday.. 8:30 A.M. to 5:30 P.M.
Thursday..... 8:30 A.M. to 5:30 P.M.
Friday..... 8:30 A.M. to 5:30 P.M.
Saturday... 8:30 A.M. to 1:30 P.M.
Sunday.... 0 A.M. to 0 P.M.

Types of practice(s) in which the pharmacy is to engage: (Check all that apply)

☐ Mail Order Pharmacy
☐ Hospital Pharmacy
☑ Retail Pharmacy
☐ Nuclear Pharmacy
☐ Long-Term Care Pharmacy
☑ Sterile Compounding
☑ Non-Sterile Compounding
☐ Other, please indicate: _____

Criminal/Disciplinary Action History – Pharmacist-in-Charge and/or Owner/Officer(s):

Has the pharmacist-in-charge or any owner/officer of the pharmacy been or currently is:

- The subject of any disciplinary action by any government agency;
- The subject of any legal or adverse action by any law enforcement agency or any local, state or federal court;
- Charged with the commission of any felony in any state or jurisdiction;
- Convicted of a felony in any state or jurisdiction?

Please indicate: ☐ Yes ☑ No

If you answered "Yes," to any of the above, please attach a letter of explanation as well as a certified copy of the final disposition for each incident. If the charges were dismissed, please provide a letter from the appropriate authority confirming dismissal of the charges.

Criminal/Disciplinary Action History – Pharmacy:

Has this pharmacy ever been the subject of any disciplinary or other adverse action by any other licensing agency, or by any other government agency, or by any local, state, or federal law enforcement agency, or by any local, state or federal court:

Please indicate: ☐ Yes ☑ No

If you answered "Yes," to the above, please attach a letter of explanation as well as a certified copy of the final disposition for each incident. If the charges were dismissed, please provide a letter from the appropriate authority confirming dismissal of the charges.

Affidavit:

Affidavit A below, must be completed by the owner, partner or by the principal officer as designated above. If the person executing Affidavit "A" is not also the pharmacist-in-charge of the pharmacy, then the pharmacist-in-charge must complete Affidavit "B."

Please note that each affidavit must be sworn to before a Notary Public or other authorized officer.

I do solemnly swear and affirm that the foregoing statements on this form or those on any attachment(s) to this form are to the best of my knowledge true and correct.

Affidavit "A"

Shaun Noorian
Print Name of Owner, Partner or Officer

Signature of above

Subscribed and sworn to before me this 24
day of June in the year 2013

Print Notary's name: Luna Melesio

Notary's signature:

My commission expires 10/24/15

Affix Seal Here:

LUNA MELESIO NOTARY PUBLIC STATE OF TEXAS EXPIRES 10/24/2015

Affidavit "B"

Souchinda Nanthavongdouangsy
Print Name of Pharmacist-in-Charge

Signature of above

Subscribed and sworn to before me this 26
day of June in the year 2013

Print Notary's name: Delia M. Tellez

Notary's signature:

My commission expires January 14, 2017

Affix Seal Here:

DELIA MARIA TELLEZ NOTARY PUBLIC STATE OF TEXAS EXPIRES JANUARY 14, 2017

Required documentation which must be enclosed with this application:

- A dated copy of the most recent inspection report resulting from an inspection of this pharmacy conducted by the regulatory or licensing agency in the state or jurisdiction in which this pharmacy is located.
- A certified letter of good standing from the licensing authority in the state or jurisdiction in which this pharmacy is licensed, permitted or registered.

Note: Unless this required documentation is supplied, the application cannot be processed.

Open Feb 26, 2014 VL (45)

CHRIS CHRISTIE
Governor

KIM GUADAGNO
Lt. Governor

New Jersey Office of the Attorney General

Division of Consumer Affairs
Board of Pharmacy
124 Halsey Street, 6th Floor, Newark NJ 07102

JOHN J. HOFFMAN
Acting Attorney General

ERIC T. KANEFSKY
Director

Mailing Address:
P.O. Box 45013
Newark, NJ 07101
(973) 504-6450

September 9, 2013

Empower Pharmacy
12123 Jones Road
Houston, TX 77070

RPIC: Souchinda Nanthavongdouangsy

Re: Application for Out-of-State Pharmacy Registration

Dear Souchinda Nanthavongdouangsy,

Your application to become registered in New Jersey as an out-of-state (non-resident) pharmacy indicates that your pharmacy produces compounded sterile products. Attached to this letter is a questionnaire which we require all pharmacies engaged in sterile compounding to complete.

Your application will remain in "pending" status until your response to the attached questionnaire is received and reviewed by the Board. You may not ship medication into New Jersey until and unless your application is approved.

Sincerely,

Anthony Rubinaccio, R.Ph.
Executive Director

AR/mrw

New Jersey Office of the Attorney General

Division of Consumer Affairs
Board of Pharmacy
124 Halsey Street, 6th Floor, Newark NJ 07102

CHRIS CHRISTIE
Governor

KIM GUADAGNO
Lt. Governor

CHRISTOPHER S. PORRINO
Attorney General

STEVE C. LEE
Director

Mailing Address:
P.O. Box 45013
Newark, NJ 07101
(973) 504-6450

October 6, 2016

EMPOWER PHARMACY
5980 W Sam Houston Pkwy N
Ste 300
Houston TX 77041

Dear EMPOWER PHARMACY:

Congratulations! This will confirm that the New Jersey Board of Pharmacy has registered you as a Out of State Pharmacy.

Your registration number is 28RO00095200 .
Your registration is effective as of 05/16/2014.
Your registration expires on 06/30/2017 .

You should receive your registration within approximately ten (10) business days. To obtain a faxed verification of your registration, please call our Automated Verification Line at (973) 273-8090.

This letter serves as a TEMPORARY AUTHORIZATION to practice Out of State Pharmacy until receipt of your registration.

If you have any questions, please contact the Board of Pharmacy at (973) 504-6450.

Sincerely,

Anthony Rubinaccio, RPh
Executive Director

Details

License Information

Accurate as of August 07, 2018 10:06 AM

Name: EMPOWER PHARMACY
Address: Houston,TX
Profession/License Type: Pharmacy,Out of State Pharmacy
License No: 28RO00095200
License Status: Active
Status Change Reason: License Issuance
Issue Date: 5/16/2014
Expiration Date: 6/30/2019

NO Board Actions. For more information contact New Jersey State Board of Pharmacy (973)504-6450.

EXHIBIT D

2017 Annual Report to the Sec. of State of Texas by

Empower Clinic Services LLC and Empower Pharmaceuticals LLC

2013 d/b/a application for “Empower Pharmacy”

Filing Number: 801062724

Texas Franchise Tax Public Information Report

Comptroller of Public Accounts FORM 05-102 (Rev.9-11/30)

To be filed by Corporations , Limited Liability Companies (LLC) and Financial Institutions

This report MUST be signed and filed to satisfy franchise tax requirements

■ Tcode 13196 Franchise

■ Taxpayer number: 3 2 0 3 8 5 0 4 5 1 3

■ Report year: 2 0 1 7

You have certain rights *under Chapter 552 and 559, Government Code, to review, request, and correct information we have on file about you. Contact us at (800) 252-1381or (512) 463-4600.*

Taxpayer name				
EMPOWER CLINIC SERVICES, L.L.C.				
Mailing address: 5980 W SAM HOUSTON PKWY N STE 300				Secretary of State (SOS) file number or Comptroller file number: 0801062724
City: HOUSTON	State: TX	ZIP Code: 77041	Plus 4:	

◯ Blacken circle if there are currently no changes from previous year; if no information is displayed, complete the applicable information in Sections A, B and C.

Principal office
Principal place of business

Please sign below!

Officer, director and manager information is reported as of the date a Public Information Report is completed. The information is updated annually as part of the franchise tax report. There is no requirement or procedure for supplementing the information as officers, directors, or managers change throughout the year.

3203850451317

SECTION A Name, title and mailing address of each officer, director or manager.

Name	Title	Director	Term expiration (m m d d y y)
ARTA S NOORIAN	DIRECTOR	● YES	
Mailing address: 5980 W SAM HOUSTON PKWY N STE 300	City: HOUSTON	State: TX	ZIP Code: 77041
Name: ARTA S NOORIAN	Title: MEMBER	Director: ◯ YES	Term expiration (m m d d y y)
Mailing address: 5980 W SAM HOUSTON PKWY N STE 300	City: HOUSTON	State: TX	ZIP Code: 77041
Name	Title	Director: ◯ YES	Term expiration (m m d d y y)
Mailing address	City	State	ZIP Code

SECTION B Enter the information required for each corporation or LLC, if any, in which this entity owns an interest of 10 percent or more.

Name of owned (subsidiary) corporation or limited liability company	State of formation	Texas SOS file number, if any	Percentage of ownership
Name of owned (subsidiary) corporation or limited liability company	State of formation	Texas SOS file number, if any	Percentage of ownership

SECTION C Enter the information required for each corporation or LLC, if any, that owns an interest of 10 percent or more in this entity or limited liability company.

Name of owned (parent) corporation or limited liability company	State of formation	Texas SOS file number, if any	Percentage of ownership

Registered agent and registered office currently on file. *(see instructions if you need to make changes)*

Agent: SHAUN NOORIAN

◯ Blacken circle if you need forms to change the registered agent or registered office information.

Office: 5980 W SAM HOUSTON PKWY N STE 300	City: HOUSTON	State: TX	ZIP Code: 77041

The above information is required by Section 171.203 of the Tax Code for each corporation or limited liability company that files a Texas Franchise Tax Report. Use additional sheets for Sections A, B, and C, if necessary. The information will be available for public inspection.

I declare that the information in this document and any attachments is true and correct to the best of my knowledge and belief, as of the date below, and that a copy of this report has been mailed to each person named in this report who is an officer, director or manager and who is not currently employed by this, or a related, corporation or limited liability company.

sign here ▸ Shaun Noorian	Title: Electronic	Date: 01-26-2017	Area code and phone number: (281) 804 - 4499

Texas Comptroller Official Use Only

VE/DE	◯	PIR IND	◯

Form 503
(Revised 05/11)

Return in duplicate to:
Secretary of State
P.O. Box 13697
Austin, TX 78711-3697
512 463-5555
FAX: 512 463-5709
Filing Fee: $25

Assumed Name Certificate

This space reserved for office use.

FILED
In the Office of the
Secretary of State of Texas
MAY 23 2013
Corporations Section

Assumed Name

1. The assumed name under which the business or professional service is, or is to be, conducted or rendered is: Empower Pharmacy

Entity Information

2. The legal name of the entity filing the assumed name is:

Empower Clinic Services, LLC

State the name of the entity as currently shown in the records of the secretary of state or on its organizational documents, if not filed with the secretary of state.

3. The entity filing the assumed name is a: (Select the appropriate entity type below.)

- ☐ For-profit Corporation
- ☐ Nonprofit Corporation
- ☐ Professional Corporation
- ☐ Professional Association
- ☑ Limited Liability Company
- ☐ Limited Partnership
- ☐ Limited Liability Partnership
- ☐ Cooperative Association
- ☐ Other _____

Specify type of entity. For example, foreign real estate investment trust, state bank, insurance company, etc.

4. The file number, if any, issued to the entity by the secretary of state is: 801062724

5. The state, country, or other jurisdiction of formation of the entity is: Texas

6. The registered office or similar office address of the entity in its jurisdiction of formation is:

12123 Jones Rd			
Street Address			
Houston	TX	USA	77070
City	*State*	*Country*	*Zip or Postal Code*

7. The entity's principal office address in Texas is: (See instructions.)

12123 Jones Rd	Houston	TX	77070
Street Address	*City*		*Zip or Postal Code*

8. The entity is not organized under the laws of Texas and is not required by law to maintain a registered agent and registered office in Texas. Its office address outside the state is:

NA			
Street Address	*City*	*State*	*Zip or Postal Code*

RECEIVED
MAY 23 2013
Secretary of State

RECEIVED
Form 503
APR 24 2013
Secretary of State

Period of Duration

☑ 9a. The period during which the assumed name will be used is 10 years from the date of filing with the secretary of state.

OR

☐ 9b. The period during which the assumed name will be used is _____ years from the date of filing with the secretary of state (not to exceed 10 years).

OR

☐ 9c. The assumed name will be used until _____ (not to exceed 10 years).
mm/dd/yyyy

County or Counties in which Assumed Name Used

10. The county or counties where business or professional services are being or are to be conducted or rendered under the assumed name are:

☑ All counties

☐ All counties with the exception of the following counties: _____

☐ Only the following counties: _____

Execution

The undersigned signs this document subject to the penalties imposed by law for the submission of a materially false or fraudulent instrument and also certifies that the person is authorized to sign on behalf of the identified entity. If the undersigned is acting in the capacity of an attorney in fact for the entity, the undersigned certifies that the entity has duly authorized the undersigned in writing to execute this document.

Date: 4/19/2013

Shaun Noorian - Officer

Signature of a person authorized by law to sign on behalf of the identified entity (see instructions)

Filing Number: 801757197

Texas Franchise Tax Public Information Report

Comptroller of Public Accounts FORM 05-102 (Rev.9-11/30)

To be filed by Corporations , Limited Liability Companies (LLC) and Financial Institutions

This report MUST be signed and filed to satisfy franchise tax requirements

■ Tcode 13196 Franchise

■ Taxpayer number: 3 2 0 5 0 5 7 5 4 0 9

■ Report year: 2 0 1 7

You have certain rights *under Chapter 552 and 559, Government Code, to review, request, and correct information we have on file about you. Contact us at (800) 252-1381or (512) 463-4600.*

Taxpayer name				
EMPOWER PHARMACEUTICALS LLC				
Mailing address: 5980 W Sam Houston Pkwy N Ste 300				Secretary of State (SOS) file number or Comptroller file number
City: Houston	State: TX	ZIP Code: 77041	Plus 4:	0801757197

◯ Blacken circle if there are currently no changes from previous year; if no information is displayed, complete the applicable information in Sections A, B and C.

Principal office

Principal place of business

Please sign below!

Officer, director and manager information is reported as of the date a Public Information Report is completed. The information is updated annually as part of the franchise tax report. There is no requirement or procedure for supplementing the information as officers, directors, or managers change throughout the year.

3205057540917

SECTION A Name, title and mailing address of each officer, director or manager.

Name	Title	Director	Term expiration (m m d d y y)
Shaun Noorian	DIRECTOR	● YES	
Mailing address: 5980 W Sam Houston Pkwy N Ste 300	City: Houston	State: Texas	ZIP Code: 77041
Name: Shaun Noorian	Title: OWNER	Director ◯ YES	Term expiration
Mailing address: 5980 W Sam Houston Pkwy N Ste 300	City: Houston	State: Texas	ZIP Code: 77041
Name	Title	Director ◯ YES	Term expiration
Mailing address	City	State	ZIP Code

SECTION B Enter the information required for each corporation or LLC, if any, in which this entity owns an interest of 10 percent or more.

Name of owned (subsidiary) corporation or limited liability company	State of formation	Texas SOS file number, if any	Percentage of ownership
Name of owned (subsidiary) corporation or limited liability company	State of formation	Texas SOS file number, if any	Percentage of ownership

SECTION C Enter the information required for each corporation or LLC, if any, that owns an interest of 10 percent or more in this entity or limited liability company.

Name of owned (parent) corporation or limited liability company	State of formation	Texas SOS file number, if any	Percentage of ownership

Registered agent and registered office currently on file. *(see instructions if you need to make changes)*

Agent: Shaun Noorian

◯ Blacken circle if you need forms to change the registered agent or registered office information.

Office:	City	State	ZIP Code
5980 W Sam Houston Pkwy N Ste 300	Houston	TX	77041

The above information is required by Section 171.203 of the Tax Code for each corporation or limited liability company that files a Texas Franchise Tax Report. Use additional sheets for Sections A, B, and C, if necessary. The information will be available for public inspection.

I declare that the information in this document and any attachments is true and correct to the best of my knowledge and belief, as of the date below, and that a copy of this report has been mailed to each person named in this report who is an officer, director or manager and who is not currently employed by this, or a related, corporation or limited liability company.

sign here	Title	Date	Area code and phone number
Shaun Noorian	Electronic	01-26-2017	(281) 804 - 4499

Texas Comptroller Official Use Only

VE/DE	◯	PIR IND	◯

EXHIBIT E

Empower website page - States served

EmpoweRx PHARMACY

FDA 503B REGISTERED

PCAB ACCREDITED Compounding Pharmacy

Drug Catalog

Where We Ship

PRODUCTS

COMPANY

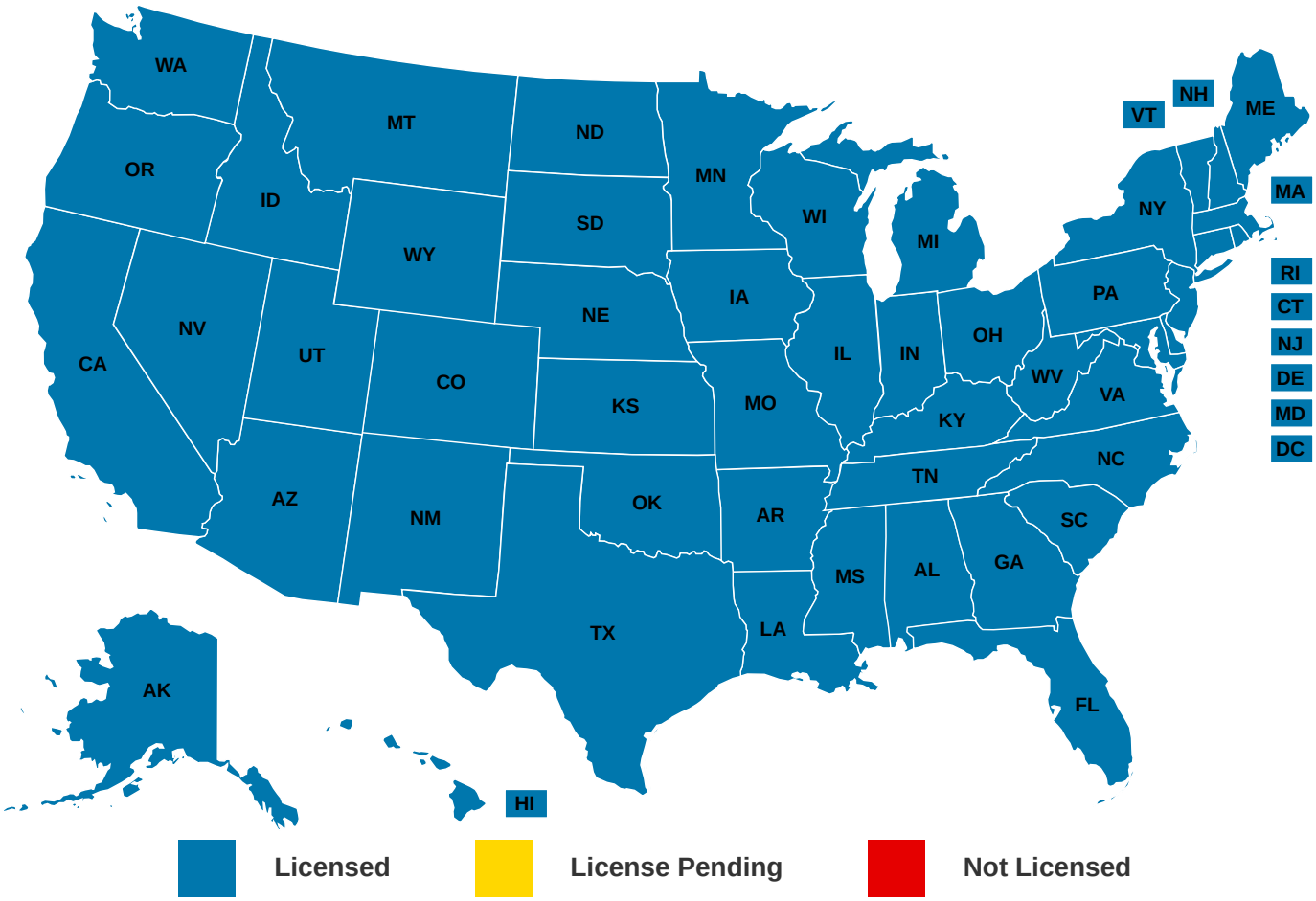
QUALITY

CONTACT US

PRESCRIPTION REFILL

PRESCRIBER LOGIN

Licensed States



We are licensed to ship to all 50 states:

Alabama, Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, District of Columbia, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Puerto Rico, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin and Wyoming

Whenever, Wherever. Using a national in-house computer tracking system, Empower Pharmacy delivers Ground or Overnight, six days a week. You can be confident the medications will be delivered when needed.

We Respect Your Privacy. Empower Pharmacy packages deliveries in discreet boxes so your personal business remains private.

Dedicated and Professional. Empower Pharmacy's team of certified compounding pharmacists are ready to answer questions, provide training and deliver highly specialized compounding services. They are ready to help guide patients through the administration of their dosage forms and provide the necessary usage instructions as well as support.

Free Supplies. We provide all the necessary supplies such as syringes, alcohol wipes, needles and reconstitution kits (prescription required). We also give our patients complimentary instruction pamphlets and documents. This translates to significant money savings and peace of mind that patients are administering their medications properly.

EXHIBIT F

STENDRA® avanafil package insert

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use STENDRA safely and effectively. See full prescribing information for STENDRA.

STENDRA® (avanafil) tablets, for oral use
Initial U.S. Approval: 2012

----------RECENT MAJOR CHANGES----------

Warnings and Precautions, Effects on the Eye (5.4) 08/2017

----------INDICATIONS AND USAGE----------

STENDRA is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of erectile dysfunction (1)

----------DOSAGE AND ADMINISTRATION----------

- The starting dose is 100 mg taken as early as approximately 15 minutes before sexual activity, on an as needed basis (2.1)
- Take STENDRA no more than once a day (2.1).
- Based on efficacy and/or tolerability, the dose may be increased to 200 mg taken as early as approximately 15 minutes before sexual activity, or decreased to 50 mg taken approximately 30 minutes before sexual activity. Use the lowest dose that provides benefit. (2.1)
- STENDRA may be taken with or without food (2.2)
- Do not use STENDRA with strong CYP3A4 inhibitors (2.3)
- If taking a moderate CYP3A4 inhibitor, the dose should be no more than 50 mg in a 24-hour period (2.3).
- In patients on stable alpha-blocker therapy, the recommended starting dose of STENDRA is 50 mg (2.3).

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 50 mg, 100 mg, 200 mg (3)

----------CONTRAINDICATIONS----------

- Administration of STENDRA to patients using any form of organic nitrate is contraindicated (4.1)
- Hypersensitivity to any component of the STENDRA tablet (4.2)
- Administration with guanylate cyclase (GC) stimulators such as riociguat (4.3)

----------WARNINGS AND PRECAUTIONS----------

- Patients should not use STENDRA if sexual activity is inadvisable due to cardiovascular status or any other reason (5.1)
- Use of STENDRA with alpha-blockers, other antihypertensives, or substantial amounts of alcohol (greater than 3 units) may lead to hypotension (2.3, 5.6, 5.7)
- Patients should seek emergency treatment if an erection lasts greater than 4 hours (5.3)
- Patients should stop STENDRA and seek medical care if a sudden loss of vision occurs in one or both eyes, which could be a sign of Non Arteritic Ischemic Optic Neuropathy (NAION). STENDRA should be used with caution, and only when the anticipated benefits outweigh the risks, in patients with a history of NAION. Patients with a "crowded" optic disc may also be at an increased risk of NAION (5.4, 6.2)
- Patients should stop taking STENDRA and seek prompt medical attention in the event of sudden decrease or loss of hearing (5.5)

----------ADVERSE REACTIONS----------

Most common adverse reactions (greater than or equal to 2%) include headache, flushing, nasal congestion, nasopharyngitis, and back pain (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact 866.928.6180 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- STENDRA can potentiate the hypotensive effect of nitrates, alpha-blockers, antihypertensives, and alcohol (7.1)
- CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, erythromycin) increase STENDRA exposure (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Do not use in patients with severe renal impairment (8.6)
- Do not use in patients with severe hepatic impairment (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 09/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

STENDRA is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of erectile dysfunction.

2 DOSAGE AND ADMINISTRATION

2.1 Erectile Dysfunction

The recommended starting dose is 100 mg. STENDRA should be taken orally as needed as early as approximately 15 minutes before sexual activity.

Based on individual efficacy and tolerability, the dose may be increased to 200 mg taken as early as approximately 15 minutes before sexual activity, or decreased to 50 mg taken approximately 30 minutes before sexual activity. The lowest dose that provides benefit should be used.

The maximum recommended dosing frequency is once per day. Sexual stimulation is required for a response to treatment.

2.2 Use with Food

STENDRA may be taken with or without food.

2.3 Concomitant Medications

Nitrates

Concomitant use of nitrates in any form is contraindicated [see *Contraindications (4.1)*].

Alpha-Blockers

If STENDRA is co-administered with an alpha-blocker, patients should be stable on alpha-blocker therapy prior to initiating treatment with STENDRA, and STENDRA should be initiated at the 50 mg dose *[see Warnings and Precautions (5.6), Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

CYP3A4 Inhibitors

- For patients taking concomitant strong CYP3A4 inhibitors (including ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin), do not use STENDRA *[see Warnings and Precautions (5.2) and Drug Interactions (7.2)]*.
- For patients taking concomitant moderate CYP3A4 inhibitors (including erythromycin, amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, and verapamil), the maximum recommended dose of STENDRA is 50 mg, not to exceed once every 24 hours *[see Warnings and Precautions (5.2) and Drug Interactions (7.2)]*.

3 DOSAGE FORMS AND STRENGTHS

STENDRA (avanafil) is supplied as oval, pale yellow tablets containing 50 mg, 100 mg, or 200 mg avanafil debossed with dosage strength.

4 CONTRAINDICATIONS

4.1 Nitrates

Administration of STENDRA with any form of organic nitrates, either regularly and/or intermittently, is contraindicated. Consistent with its known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway, STENDRA has been shown to potentiate the hypotensive effects of nitrates.

In a patient who has taken STENDRA, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 12 hours should elapse after the last dose of STENDRA before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate hemodynamic monitoring *[see Contraindications (4.1), Dosage and Administration (2.3), and Clinical Pharmacology (12.2)]*.

4.2 Hypersensitivity Reactions

STENDRA is contraindicated in patients with a known hypersensitivity to any component of the tablet. Hypersensitivity reactions have been reported, including pruritis and eyelid swelling.

4.3. Concomitant Guanylate Cyclase (GC) Stimulators

Do not use STENDRA in patients who are using a GC stimulator, such as riociguat. PDE5 inhibitors, including STENDRA may potentiate the hypotensive effects of GC stimulators.

5 WARNINGS AND PRECAUTIONS

Evaluation of erectile dysfunction (ED) should include an appropriate medical assessment to identify potential underlying causes, as well as treatment options.

Before prescribing STENDRA, it is important to note the following:

5.1 Cardiovascular Risks

There is a potential for cardiac risk during sexual activity in patients with pre-existing cardiovascular disease. Therefore, treatments for ED, including STENDRA, should not be used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status.

Patients with left ventricular outflow obstruction (e.g., aortic stenosis, idiopathic hypertrophic subaortic stenosis) and those with severely impaired autonomic control of blood pressure can be particularly sensitive to the actions of vasodilators, including STENDRA.

The following groups of patients were not included in clinical safety and efficacy trials for STENDRA, and therefore until further information is available, STENDRA is not recommended for the following groups:

- Patients who have suffered a myocardial infarction, stroke, life-threatening arrhythmia, or coronary revascularization within the last 6 months;
- Patients with resting hypotension (blood pressure less than 90/50 mmHg) or hypertension (blood pressure greater than 170/100 mmHg);
- Patients with unstable angina, angina with sexual intercourse, or New York Heart Association Class 2 or greater congestive heart failure.

As with other PDE5 inhibitors STENDRA has systemic vasodilatory properties and may augment the blood pressure-lowering effect of other anti-hypertensive medications. STENDRA 200 mg resulted in transient decreases in sitting blood pressure in healthy volunteers of 8.0 mmHg systolic and 3.3 mmHg diastolic *[see Clinical Pharmacology (12.2)]*, with the maximum decrease observed at 1 hour after dosing. While this normally would be expected to be of little consequence in most patients, prior to prescribing STENDRA, physicians should carefully consider whether patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity.

5.2 Concomitant Use of CYP3A4 Inhibitors

STENDRA metabolism is principally mediated by the CYP450 isoform 3A4 (CYP3A4). Inhibitors of CYP3A4 may reduce STENDRA clearance and increase plasma concentrations of avanafil.

For patients taking concomitant strong CYP3A4 inhibitors (including ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin), do not use STENDRA *[see Drug Interactions (7.2)]*.

For patients taking concomitant moderate CYP3A4 inhibitors (including erythromycin, amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, and verapamil), the maximum recommended dose of STENDRA is 50 mg, not to exceed once every 24 hours *[see Drug Interactions (7.2)]*.

5.3 Prolonged Erection

Prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported with other PDE5 inhibitors. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If not treated immediately, penile tissue damage and permanent loss of potency could result.

STENDRA should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis, or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia).

5.4 Effects on Eye

Physicians should advise patients to stop use of all PDE5 inhibitors, including STENDRA and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a rare condition and a cause of decreased vision including permanent loss of vision that has been reported rarely postmarketing in temporal association with the use of all PDE5 inhibitors. Based on published literature, the annual incidence of NAION is 2.5-11.8 cases per 100,000 in males aged ≥ 50.

An observational case-crossover study evaluated the risk of NAION when PDE5 inhibitor use, as a class, occurred immediately before NAION onset (within 5 half-lives), compared to PDE5 inhibitor use in a prior time period. The results suggest an approximate 2-fold increase in the risk of NAION, with a risk estimate of 2.15 (95% CI 1.06, 4.34). A similar study reported a consistent result, with a risk estimate of 2.27 (95% CI 0.99, 5.20). Other risk factors for NAION, such as the presence of "crowded" optic disc, may have contributed to the occurrence of NAION in these studies.

Neither the rare postmarketing reports, nor the association of PDE5 inhibitor use an NAION in the observational studies, substantiate a causal relationship between PDE5 inhibitor use and NAION *[see Adverse Reactions (6.2)]*.

Physicians should consider whether their patients with underlying NAION risk factors could be adversely affected by use of PDE5 inhibitors. Individuals who have already experience NAION are at increased risk of NAION recurrence. Therefore, PDE5 inhibitors, including STENDRA should be used with caution in these patients and only when the anticipated benefits outweigh the risks. Individuals with "crowded" optic disc are also considered at greater risk for NAION compared to the general population, however, evidence is insufficient to support screening of prospective users of PDE5 inhibitors, including STENDRA, for this uncommon condition.

5.5 Sudden Hearing Loss

Use of PDE5 inhibitors has been associated with sudden decrease or loss of hearing, which may be accompanied by tinnitus or dizziness. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors *[see Adverse Reactions (6)]*. Patients experiencing these symptoms should be advised to stop taking STENDRA and seek prompt medical attention.

5.6 Alpha-Blockers and Other Antihypertensives

Physicians should discuss with patients the potential for STENDRA to augment the blood pressure-lowering effect of alpha-blockers and other antihypertensive medications *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

Caution is advised when PDE5 inhibitors are co-administered with alpha-blockers. Phosphodiesterase type 5 inhibitors, including STENDRA, and alpha-adrenergic blocking agents are both vasodilators with blood pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly leading to symptomatic hypotension (e.g., dizziness, lightheadedness, fainting).

Consideration should be given to the following:

- Patients should be stable on alpha-blocker therapy prior to initiating treatment with a PDE5 inhibitor. Patients who demonstrate hemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of PDE5 inhibitors.
- In those patients who are stable on alpha-blocker therapy, PDE5 inhibitors should be initiated at the lowest dose (STENDRA 50 mg).
- In those patients already taking an optimized dose of a PDE5 inhibitor, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure when taking a PDE5 inhibitor.

Safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and other anti-hypertensive drugs [see *Dosage and Administration (2)* and *Drug Interactions (7.1)*].

5.7 Alcohol

Patients should be made aware that both alcohol and PDE5 inhibitors including **STENDRA** act as vasodilators. When vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. Therefore, physicians should inform patients that substantial consumption of alcohol (e.g., greater than 3 units) in combination with **STENDRA** may increase the potential for orthostatic signs and symptoms, including increase in heart

rate, decrease in standing blood pressure, dizziness, and headache *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

5.8 Combination with Other PDE5 Inhibitors or Erectile Dysfunction Therapies

The safety and efficacy of combinations of STENDRA with other treatments for ED has not been studied. Therefore, the use of such combinations is not recommended.

5.9 Effects on Bleeding

The safety of STENDRA is unknown in patients with bleeding disorders and patients with active peptic ulceration. *In vitro* studies with human platelets indicate that STENDRA potentiates the anti-aggregatory effect of sodium nitroprusside (a nitric oxide [NO] donor).

5.10 Counseling Patients about Sexually Transmitted Diseases

The use of STENDRA offers no protection against sexually transmitted diseases. Counseling patients about the protective measures necessary to guard against sexually transmitted diseases, including Human Immunodeficiency Virus (HIV), should be considered.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

STENDRA was administered to 2215 men during clinical trials. In trials of STENDRA for use as needed, a total of 493 patients were exposed for greater than or equal to 6 months, and 153 patients were treated for greater than or equal to 12 months.

In three randomized, double-blind, placebo-controlled trials lasting up to 3 months in duration, the mean age of patients was 56.4 years (range from 23 to 88 years). 83.9 % of patients were White, 13.8% were Black, 1.4% Asian, and < 1% Hispanic. 41.1% were current or previous smokers. 30.6% had diabetes mellitus.

The discontinuation rate due to adverse reactions for patients treated with STENDRA 50 mg, 100 mg, or 200 mg was 1.4%, 2.0%, and 2.0%, respectively, compared to 1.7% for placebo-treated patients.

Table 1 presents the adverse reactions reported when STENDRA was taken as recommended (on an as-needed basis) from these 3 clinical trials.

Table 1: Adverse Reactions Reported by Greater Than or Equal to 2% of Patients Treated with STENDRA From 3 Placebo-Controlled Clinical Trials Lasting 3 Months for STENDRA Use as Needed

Adverse Reaction	Placebo (N = 349)	STENDRA 50 mg (N = 217)	STENDRA 100 mg (N = 349)	STENDRA 200 mg (N = 352)
Headache	1.7%	5.1%	6.9%	10.5%
Flushing	0.0%	3.2%	4.3%	4.0%
Nasal congestion	1.1%	1.8%	2.9%	2.0%
Nasopharyngitis	2.9%	0.9%	2.6%	3.4%
Back pain	1.1%	3.2%	2.0%	1.1%

Adverse reactions reported by greater than or equal to 1%, but less than 2% of patients in any STENDRA dose group, and greater than placebo included: upper respiratory infection (URI), bronchitis, influenza, sinusitis, sinus congestion, hypertension, dyspepsia, nausea, constipation, and rash.

In an, open-label, long-term extension study of two of these randomized, double-blind, placebo-controlled trials, the total duration of treatment was up to 52 weeks. Among the 712 patients who participated in this open-label extension study, the mean age of the population was 56.4 years (range from 23 to 88 years). The discontinuation rate due to adverse reactions for patients treated with STENDRA (50 mg, 100 mg, or 200 mg) was 2.8%.

In this extension trial, all eligible patients were initially assigned to STENDRA 100 mg. At any point during the trial, patients could request to have their dose of STENDRA increased to 200 mg or decreased to 50 mg based on their individual response to treatment. In total, 536 (approximately 75%) patients increased their dose to 200 mg and 5 (less than 1%) patients reduced their dose to 50 mg.

Table 2 presents the adverse reactions reported when STENDRA was taken as recommended (on an as-needed basis) in this open-label extension trial.

Table 2: Adverse Reactions Reported by Greater Than or Equal to 2% of Patients Treated With STENDRA in an Open-Label Extension Trial

Adverse Reaction	STENDRA (N = 711)
Headache	5.6%
Flushing	3.5%
Nasopharyngitis	3.4%
Nasal congestion	2.1%

Adverse reactions reported by greater than or equal to 1%, but less than 2% of patients in the open-label extension study included: upper respiratory infection (URI), influenza, sinusitis, bronchitis, dizziness, back pain, arthralgia, hypertension, and diarrhea.

The following events occurred in less than 1% of patients in the three placebo-controlled 3-month clinical trials and/or the open-label, long-term extension study lasting 12 months. A causal relationship to STENDRA is uncertain. Excluded from this list are those events that were minor, those with no plausible relation to drug use and reports too imprecise to be meaningful.

Body as a whole — edema peripheral, fatigue

Cardiovascular — angina, unstable angina, deep vein thrombosis, palpitations

Digestive — gastritis, gastroesophageal reflux disease, hypoglycemia, blood glucose increased, alanine aminotransferase increased, oropharyngeal pain, stomach discomfort, vomiting

Musculoskeletal — muscle spasms, musculoskeletal pain, myalgia, pain in extremity

Nervous — depression, insomnia, somnolence, vertigo

Respiratory — cough, dyspnea exertional, epistaxis, wheezing

Skin and Appendages – pruritus

Urogenital – balanitis, erection increased, hematuria, nephrolithiasis, pollakiuria, urinary tract infection

In an additional, randomized, double-blind, placebo-controlled study lasting up to 3 months in 298 men who had undergone bilateral nerve-sparing radical prostatectomy for prostate cancer, the mean age of patients was 58.4 years (range 40 – 70). Table 3 presents the adverse reactions reported in this additional study.

Table 3: Adverse Reactions Reported by Greater than or Equal to 2% of Patients Treated with STENDRA in a Placebo-Controlled Clinical Trial Lasting 3 Months in Patients Who Underwent Bilateral Nerve-Sparing Radical Prostatectomy

Adverse Reaction	Placebo (N = 100)	STENDRA 100 mg (N = 99)	STENDRA 200 mg (N = 99)
Headache	1.0%	8.1%	12.1%
Flushing	0.0%	5.1%	10.1%
Nasopharyngitis	0.0%	3.0%	5.1%
Upper respiratory infection	0.0%	2.0%	3.0%
Nasal congestion	1.0%	3.0%	1.0%
Back pain	1.0%	3.0%	2.0%
Electrocardiogram abnormal	0.0%	1.0%	3.0%
Dizziness	0.0%	1.0%	2.0%

A randomized, double-blind, placebo-controlled 2 months study was conducted in 435 subjects with a mean age of 58.2 years (range 24 to 86 years) to determine the time to onset of effect of STENDRA, defined as the time to the first occurrence of an erection sufficient for sexual intercourse. Table 4 presents the adverse reactions occurring in ≥ 2% of subjects treated with STENDRA.

Table 4: Adverse Reactions Reported by ≥ 2% of Patients Treated with STENDRA in a Placebo-Controlled Clinical Trial Lasting 2 Months to Determine the Time to Onset of Effect (Study 3)

Adverse Reaction	Placebo (N = 143)	STENDRA 100 mg (N = 146)	STENDRA 200 mg (N = 146)
Headache	0.7%	1.4%	8.9%
Nasal congestion	0.0%	0.7%	4.1%
Gastroenteritis viral	0.0%	0.0%	2.1%

Across all trials with any STENDRA dose, 1 subject reported a change in color vision.

6.2 Postmarketing Experience

Ophthalmologic:

Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking [see *Warnings and Precautions (5.4)* and *Patient Counseling Information (17.6)*].

7 DRUG INTERACTIONS

7.1 Potential for Pharmacodynamic Interactions with STENDRA

Nitrates

Administration of STENDRA to patients who are using any form of organic nitrate, is contraindicated. In a clinical pharmacology trial, STENDRA was shown to potentiate the hypotensive effect of nitrates. In a patient who has taken STENDRA, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 12 hours should elapse after the last dose of STENDRA before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate hemodynamic monitoring *[see Contraindications (4.1), Dosage and Administration (2.3), and Clinical Pharmacology (12.2)]*.

Alpha-Blockers

Caution is advised when PDE5 inhibitors are co-administered with alpha-blockers. PDE5 inhibitors, including STENDRA, and alpha-adrenergic blocking agents are both vasodilators with blood pressure-lowering effects. When vasodilators are

used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly leading to symptomatic hypotension (e.g., dizziness, lightheadedness, fainting) *[see Warnings and Precautions (5.6), Dosage and Administration (2.3), and Clinical Pharmacology (12.2)]*.

Antihypertensives

PDE5 inhibitors, including STENDRA, are mild systemic vasodilators. A clinical pharmacology trial was conducted to assess the effect of STENDRA on the potentiation of the blood pressure-lowering effects of selected antihypertensive medications (amlodipine and enalapril). Additional reductions in blood pressure of 3 to 5 mmHg occurred following co-administration of a single 200 mg dose of STENDRA with these agents compared with placebo *[see Warnings and Precautions (5.6) and Clinical Pharmacology (12.2)]*.

Alcohol

Both alcohol and PDE5 inhibitors, including STENDRA, act as vasodilators. When vasodilators are taken in combination, blood pressure-lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., greater than 3 units) in combination with STENDRA can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache *[see Drug Interactions (7.1) and Clinical Pharmacology (12.2)]*.

7.2 Potential for Other Drugs to Affect STENDRA

STENDRA is a substrate of and predominantly metabolized by CYP3A4. Studies have shown that drugs that inhibit CYP3A4 can increase avanafil exposure.

Strong CYP3A4 Inhibitors

Ketoconazole (400 mg daily), a selective and strong inhibitor of CYP3A4, increased STENDRA 50 mg single-dose systemic exposure (AUC) and maximum concentration (C_{max}) equal to 13-fold and 3-fold, respectively, and prolonged the half-life of avanafil to approximately 9 hours. Other potent inhibitors of CYP3A4 (e.g. , itraconazole, clarithromycin, nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atanazavir and telithromycin) would be expected to have similar effects. Do not use STENDRA in patients taking strong CYP3A4 inhibitors *[see Warnings and Precautions (5.2) and Dosage and Administration (2.3)]*.

HIV Protease inhibitor — Ritonavir (600 mg twice daily), a strong CYP3A4 inhibitor, which also inhibits CYP2C9, increased STENDRA 50 mg single-dose C_{max} and AUC equal to approximately 2-fold and 13-fold, and prolonged the half-life of avanafil to approximately 9 hours in healthy volunteers. Do not use STENDRA in patients taking ritonavir.

Moderate CYP 3A4 Inhibitors

Erythromycin (500 mg twice daily) increased STENDRA 200 mg single-dose C_{max} and AUC equal to approximately 2-fold and 3-fold, respectively, and prolonged the half-life of avanafil to approximately 8 hours in healthy volunteers. Moderate CYP3A4 inhibitors (e.g., erythromycin, amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, and verapamil) would be expected to have similar effects. Consequently, the maximum recommended dose of STENDRA is 50 mg, not to exceed once every 24 hours for patients taking concomitant moderate CYP3A4 inhibitors *[see Warnings and Precautions (5.2) and Drug Interactions (7.2)]*.

Although specific interactions have not been studied, other CYP3A4 inhibitors, including grapefruit juice are likely to increase avanafil exposure.

Weak CYP3A4 Inhibitors

No in vivo drug-drug interaction studies with weak CYP3A4 inhibitors were conducted.

CYP3A4 Substrate

When administered with STENDRA 200 mg, amlodipine (5 mg daily) increased the C_{max} and AUC of avanafil by approximately 22% and 70%, respectively. The half-life of STENDRA was prolonged to approximately 10 hrs. The C_{max} and AUC of amlodipine decreased by approximately 9% and 4%, respectively *[see Dosage and Administration (2.3)]*.

Cytochrome P450 Inducers

The potential effect of CYP inducers on the pharmacokinetics of avanafil was not evaluated. The concomitant use of STENDRA and CYP inducers is not recommended.

7.3 Potential for STENDRA to Affect Other Drugs

In vitro studies

Avanafil had no effect on CYP1A1/2, 2A6, 2B6 and 2E1 (IC_{50} greater than 100 micromolar) and weak inhibitory effects toward other isoforms (CYP2C8, 2C9, 2C19, 2D6, 3A4). Major circulating metabolites of avanafil (M4 and M16) had no effect on CYPs 1A, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4. Avanafil and its metabolites (M4 and M16) are unlikely to cause clinically significant inhibition of CYPs 1A, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4.

In vivo studies

Warfarin —A single 200 mg dose of STENDRA did not alter the changes in PT or INR induced by warfarin, and did not affect collagen-induced platelet aggregation or the AUC or C_{max} of R- or S-warfarin, a 2C9 substrate.

Desipramine — A single STENDRA 200 mg dose increased AUC and C_{max} of a single 50 mg dose of desipramine, a CYP2D6 substrate, by 5.7% and 5.2%, respectively.

Omeprazole — A single STENDRA 200 mg dose increased AUC and C_{max} of a single 40 mg dose of omeprazole, a CYP2C19 substrate, given once daily for 8 days by 5.9% and 8.6%, respectively.

Rosiglitazone — A single STENDRA 200 mg dose increased AUC by 2.0% and decreased C_{max} by 14% of a single 8 mg dose of rosiglitazone, a CYP2C8 substrate.

Amlodipine — A single STENDRA 200 mg dose did not affect the pharmacokinetics of amlodipine (5 mg daily), a CYP3A4 substrate *[see Dosage and Administration (2.3)]*.

Alcohol — A single oral dose of STENDRA 200 mg did not affect alcohol (0.5 g ethanol/kg) plasma concentrations *[see Warnings and Precautions (5.7)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

STENDRA is not indicated for use in women. There are no adequate and well-controlled studies of STENDRA in pregnant women.

Fetal Risk Summary

Based on animal data, STENDRA is predicted to have a low risk for major developmental abnormalities in humans.

Animal Data

In pregnant rats administered 100, 300, or 1000 mg/kg/day from gestation days 6 to 17, no evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed at exposures up to approximately 8 times the exposure at the Maximum Recommended Human Dose (MRHD) of 200 mg based on AUCs for total avanafil (protein bound plus free avanafil). At the maternally toxic dose (1000 mg/kg/day), a dose producing exposures approximately 30 times the MRHD on an AUC basis, decreased fetal body weight occurred with no signs of teratogenicity. In pregnant rabbits administered 30, 60, 120, or 240 mg/kg/day from gestation days 6 to 18, no teratogenicity was observed at exposures up to approximately 6 times the human exposure at the MRHD based on AUC. At the high dose associated with maternally-reduced body weights, increased postimplantation loss was observed consistent with increased late resorptions.

In a pre- and post-natal development study in rats given 100, 300, or 600 mg/kg/day on gestation days 6 through lactation day 20, offspring growth and maturation were reduced when maternal rats were given avanafil doses greater than or equal to 300 mg/kg/day resulting in exposures greater than or equal to 17 times the human exposure. There was no effect on reproductive performance of the maternal rats or offspring, or on the behavior of the offspring at up to the highest dose tested. The no observed adverse effect level (NOAEL) for developmental toxicity (100 mg/kg/day) was approximately 2-fold greater than the systemic exposure in humans at the MRHD.

8.4 Pediatric Use

STENDRA is not indicated for use in pediatric patients. Safety and efficacy in patients below the age of 18 years has not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of avanafil, approximately 23% were 65 and over. No overall differences in efficacy and safety were observed between subjects over 65 years of age compared to younger subjects; therefore no dose adjustment is warranted based on age alone. However, a greater sensitivity to medication in some older individuals should be considered *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

In a clinical pharmacology trial using single 200 mg doses of STENDRA, avanafil exposure (AUC or C_{max}) in normal subjects was comparable to patients with mild (creatinine clearance greater than or equal to 60 to less than 90 mL/min) or moderate (creatinine clearance greater than or equal to 30 to less than 60 mL/min) renal impairment. No dose adjustment is necessary for patients with mild to moderate renal impairment (creatinine clearance greater than or equal to 30 to less than 90 mL/min). The pharmacokinetics of avanafil in patients with severe renal disease or on renal dialysis has not been studied; do not use STENDRA in such patients *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

In a clinical pharmacology trial, avanafil AUC and C_{max} in patients with mild hepatic impairment (Child-Pugh Class A) was comparable to that in healthy subjects when a dose of 200 mg was administered. Avanafil C_{max} was approximately 51% lower and AUC was 11% higher in patients with moderate hepatic impairment (Child Pugh Class B) compared to subjects with normal hepatic function. No dose adjustment is necessary for patients with mild to moderate hepatic impairment (Child Pugh Class A or B). The pharmacokinetics of avanafil in patients with severe hepatic disease has not been studied; do not use STENDRA in such patients *[see Clinical Pharmacology (12.3)]*.

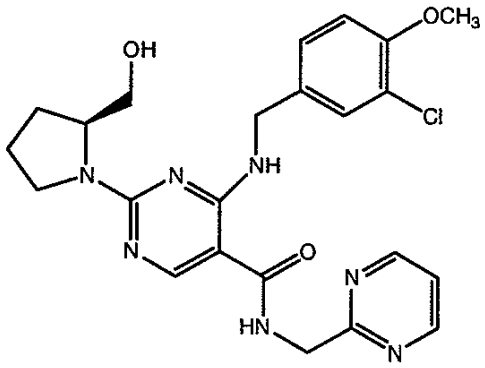
10 OVERDOSAGE

Single doses up to 800 mg have been given to healthy subjects, and multiple doses up to 300 mg have been given to patients. In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance because avanafil is highly bound to plasma proteins and is not significantly eliminated in the urine.

11 DESCRIPTION

STENDRA (avanafil) is a selective inhibitor of cGMP-specific PDE5.

Avanafil is designated chemically as (S)-4-[(3-Chloro-4-methoxybenzyl)amino]-2-[2-(hydroxymethyl)-1-pyrrolidinyl]-*N*-(2-pyrimidinylmethyl)-5-pyrimidinecarboxamide and has the following structural formula:



Avanafil occurs as white crystalline powder, molecular formula $C_{23}H_{26}ClN_7O_3$ and molecular weight of 483.95 and is slightly soluble in ethanol, practically insoluble in water, soluble in 0.1 mol/L hydrochloric acid. STENDRA, for oral administration, is supplied as oval, pale yellow tablets containing 50 mg, 100 mg, or 200 mg avanafil debossed with dosage strengths. In addition to the active ingredient, avanafil, each tablet contains the following inactive ingredients: mannitol, fumaric acid, hydroxypropylcellulose, low substituted hydroxypropylcellulose, calcium carbonate, magnesium stearate, and ferric oxide yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The physiologic mechanism of erection of the penis involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO then activates the enzyme guanylate cyclase, which results in increased levels of cGMP, producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood. Avanafil has no direct relaxant effect on isolated human corpus cavernosum, but enhances the effect of NO by inhibiting PDE5, which is responsible for degradation of cGMP in the corpus cavernosum. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 has no effect in the absence of sexual stimulation.

Studies in vitro have shown that avanafil is selective for PDE5. Its effect is more potent on PDE5 than on other known phosphodiesterases (greater than 100-fold for PDE6; greater than 1,000-fold for PDE4, PDE8 and PDE10; greater than 5,000-fold for PDE2 and PDE7; greater than 10,000-fold for PDE1, PDE3, PDE9, and PDE11). Avanafil is greater than 100-fold more potent for PDE5 than PDE6, which is found in the retina and is responsible for phototransduction. In addition to human corpus cavernosum smooth muscle, PDE5 is also found in other tissues including platelets, vascular and visceral smooth muscle, and skeletal muscle, brain, heart, liver, kidney, lung, pancreas, prostate, bladder, testis, and seminal vesicle. The inhibition of PDE5 in these tissues by avanafil may be the basis for the enhanced platelet anti-aggregatory activity of NO observed in vitro and peripheral vasodilatation in vivo.

12.2 Pharmacodynamics

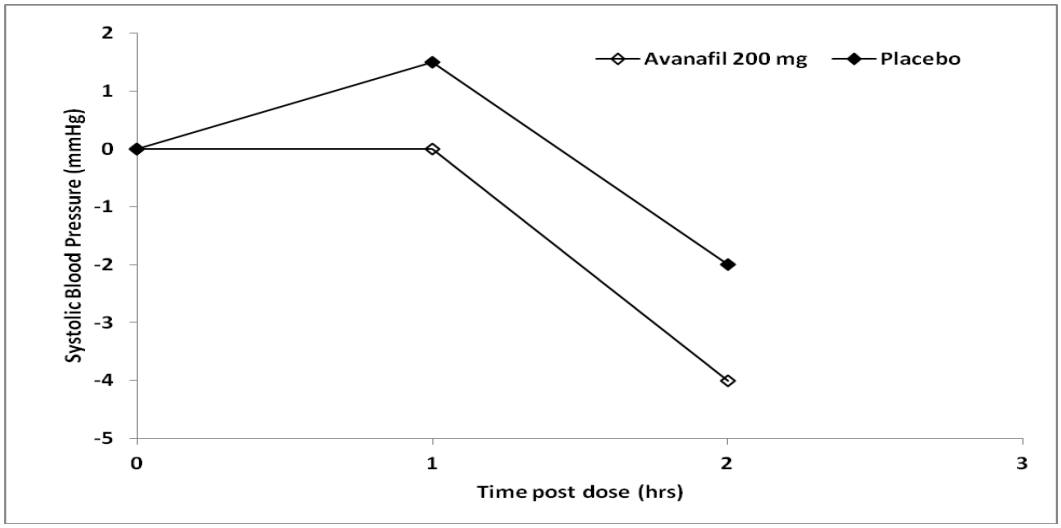
Effects of STENDRA on Erectile Response

In a single-blind, placebo-controlled, single-dose trial of 82 patients with either organic and/or psychogenic ED, visual sexual stimulation resulted in improved erections after STENDRA administration compared to placebo, as assessed by an objective measurement of hardness and duration of erections (RigiScan®). Efficacy was assessed by RigiScan at discrete time intervals ranging from 20 – 40 minutes after dosing to 100 – 120 minutes after dosing.

Effects of STENDRA on Blood Pressure

Single oral doses of STENDRA (200 mg) administered to healthy male volunteers resulted in mean changes from baseline in systolic/diastolic blood pressure of -5.3/-3.7 mmHg at 1 hour after dosing, compared to mean changes from baseline in the placebo group of 2.7/-0.4 mmHg. The reductions in systolic/diastolic blood pressure at 1 hour after dosing of STENDRA 200 mg compared to placebo were 8.0/3.3 mmHg.

Figure 1: Median Change from Baseline in Sitting Systolic Blood Pressure, Healthy Volunteers Day 4



Effects on Cardiac Electrophysiology

The effect of single 100 or 800 mg doses of STENDRA on the QT interval were evaluated in a randomized, double-blind, placebo, and active (moxifloxacin) –controlled crossover study in 52 healthy male subjects aged 18 to 45 years. There were no significant effects of the 100 mg dose. The mean QTc (Fridericia QT correction) for avanafil 800 mg, relative to placebo was 9.4 milliseconds (two-sided 90% CI=7.2, 11.6). An 800 mg dose of STENDRA (4 times the highest recommended dose) was chosen because this dose yields exposures greater than those observed upon co-administration of avanafil with

strong CYP3A4 inhibitors. A double-blind, randomized, placebo- and active-controlled (moxifloxacin), thorough QT/QTc trial of STENDRA (100 and 800 mg) in healthy male subjects demonstrated that STENDRA did not cause any significant changes in QTc interval or ventricular repolarization.

Effects of STENDRA on Blood Pressure When Administered with Nitrates

In a clinical pharmacology trial, a single dose of STENDRA 200 mg was shown to potentiate the hypotensive effect of nitrates. The use of STENDRA in patients taking any form of nitrates is contraindicated [*see Contraindications (4.1)*].

A trial was conducted to assess the degree of interaction between nitroglycerin and STENDRA, should nitroglycerin be required in an emergency situation after STENDRA was taken. This was a single-center, double-blind, randomized, 3-way crossover trial of healthy males from 30 to 60 years of age. Subjects were divided among 5 trial groups with the trial group being determined by the time interval between treatment with trial drug and glyceryl trinitrate administration. Subjects were assigned to trial groups sequentially and hemodynamic results from the previous group were reviewed for serious adverse events (SAEs) before the next group received treatment. Each subject was dosed with all 3 study drugs (STENDRA 200 mg, sildenafil citrate 100 mg, and placebo) in random order. Subjects were administered a single dose of 0.4 mg sublingual nitroglycerin (NTG) at pre-specified time points, following their dose of trial drug (0.5, 1, 4, 8 or 12 hours). Overall, 14 (15%) subjects treated with placebo and 28 (28%) subjects treated with avanafil, had clinically significant decreases in standing SBP, defined as greater than or equal to 30 mmHg decrease in SBP, after glyceryl trinitrate administration. Mean maximum decreases are shown in Table 5.

Table 5: Mean Maximum Decreases from Baseline in Sitting and Standing Systolic Blood Pressure/Diastolic Blood Pressure (mmHg) following Placebo or 200 mg STENDRA with 0.4 mg sublingual nitroglycerin

Placebo with nitroglycerin	
Sitting	13.4/11.8
Standing	21.1/16.5
STENDRA with nitroglycerin	
Sitting	21.6/18.2
Standing	28.0/23.5

Like other PDE5 inhibitors, STENDRA administration with nitrates is contraindicated. In a patient who has taken STENDRA, where nitrate administration is deemed medically necessary in a life threatening situation, at least 12 hours should elapse after the last dose of STENDRA before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring *[see Contraindications (4.1)]*.

Effects of STENDRA on Blood Pressure When Administered with Alpha-Blockers

A single-center, randomized, double-blinded, placebo-controlled, two-period crossover trial was conducted to investigate the potential interaction of STENDRA with alpha-blocker agents in healthy male subjects which consisted of two cohorts:

Cohort A (N=24): Subjects received oral doses of doxazosin once daily in the morning at 1 mg for 1 day (Day 1), 2 mg for 2 days (Days 2 – 3), 4 mg for 4 days (Days 4 – 7), and 8 mg for 11 days (Days 8 – 18). On Days 15 and 18, the subjects also received a single oral dose of either 200 mg STENDRA or placebo, according to the treatment randomization code. The STENDRA or placebo doses were administered 1.3 hours after the doxazosin administration on Days 15 and 18. The co-administration was designed so that doxazosin (T_{max} ~2 hours) and STENDRA (T_{max} ~0.7 hours) would reach their peak plasma concentrations at the same time.

Cohort B (N=24): Subjects received 0.4 mg daily oral doses of tamsulosin in the morning for 11 consecutive days (Days 1 – 11). On Days 8 and 11, the subjects also received a single oral dose of either 200 mg STENDRA or placebo, according to the treatment randomization code. The STENDRA or placebo doses were administered 3.3 hours after the tamsulosin administration on Days 8 and 11. The co-administration was designed so that tamsulosin (T_{max} ~4 hours) and STENDRA (T_{max} ~0.7 hours) would reach their peak plasma concentrations at the same time.

Supine and sitting BP and pulse rate measurements were recorded before and after STENDRA or placebo dosing.

A total of seven subjects in Cohort A (doxazosin) experienced potentially clinically important absolute values or changes from baseline in standing SBP or DBP. Three subjects experienced standing SBP values less than 85 mmHg. One subject experienced a decrease from baseline in standing SBP greater than 30 mmHg following STENDRA. Two subjects experienced standing DBP values less than 45 mmHg following STENDRA. Four subjects experienced decreases from

baseline in standing DBP greater than 20 mmHg following STENDRA. One subject experienced such decreases following placebo. There were no severe adverse events related to hypotension reported during the trial. There were no cases of syncope.

A total of five subjects in Cohort B (tamsulosin) experienced potentially clinically important absolute values or changes from baseline in standing SBP or DBP. Two subjects experienced standing SBP values less than 85 mmHg following STENDRA. One subject experienced a decrease from baseline in standing SBP greater than 30 mmHg following STENDRA. Two subjects experienced standing DBP values less than 45 mmHg following STENDRA. Four subjects experienced decreases from baseline in standing DBP greater than 20 mmHg following STENDRA; one subject experienced such decreases following placebo. There were no severe adverse events related to hypotension reported during the trial. There were no cases of syncope.

Table 6 presents the placebo-subtracted mean maximum decreases from baseline (95% CI) in systolic blood pressure results for the 24 subjects who received STENDRA 200 mg and matching placebo.

Table 6: Placebo-Subtracted Mean (95% CI) Maximum Decreases from Baseline in Standing and Supine Systolic Blood Pressure (mmHg) with 200 mg STENDRA

Doxazosin	
Supine	-6.0 (-9.1, -2.9)
Standing	-2.5 (-6.5, 1.5)
Tamsulosin	
Supine	-3.1 (-6.4, 0.1)
Standing	-3.6 (-8.1, 0.9)

Blood pressure effects (standing SBP) in normotensive men on stable dose doxazosin (8 mg) following administration of STENDRA 200 mg or placebo, are shown in Figure 2. Blood pressure effects (standing SBP) in normotensive men on stable dose tamsulosin (0.4 mg) following administration of STENDRA 200 mg or placebo are shown in Figure 3.

Figure 2: Mean (SD) Change From Baseline in Standing Systolic Blood Pressure Over Time Following Administration of a Single Dose 200 mg Dose of STENDRA with Doxazosin

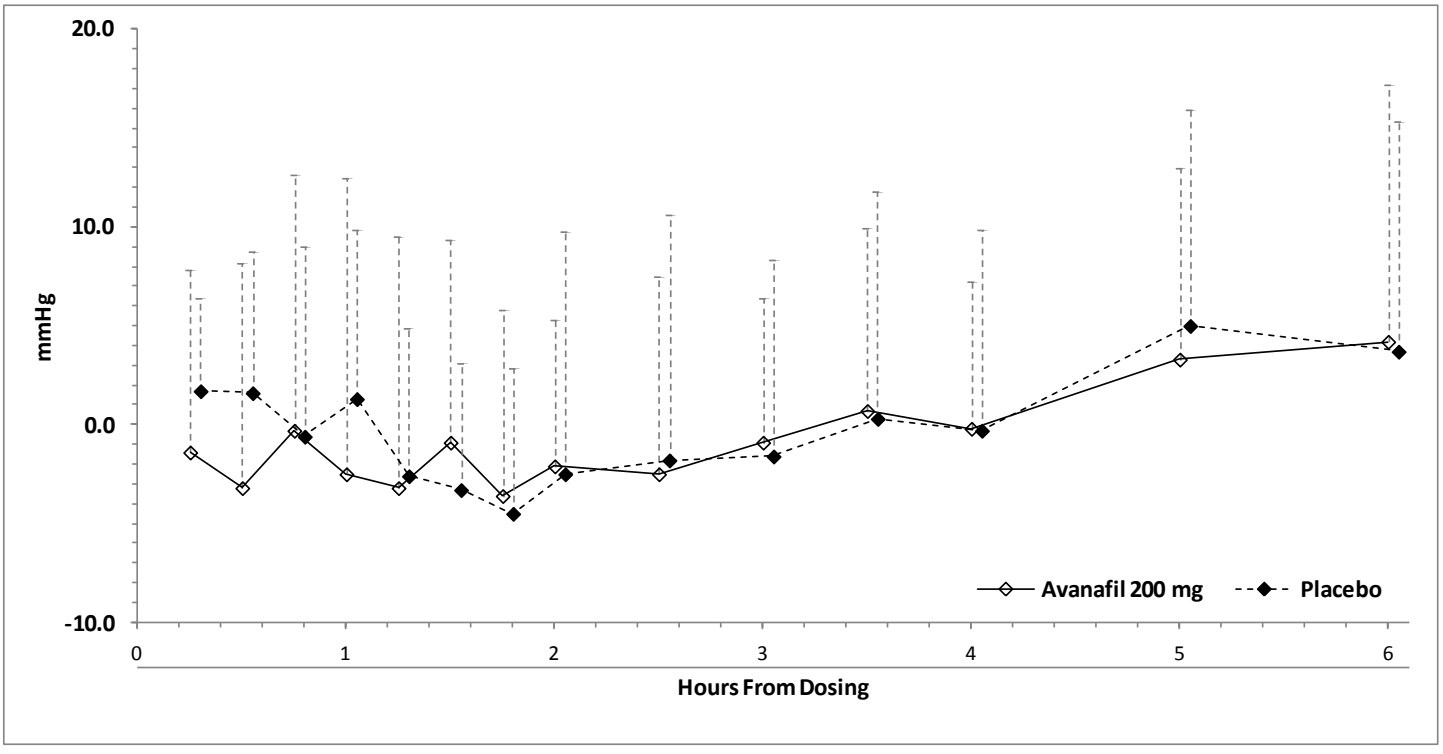
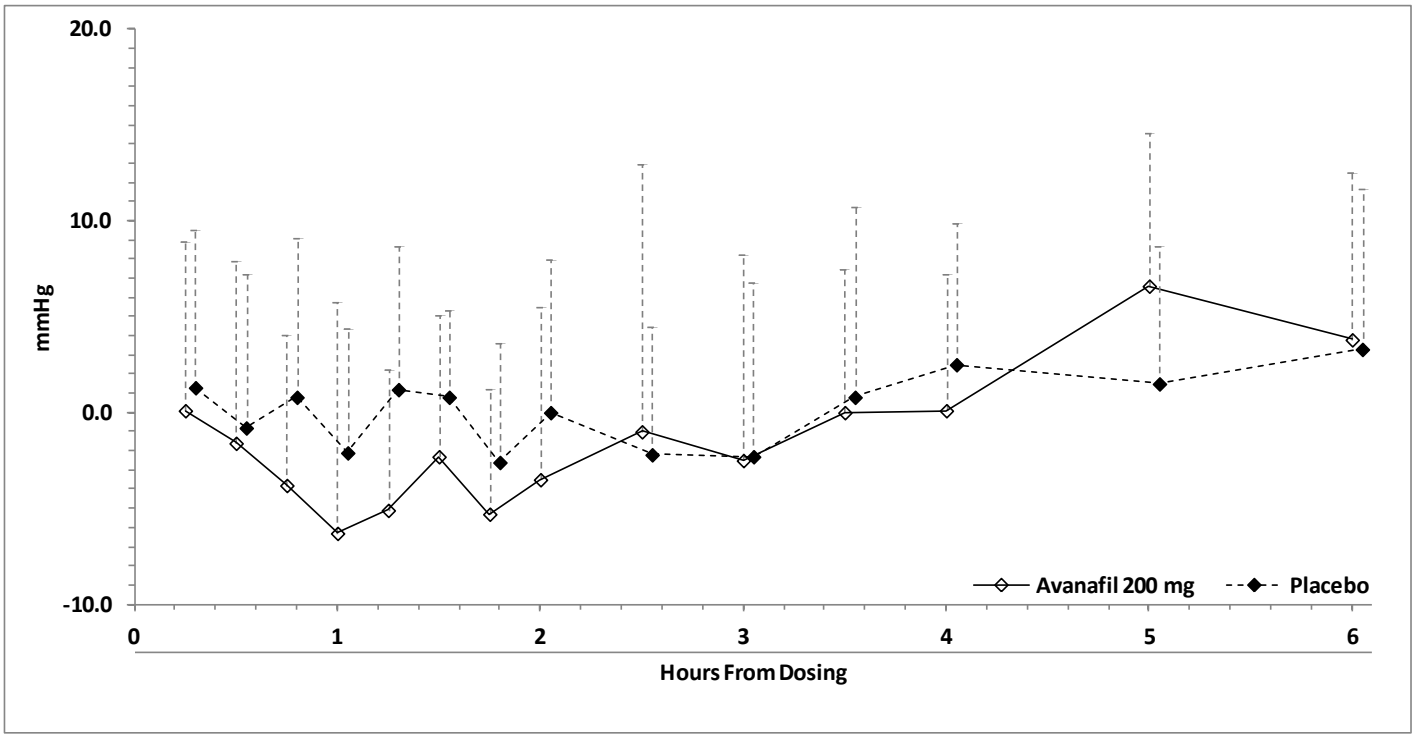


Figure 3: Mean (SD) Change From Baseline in Standing Systolic Blood Pressure Over Time Following Administration of a Single Dose 200 mg Dose of STENDRA with Tamsulosin



Effects of STENDRA on Blood Pressure When Administered with Enalapril

A trial was conducted to assess the interaction of enalapril (20 mg daily) and STENDRA 200 mg. Single doses of 200 mg STENDRA co-administered with enalapril caused a mean maximum decrease in supine systolic/diastolic blood pressure of 1.8/3.5 mmHg (compared to placebo), accompanied by a mean maximum increase in pulse rate of 1.0 bpm.

Effects of STENDRA on Blood Pressure When Administered with Amlodipine

A trial was conducted to assess the interaction of amlodipine (5 mg daily) and STENDRA 200 mg. Single doses of 200 mg STENDRA co-administered with amlodipine caused a mean maximum decrease in supine systolic blood pressure of 1.2 mmHg (compared to placebo), accompanied by a mean maximum increase in pulse rate of 1.0 bpm; the mean maximum decrease in diastolic blood pressure was less than that observed in the placebo group. There was no effect of STENDRA on amlodipine plasma concentrations. Concomitant amlodipine was associated with 22% and 70% increases in avanafil C_{max} and AUC, respectively.

Effects of STENDRA on Blood Pressure When Administered with Alcohol

Alcohol and PDE5 inhibitors, including STENDRA, are mild systemic vasodilators. The interaction of STENDRA with alcohol was evaluated in a clinical pharmacology trial. Alcohol was administered at a dose of 0.5 g/kg, which is equivalent to approximately 3 ounces of 80-proof vodka in a 70-kg male, and STENDRA was administered at a dose of 200 mg. All patients consumed the entire alcohol dose within 15 minutes of starting. Blood alcohol levels of 0.057% were confirmed. There were no reports of orthostatic hypotension or dizziness. Additional maximum supine systolic/diastolic blood pressure decreases of 3.5/4.5 mm Hg and additional maximum pulse rate increase of 9.3 bpm were observed when avanafil was taken with alcohol compared to alcohol alone. Avanafil did not affect alcohol plasma concentrations.

Effects of STENDRA on Semen

A single 200 mg dose of STENDRA had no acute effect on sperm motility or sperm morphology in a group of healthy male subjects. The effect of avanafil on human spermatogenesis is unknown.

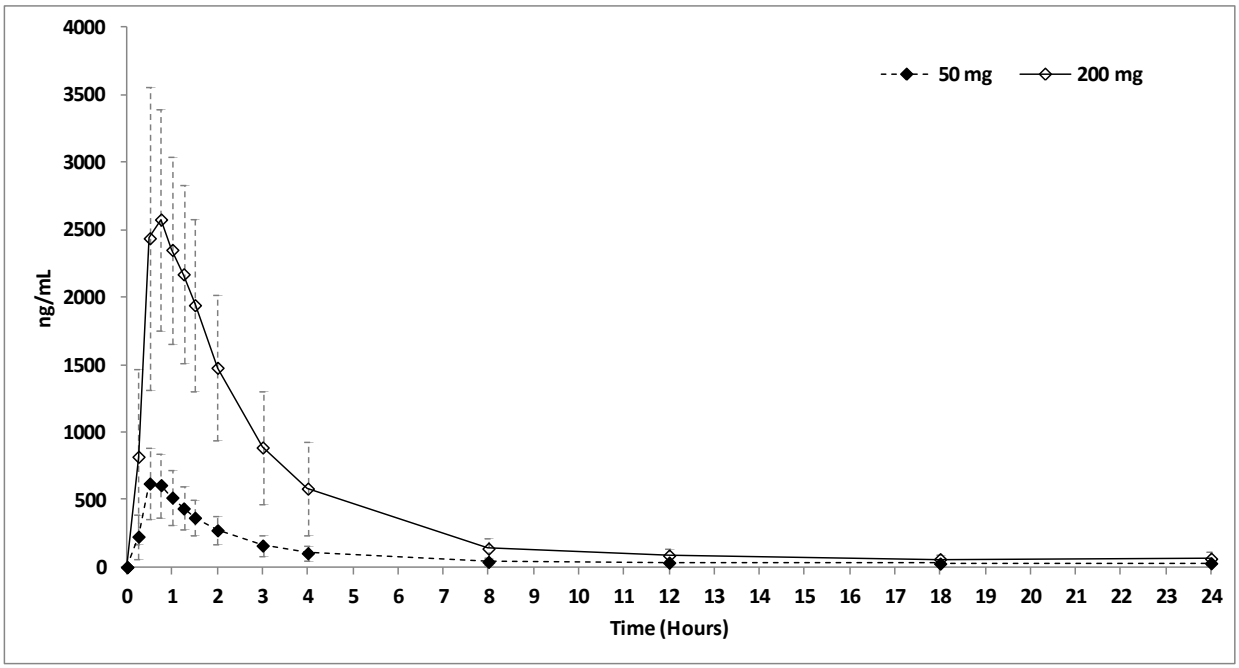
Effects of STENDRA on Vision

Single oral doses of Type 5 phosphodiesterase inhibitors have demonstrated transient dose-related impairment of color discrimination (blue/green), using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina.

12.3 Pharmacokinetics

Mean STENDRA plasma concentrations measured after the administration of a single oral dose of 50 or 200 mg to healthy male volunteers are depicted in Figure 4. The pharmacokinetics of STENDRA are dose proportional from 12.5 to 600 mg.

Figure 4: Plasma Avanafil Concentrations (mean ± SD) Following a Single 50 mg or 200 mg STENDRA Dose



Absorption and Distribution

STENDRA is rapidly absorbed after oral administration, with a median T_{max} of 30 to 45 minutes in the fasted state. When STENDRA (200 mg) is taken with a high fat meal, the rate of absorption is reduced, with a mean delay in T_{max} of 1.12 to 1.25 hours and a mean reduction in C_{max} of 39% (200 mg). There was an approximate 3.8% decrease in AUC. The small changes in avanafil C_{max} and AUC are considered of minimal clinical significance; therefore, STENDRA may be administered with or without food. The mean accumulation ratio is approximately 1.2. Avanafil is approximately 99% bound to plasma proteins. Protein binding is independent of total drug concentrations, age, renal and hepatic function.

Based upon measurements of avanafil in semen of healthy volunteers 45-90 minutes after dosing, less than 0.0002% of the administered dose appeared in the semen of patients.

Metabolism and Excretion

Avanafil is cleared predominantly by hepatic metabolism, mainly by the CYP3A4 enzyme and to a minor extent by CYP2C isoform. The plasma concentrations of the major circulating metabolites, M4 and M16, are approximately 23% and 29% that of the parent compound, respectively. The M4 metabolite has an *in vitro* inhibitory potency for PDE5 18% of that of avanafil and M4 accounts for approximately 4% of the pharmacologic activity of avanafil. The M16 metabolite was inactive against PDE5.

Avanafil was extensively metabolized in humans. After oral administration, avanafil is excreted as metabolites predominantly in the feces (approximately 62% of administered oral dose) and to a lesser extent in the urine (approximately 21% of the administered oral dose). STENDRA has a terminal elimination half-life of approximately 5 hours.

Geriatric

The pharmacokinetics of a single 200 mg STENDRA administered to fourteen healthy elderly male volunteers (65-80 years) and eighteen healthy younger male volunteers (18-43 years of age) were compared. $AUC_{0\text{-}inf}$ increased by 6.8% and

C_{max} decreased by 2.1% in the elderly group, compared to the younger group. However, greater sensitivity to medications in some older individuals should be considered *[see Use in Specific Populations (8.5)]*.

Renal Impairment

The pharmacokinetics of a single 200 mg STENDRA administered to nine patients with mild (creatinine clearance greater than or equal to 60 and less than 90 mL/min) and to ten patients with moderate (creatinine clearance greater than or equal to 30 to less than 60 mL/min) renal impairment were evaluated. $AUC_{0\text{-}inf}$ decreased by 2.9% and C_{max} increased by 2.8% in patients with mild renal impairment, compared to healthy volunteers with normal renal function. $AUC_{0\text{-}inf}$ increased by 9.1% and C_{max} decreased by 2.8% in patients with moderate renal impairment, compared to healthy volunteers with normal renal function. There is no data available for subjects with severe renal insufficiency or end-stage renal disease on hemodialysis *[see Use in Specific Populations (8.6)]*.

Hepatic Impairment

The pharmacokinetics of a single 200 mg STENDRA administered to eight patients with mild hepatic impairment (Child-Pugh A) and eight patients with moderate hepatic impairment (Child-Pugh B) were evaluated. $AUC_{0\text{-}inf}$ increased by 3.8% and C_{max} decreased by 2.7% in patients with mild hepatic impairment, compared to healthy volunteers with normal hepatic function. $AUC_{0\text{-}inf}$ increased by 11.2% and C_{max} decreased by 51% in patients with moderate hepatic impairment, compared to healthy volunteers with normal hepatic function. There is no data available for subjects with severe hepatic impairment (Child-Pugh Class C) *[see Use in Specific Populations (8.6)]*.

Drug Interactions

Effect of CYP3A4 Inhibitors on Avanafil: Strong and moderate CYP3A4 inhibitors increase plasma concentrations of STENDRA. The effect of strong CYP3A4 inhibitors, ketoconazole and ritonavir, and moderate CYP3A4 inhibitor, erythromycin, on avanafil pharmacokinetics was studied in an open-label, randomized, one-sequence crossover, three-way parallel study.

Strong CYP3A4 Inhibitors

Fifteen healthy male volunteers received 400 mg ketoconazole (2 tablets containing 200 mg ketoconazole) once daily for 5 days (Days 2-6) and a single 50 mg avanafil on Days 1 and 6. Twenty-four hour pharmacokinetics of avanafil on Days 1 and 6 were compared. Co-administration with the strong CYP3A4 inhibitor ketoconazole resulted in an approximate 13-fold increase in $AUC_{0\text{-}inf}$ and 3.1-fold increase in C_{max}. Fourteen healthy male volunteers received 300 mg ritonavir (3 tablets containing 100 mg ritonavir) twice daily for 1 day (Day 2), 400 mg twice daily for 1 day (Day 3), 600 mg twice daily for 5 days (Days 4-8), and a single 50 mg avanafil on Days 1 and 8. Twenty-four hour pharmacokinetics of avanafil on Days 1 and 8 were compared. Co-administration with the strong CYP3A4 inhibitor ritonavir resulted in an approximate 13-fold increase in $AUC_{0\text{-}inf}$ and 2.4-fold increase in C_{max} of avanafil.

Moderate CYP3A4 Inhibitors

Fifteen healthy male volunteers received 500 mg erythromycin (2 tablets containing 250 mg erythromycin) every 12 hrs for 5 days (Days 2-6) and a single 200 mg avanafil (2 tablets containing 100 mg avanafil) on Days 1 and 6. Twenty-four hour pharmacokinetics of avanafil on Days 1 and 6 were compared. Co-administration with the moderate CYP3A4 inhibitor erythromycin resulted in an approximate 3.6-fold increase in $AUC_{0\text{-}inf}$ and 2.0-fold increase in C_{max} of avanafil.

Effect of Avanafil on Other Drugs:

Warfarin

The effect of avanafil on warfarin pharmacokinetics and pharmacodynamics was evaluated in a double-blind, randomized, placebo-controlled, two-way crossover study. Twenty-four healthy male volunteers were randomized to receive either 200 mg avanafil or matching placebo for 9 days. On Day 3 of each period, volunteers received a single 25 mg warfarin. Pharmacokinetics of R- and S-warfarin, PT, and INR prior to warfarin dosing and up to 168 hrs after warfarin administration were compared. Platelet aggregation prior to warfarin dosing and up to 24 hrs after warfarin administration were compared. PT, INR, and platelet aggregation did not change with avanafil administration: 23.1 sec, 2.2, and 75.5%, respectively. Co-administration with avanafil resulted in an approximate 1.6% increase in $AUC_{0\text{-}inf}$ and 5.2% decrease in C_{max} of S-warfarin.

Omeprazole, Rosiglitazone, and Desipramine

The effect of avanafil on the pharmacokinetics of omeprazole (a CYP2C19 substrate), rosiglitazone (a CYP2C8 substrate), and desipramine (a CYP2D6 substrate) was evaluated in an open-label, three cohort, crossover study. Nineteen healthy male volunteers received a single 40 omeprazole delayed-release capsule once daily for 8 days (Days 1-8), and a single 200 mg avanafil on Day 8. Twelve hour pharmacokinetics of omeprazole on Days 7 and 8 were compared. Co-administration with avanafil resulted in an approximate 5.9% increase in $AUC_{0\text{-}inf}$ and 8.6% increase in C_{max} of omeprazole. Twenty healthy male volunteers received a single 8 mg rosiglitazone tablet then a single 200 mg avanafil. Twenty-four hour pharmacokinetics of rosiglitazone with and without avanafil were compared. Co-administration with avanafil resulted in an approximate 2.0% increase in $AUC_{0\text{-}inf}$ and 14% decrease in C_{max} of rosiglitazone. Twenty healthy male volunteers received a single 50 mg desipramine tablet then a single 200 mg avanafil tablet 2 hours after desipramine. Ninety-six hour pharmacokinetics of desipramine with and without avanafil were compared. Co-administration with avanafil resulted in an approximate 5.7% increase in $AUC_{0\text{-}inf}$ and 5.2% increase in C_{max} of desipramine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Carcinogenesis

Avanafil was not carcinogenic to CD-1 mice when administered daily at doses of 100, 200, or 600 mg/kg/day orally by gavage for at least 98 weeks (approximately 11 times the MRHD on an AUC basis) or to Sprague Dawley rats when administered daily at doses of 100, 300, or 1000 mg/kg/day orally by gavage for at least 100 weeks (approximately 8 times for males and 34 times for females above the MRHD on an AUC basis).

Mutagenesis

Avanafil was not genotoxic in a series of tests. Avanafil was not mutagenic in Ames assays. Avanafil was not clastogenic in chromosome aberration assays using Chinese hamster ovary and lung cells, or in vivo in the mouse micronucleus assay. Avanafil did not affect DNA repair when tested in the rat unscheduled DNA synthesis assay.

Impairment of Fertility

In a rat fertility and early embryonic development study administered 100, 300, or 1000 mg/kg/day for 28 days prior to pairing and continued until euthanasia for males, and 14 days prior to pairing to gestation day 7 for females, a decrease in fertility, no or reduced sperm motility, altered estrous cycles, and an increased percentage of abnormal sperm (broken sperm with detached heads) occurred at exposures in males approximately 11 times the human exposure at a dose of 200 mg. The altered sperm effects were reversible at the end of a 9-week drug-free period. Systemic exposure at the NOAEL (300 mg/kg/day) was comparable to the human AUC at the MRHD of 200 mg.

13.2 Animal Toxicology and/or Pharmacology

Repeated oral administration of avanafil in multiple species resulted in signs of centrally-mediated toxicity including ataxia, tremor, convulsion, hypoactivity, recumbency, and/or prostration at doses resulting in exposures approximately 5-8 times the MRHD based on Cmax and 8-30 times the MRHD based on AUC.

14 CLINICAL STUDIES

STENDRA was evaluated in three randomized, double-blind, placebo-controlled, parallel trials of 2 to 3 months in duration. STENDRA was taken as needed at doses of 50 mg, 100 mg, and 200 mg (Study 1) and 100 mg and 200 mg (Study 2 and Study 3). Patients were instructed to take 1 dose of study drug approximately 30 minutes (Study 1 and Study 2) or approximately 15 minutes (Study 3) prior to initiation of sexual activity. Food and alcohol intake was not restricted.

In addition, a subset of patients from 2 of these trials were enrolled into an open-label extension trial. In the open-label extension trial, all eligible patients were initially assigned to avanafil 100 mg. At any point during the trial, patients could request to have their dose of avanafil increased to 200 mg or decreased to 50 mg based on their individual response to treatment.

The 3 primary outcome measures in Study 1 and 2 were the erectile function domain of the International Index of Erectile Function (IIEF) and Questions 2 and 3 from Sexual Encounter Profile (SEP). The IIEF is a 4-week recall questionnaire that was administered at baseline and at 4-week intervals during treatment. The IIEF erectile function domain has a 30-point total score, where the higher scores reflect better erectile function. The SEP included diary-based measures of erectile function. Patients recorded information regarding each sexual attempt made throughout the trial. Question 2 of the SEP asks

"Were you able to insert your penis into your partner's vagina?" Question 3 of the SEP asks "Did your erection last long enough for you to have successful intercourse?"

In Study 3, the primary efficacy variable was the per-subject proportion of sexual attempts that had an erectogenic effect within approximately 15 minutes following dosing, where an erectogenic effect was defined as an erection sufficient for vaginal penetration and that enabled satisfactory completion of sexual intercourse.

Results are shown from the two, Phase 3, randomized, double-blind, placebo-controlled, parallel studies, one in the general ED population (Study 1) and the other in the diabetic population with ED (Study 2).

Results in the General ED Population (Study 1):

STENDRA was evaluated in 646 men with ED of various etiologies (organic, psychogenic, mixed), in a randomized, double-blinded, parallel, placebo controlled fixed dose trial of 3 months duration. The mean age was 55.7 years (range 23 to 88 years). The population was 85.6% White, 13.2% Black, 0.9% Asian, and 0.3% of other races. The mean duration of ED was approximately 6.5 years. STENDRA at doses of 50 mg, 100 mg, and 200 mg demonstrated statistically significant improvement in all 3 primary efficacy variables relative to placebo (see Table 7).

Table 7: Mean Change From Baseline for Primary Efficacy Variables in General ED Population (Study 1)

	Placebo (N=155)	**STENDRA 50 mg (N=154)**	**STENDRA 100 mg (N=157)**	**STENDRA 200 mg (N=156)**
IIEF EF Domain Score				
Endpoint	15.3	18.1	20.9	22.2
Change from baseline†	2.9	5.4	8.3	9.5
p-value*		0.0014	<0.0001	<0.0001
Vaginal Penetration (SEP2)				
Endpoint	53.8%	64.3%	73.9%	77.3%
Change from baseline†	7.1%	18.2%	27.2%	29.8%
p-value*	-	0.0009	<0.0001	<0.0001
Successful Intercourse (SEP3)				
Endpoint	27.0%	41.3%	57.1%	57.0%
Change from baseline†	14.1%	27.8%	43.4%	44.2%
p-value*	-	0.0002	<0.0001	<0.0001

† least-square from ANCOVA model * comparison to placebo for change from baseline

Results in the ED Population with Diabetes Mellitus (Study 2)

STENDRA was evaluated in ED patients (n=390) with type 1 or type 2 diabetes mellitus in a randomized, double-blind, parallel, placebo-controlled fixed dose trial of 3 months in duration. The mean age was 58 years (range 30 to 78 years). The population was 80.5% White, 17.2% Black, 1.5% Asian, and 0.8% of other races. The mean duration of ED was approximately 6 years. In this trial, STENDRA at doses of 100 mg and 200 mg demonstrated statistically significant improvement in all 3 primary efficacy variables as measured by the erectile function domain of the IIEF questionnaire; SEP2 and SEP3 (see Table 8).

Table 8: Mean Change From Baseline for Primary Efficacy Variables in ED Population with Diabetes Mellitus (Study 2)

	Placebo (N=127)	STENDRA 100 mg (N=126)	STENDRA 200 mg (N=126)
IIEF EF Domain Score			
Endpoint	13.2	15.8	17.3
Change from baseline†	1.8	4.5	5.4
p-value*	-	0.0017	<0.0001
Vaginal Penetration (SEP2)			
Endpoint	42.0%	54.0%	63.5%
Change from baseline†	7.5%	21.5%	25.9%
p-value*	-	0.0004	<0.0001
Successful Intercourse (SEP3)			
Endpoint	20.5%	34.4%	40.0%
Change from baseline†	13.6%	28.7%	34.0%
p-value*	-	<0.0001	<0.0001

† least-square estimate from ANCOVA model * comparison to placebo for change from baseline

Time to Onset of Effect (Study 3)

STENDRA was evaluated in 440 subjects with ED including diabetics (16.4%) and subjects with severe ED (41.4%) in a randomized double-blind, parallel, placebo-controlled study of 2 months duration. The mean age was 58.2 years (range 24 to 86 years). The population was 75.7% White, 21.4% Black, 1.6% Asian, and 1.4% of other races. Subjects were encouraged to attempt intercourse approximately 15 minutes after dosing and used a stopwatch for measurement of time to onset of effect, defined as the time to the first occurrence of an erection sufficient for sexual intercourse.

STENDRA 100 mg and 200 mg demonstrated statistically significant improvements relative to placebo in the primary efficacy variable, percentage of all attempts resulting in an erection sufficient for penetration at approximately 15 minutes after dosing followed by successful intercourse (SEP3) (see Table 9).

Table 9: Percentage of All Attempts Resulting in an Erection Sufficient for Penetration at Approximately 15 minutes After Dosing Followed by Successful Intercourse (SEP3) During the 8-Week Treatment Period in the Time to Onset of Effect (Study 3)

	Placebo (N=136)	STENDRA 100 mg (N=139)	STENDRA 200 mg (N=139)
Percentage of Successful Intercourse (SEP3)			
Mean	14.9	25.9	29.1
Median	0.0	11.1	13.3
p-value*	-	0.001	<0.001

*comparison to placebo using rank-ANCOVA model.

16 HOW SUPPLIED/STORAGE AND HANDLING

STENDRA (avanafil) is supplied as oval, pale yellow tablets containing 50 mg, 100 mg, or 200 mg avanafil debossed with dosage strengths.

	50 mg	100 mg	200 mg
Bottle of 30	NDC 76299-320-85	NDC 76299-321-85	NDC 76299-322-85
Bottle of 100	NDC 76299-320-88	NDC 76299-321-88	NDC 76299-322-88

Recommended Storage: Store at 20-25°C (68-77°F); excursions permitted to 30°C (86°F) [see USP Controlled Room Temperature].

Protect from light [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

"See FDA-approved patient labeling (Patient Information)"

17.1 Nitrates

Physicians should discuss with patients the contraindication of STENDRA with regular and/or intermittent use of organic nitrates. Patients should be counseled that concomitant use of STENDRA with nitrates could cause blood pressure to suddenly drop to an unsafe level, resulting in dizziness, syncope, or even heart attack or stroke.

Physicians should discuss with patients the appropriate action in the event that they experience anginal chest pain requiring nitroglycerin following intake of STENDRA. In such a patient, who has taken STENDRA, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 12 hours should elapse after the last dose of STENDRA before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring. Patients who experience anginal chest pain after taking STENDRA should seek immediate medical attention *[see Contraindications (4.1) and Warnings and Precautions (5.1)]*.

17.2 Cardiovascular Considerations

Physicians should discuss with patients the potential cardiac risk of sexual activity in patients with preexisting cardiovascular risk factors. Patients who experience symptoms upon initiation of sexual activity should be advised to refrain from further sexual activity and should seek immediate medical attention *[see Warnings and Precautions (5.1)]*.

17.3 Concomitant Use with Drugs Which Lower Blood Pressure

Physicians should advise patients of the potential for STENDRA to augment the blood pressure-lowering effect of alpha-blockers and other antihypertensive medications *[see Warnings and Precautions (5.6), Drug Interactions (7.1), and Clinical Pharmacology (12.2)]*.

17.4 Potential for Drug Interactions

Patients should be advised to contact the prescribing physician if new medications that may interact with STENDRA are prescribed by another healthcare provider.

17.5 Priapism

There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Physicians should advise patients who have an erection lasting greater than 4 hours, whether painful or not, to seek emergency medical attention.

17.6 Vision

Physicians should advise patients to stop use of all PDE5 inhibitors, including STENDRA, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision that has been reported rarely in temporal association with the use of PDE5 inhibitors. Physicians should discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye. Physicians should also discuss with patients the increased

risk of NAION among the general population in patients with a "crowded" optic disc, although evidence is insufficient to support screening of prospective users of PDE5 inhibitor, including STENDRA, for these uncommon conditions [see *Warnings and Precautions (5.4)* and *Postmarketing Experience (6.2)*] .

17.7 Sudden Hearing Loss

Physicians should advise patients to stop taking PDE5 inhibitors, including STENDRA, and seek prompt medical attention in the event of sudden decrease or loss of hearing. Use of PDE5 inhibitors has been associated with sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors *[see Adverse Reactions (6)]*.

17.8 Alcohol

Patients should be made aware that both alcohol and PDE5 inhibitors including STENDRA act as mild vasodilators. When mild vasodilators are taken in combination, blood pressure-lowering effects of each individual compound may be increased. Therefore, physicians should inform patients that substantial consumption of alcohol (e.g., greater than 3 units) in combination with STENDRA can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache. *[see Warnings and Precautions (5.7) and Clinical Pharmacology (12.2)]*.

17.9 Sexually Transmitted Disease

The use of STENDRA offers no protection against sexually transmitted diseases. Counseling of patients about the protective measures necessary to guard against sexually transmitted diseases, including Human Immunodeficiency Virus (HIV) should be considered.

17.10 Recommended Administration

Physicians should discuss with patients the appropriate use of STENDRA and its anticipated benefits. It should be explained that sexual stimulation is required for an erection to occur after taking STENDRA. Patients should be counseled regarding the dosing of STENDRA. Inform patients that the recommended starting dose of STENDRA is 100 mg, taken as early as approximately 15 minutes before initiation sexual activity. Based on efficacy and tolerability, the dose may be increased to 200 mg taken as early as approximately 15 minutes before sexual activity, or decreased to 50 mg taken approximately 30 minutes before sexual activity. The lowest dose that provides benefit should be used. Patients should be advised to contact their healthcare provider for dose modification.

17.11 Guanylate Cyclase (GC) Stimulators

Physicians should discuss with patients the contraindication of STENDRA with use of guanylate cyclase stimulators such as riociguat [see *Contraindications (4.3)*].

Patient Information
STENDRA® (sten-druh)
(avanafil)
Tablets

Read this Patient Information before you start taking STENDRA and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about STENDRA?

STENDRA can cause your blood pressure to drop suddenly to an unsafe level if it is taken with certain other medicines. Do not take STENDRA if you take any medicines called "nitrates." Nitrates are used to treat chest pain (angina). A sudden drop in blood pressure can cause you to feel dizzy, faint, or have a heart attack or stroke.

Do not take STENDRA if you take medicines called guanylate cyclase stimulators which include:

- riociguat (Adempas®) a medicine that treats pulmonary arterial hypertension and chronic-thromboembolic pulmonary hypertension

Ask your healthcare provider or pharmacist if any of your medicines are nitrates or guanylate cyclase stimulators, such as riociguat.

Tell all your healthcare providers that you take STENDRA. If you need emergency medical care for a heart problem, it will be important for your healthcare provider to know when you last took STENDRA.

Stop sexual activity and get medical help right away if you get symptoms such as chest pain, dizziness, or nausea during sex. Sexual activity can put an extra strain on your heart, especially if your heart is already weak from a heart attack or heart disease.

What is STENDRA?

STENDRA is a prescription medicine used to treat erectile dysfunction (ED).

STENDRA is not for use in women or children.

It is not known if STENDRA is safe and effective in women or children under 18 years of age.

Who should not take STENDRA?

Do not take STENDRA if you:

- take medicines called "nitrates"
- use street drugs called "poppers" such as amyl nitrate and butyl nitrate
- are allergic to avanafil or any of the ingredients in STENDRA. See the end of this leaflet for a complete list of ingredients in STENDRA.

What should I tell my healthcare provider before taking STENDRA?

Before you take STENDRA, tell your healthcare provider if you:

- have or have had heart problems such as a heart attack, irregular heartbeat, angina, or heart failure
- have had heart surgery within the last 6 months
- have had a stroke
- have low blood pressure, or high blood pressure that is not controlled
- have a deformed penis shape

- have had an erection that lasted for more than 4 hours
- have problems with your blood cells such as sickle cell anemia, multiple myeloma, or leukemia
- have retinitis pigmentosa, a rare genetic (runs in families) eye disease
- have ever had severe vision loss, including an eye problem called non-arteritic anterior ischemic optic neuropathy (NAION)
- have bleeding problems
- have or have had stomach ulcers
- have liver problems
- have kidney problems or are having kidney dialysis
- have any other medical conditions

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

STENDRA may affect the way other medicines work, and other medicines may affect the way STENDRA works causing side effects. Especially tell your healthcare provider if you take any of the following:

- medicines called nitrates (see **What is the most important information I should know about STENDRA?**)
- medicines called guanylate cyclose stimulators, such a riociguat (see **What is the most important information I should know about STENDRA?)**
- medicines called HIV protease inhibitors, such as ritonavir (Norvir), indinavir (Crixivan), saquinavir (Fortavase or Invirase) or atazanir (Reyataz)
- some types of oral antifungal medicines, such as ketoconazole (Nizoral), and itraconozale (Sporonox)
- some types of antibiotics, such as clarithromycin (Biaxin), telithromycin (Ketek), or erythromycin
- medicines called alpha blockers. These include Hytrin (terazosin), Flomax (tamsulosin HCl), Cardura (doxazosin), Minipress (prazosin HCl), Uroxatral (alfuzosin HCl), Jalyn (dutasteride and tamsulosin HCl), or Rapaflo (silodosin). Alpha-blockers are sometimes prescribed for prostate problems or high blood pressure. In some patients, the use of STENDRA with alpha-blockers can lead to a drop in blood pressure or to fainting.
- other medicines that treat high blood pressure
- other medicines or treatments for ED

Ask your healthcare provider or pharmacist for a list of these medicines, if you are not sure.

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take STENDRA?

- Take STENDRA exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much STENDRA to take and when to take it.
- Take STENDRA 100 mg or 200 mg as early as approximately 15 minutes before sexual activity.
- Take STENDRA 50 mg as early as approximately 30 minutes before sexual activity
- **Do not** take STENDRA more than 1 time a day.
- Your healthcare provider may change your dose if needed.
- You should take the lowest dose of STENDRA that works for you. You and your healthcare provider should decide about the lowest dose of STENDRA that works for you.

- STENDRA may be taken with or without food.
- **Do not** drink too much alcohol when taking STENDRA (for example, 3 glasses of wine, or 3 shots of whiskey). Drinking too much alcohol when taking STENDRA can increase your chances of getting a headache or getting dizzy, increasing your heart rate, or lowering your blood pressure.

What are the possible side effects of STENDRA?

The most common side effects of STENDRA are:

- headache
- flushing
- stuffy or runny nose
- sore throat
- back pain

STENDRA may uncommonly cause:

- **an erection that will not go away (priapism).** If you have an erection that lasts more than 4 hours, get medical help right away.
- **sudden vision loss in 1 or both eyes.** Sudden vision loss in 1 or both eyes can be a sign of a serious eye problem called non-arteritic anterior ischemic optic neuropathy (NAION). It is uncertain whether PDE5 inhibitors directly cause vision loss. Stop taking STENDRA and call your healthcare provider right away if you have sudden vision loss in 1 or both eyes.
- **sudden hearing decrease or hearing loss.** Some people may also have ringing in their ears (tinnitus) or dizziness.

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

These are not all the possible side effects of STENDRA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store STENDRA?

- Store STENDRA at 68°F to 77°F (20°C to 25°C).
- Keep STENDRA out of the light.

Keep STENDRA and all medicines out of the reach of children

General information about the safe and effective use of STENDRA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use STENDRA for a condition for which it was not prescribed. Do not give STENDRA to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about STENDRA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about STENDRA that is written for health professionals.

For more information, go to www.STENDRA.com or call 1-844-458-4887.

What are the ingredients in STENDRA?

Active ingredient: avanafil

Inactive ingredients: mannitol, fumaric acid, hydroxypropylcellulose, low substituted hydroxypropylcellulose, calcium carbonate, magnesium stearate, and ferric oxide yellow

This Patient Information has been approved by the U.S. Food and Drug Administration.

Norvir (ritonavir) is a trademark of Abbott Laboratories
Crixivan (indinavir sulfate) is a trademark of Merck Sharp & Dohme Corp.
Invirase (saquinavir mesylate) is a trademark of Hoffmann-LA Roche, Inc.
Reyataz (atazanavir sulfate) is a trademark of Bristol-Myers Squibb Co.
Biaxin (clarithromycin) is a trademeark of Abbott Laboratories
Ketek (telithromycin) is a trademark of Aventis Pharma S.A.
Nizoral (ketoconazole) is a trademark of Johnson & Johnson
Sporanox (itraconazole) is a trademark of Johnson & Johnson
Hytrin (terazosin HCl) is a trademark of Abbott Laboratories
Flomax (tamsulosin HCl) is a trademark of Yamanouchi Pharmaceutical Co., Ltd.
Cardura (doxazosin mesylate) is a trademark of Pfizer Inc.
Minipress (prazosin HCl) is a trademark of Pfizer Inc.
Uroxatral (alfuzosin HCl) is a trademark of Sanofi Societi Anonyme France
Jalyn (dutasteride and tamsulosin HCl) is a trademark of Glaxo Group Limited
Rapaflo (silodosin) is a trademark of Watson Pharmaceuticals, Inc.

Manufactured for: Mist Pharmaceuticals, LLC, Cranford, NJ 07016
By: Sanofi Winthrope Industrie, Ambares, France;

MIST
PHARMACEUTICALS

US Patent Number: 6,656,935 and 7,501,409

STENDRA is a registered U.S. trademark of Metuchen Pharmaceuticals, LLC.

332F007 / 332F008

EXHIBIT G

FDA *Orange Book* listing for avanafil

Patent and Exclusivity for: N202276

Product 001
AVANAFIL (STENDRA) TABLET 50MG

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested
001	6656935	04/27/2025	DS	DP	U-155	
001	7501409	05/05/2023		DP		

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration

There is no unexpired exclusivity for this product in the Orange Book database.

View a list of all patent use codes (results_patent.cfm)
View a list of all exclusivity codes (results_exclusivity.cfm)

EXHIBIT H

Empower on-line catalog page for avanafil oral tablets

EmpoweRx PHARMACY

FDA 503B REGISTERED

PCAB ACCREDITED Compounding Pharmacy

Drug Catalog

Where We Ship

PRODUCTS

COMPANY

QUALITY

CONTACT US

PRESCRIPTION REFILL

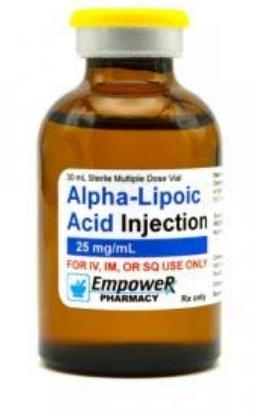
PRESCRIBER LOGIN

Show Filters

Drug Catalog

7-KETO DHEA CAPSULES

ALPHA LIPOIC ACID INJECTION



ANASTROZOLE CAPSULES

ANDRO-BLOCK 2 TOPICAL SOLUTION

ANDRO-BLOCK F TOPICAL SOLUTION

ARGININE / LYSINE CREAM

ASCORBIC ACID INJECTION

AVANAFIL ODT

B-COMPLEX INJECTION

BCAA INJECTION

BIMIX INJECTION

BLT CREAM

EmpoweRx PHARMACY

Drug Catalog

Where We Ship

FDA 503B REGISTERED

PCAB ACCREDITED Compounding Pharmacy

AVANAFIL ODT

Available in Blister Packs of 10

men. Avanafil belongs to the phosphodiesterase type 5 (PDE5) inhibitors drug class, a class of drugs commonly indicated for treatment of erectile dysfunction (ED).[1] PDE5 inhibitors do not inhibit prostaglandins as do some agents for treating impotence (e.g., alprostadil). The safety and efficacy of avanafil was studied in three clinical trials; compared to placebo, improved erections were recorded in patients with organic and/or psychogenic ED when avanafil was administered prior to visual sexual stimulation. Avanafil is taken prior to sexual activity without regard to food. Patients with preexisting cardiovascular disease should discuss the potential cardiac risks associated with sexual activity with their healthcare professional. As with other PDE5 inhibitors, avanafil has systemic vasodilatory proprieties. In clinical evaluation, avanafil (200 mg) reduced the sitting blood pressure of healthy subjects by 8 mmHg systolic and 3.3 mmHg diastolic, with the maximum decrease observed at 1 hour after dosing. Patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity. Avanafil should not be used by men who also take nitrates because the combination can cause a sudden drop in blood pressure that can be dangerous. According

to ED treatment guidelines, oral phosphodiesterase type 5 inhibitors (PDE5 inhibitor) are considered first-line therapy.[2]

Mechanism of Action: Avanafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). The physiologic mechanism of erection of the penis involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. Nitric oxide then activates the enzyme guanylate cyclase, which results in increased levels of cGMP. Cyclic guanosine monophosphate causes smooth muscle relaxation in the corpus cavernosum thereby allowing inflow of blood; the exact mechanism by which cGMP stimulates relaxation of smooth muscles has not been determined. Phosphodiesterase type 5 is responsible for degradation of cGMP in the corpus cavernosum. Avanafil enhances the effect of NO by inhibiting PDE5 thereby raising concentrations of cGMP in the corpus cavernosum. Avanafil has no direct relaxant effect on isolated human corpus cavernosum and, at recommended doses, has no effect in the absence of sexual stimulation.[3]

In vitro studies show that avanafil is selective for PDE5, with a greater effect on PDE5 compared to other known phosphodiesterases (greater than 100-fold for PDE6; greater than 1,000-fold for PDE4, PDE8 and PDE10; greater than 5,000-fold for PDE2 and PDE7; greater than 10,000-fold for PDE1, PDE3, PDE9, and PDE11). Avanafil has a 100-fold greater affinity for PDE5 than PDE6, which is found in the retina and is responsible for phototransduction. PDE5 is also found in other tissues including platelets, vascular and visceral smooth muscle, and skeletal muscle, brain, heart, liver, kidney, lung, pancreas, prostate, bladder, testis, and seminal vesicle. The inhibition of PDE5 in these tissues by avanafil may be the basis for the enhanced platelet anti-aggregatory activity of NO observed in vitro and peripheral vasodilatation in vivo.[3]

Pharmacokinetics: Avanafil is administered orally. The drug is approximately 99% bound to plasma proteins. It is predominately metabolized by hepatic cytochrome P450 (CYP) enzymes. CYP3A4 is the major metabolizing enzyme and CYP2C is a minor one. In vitro, an active metabolite (M4), has been found to have 18% of the inhibitory potency for PDE5 of that of the parent drug and accounts for approximately 4% of the pharmacologic activity of avanafil. Avanafil is excreted as metabolites; approximately 62% and 21% of the dose appears in the feces and urine, respectively. The half-life is approximately 5 hours.[3]

Affected cytochrome P450 isoenzymes and drug transporters: CYP2C2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4

Avanafil has weak inhibitory effects toward CYP2C8, 2C9, 2C19, 2D6, and 3A4 isoforms.

•Route-Specific Pharmacokinetics

Oral Route

Following oral administration, avanafil exhibits a median Tmax of 30 to 45 minutes in the fasted state. A high fat meal reduces avanafil drug exposure, delaying Tmax to 1.12—1.25 hours, reducing Cmax by 24%—39% (depending on dose), and decreasing AUC by approximately 3.8%. These changes are not considered clinically significant, thus, avanafil may be administered without regard to food.[3]

•Special Populations

Hepatic Impairment

The pharmacokinetics of avanafil have been studied in patients with mild and moderate hepatic impairment. Avanafil exposure was similar after a single avanafil (200 mg) dose in normal subjects compared to patients with mild hepatic impairment (Child-Pugh Class A). Avanafil Cmax was approximately 51% lower and AUC was 11% higher in patients with moderate hepatic impairment (Child Pugh Class B) compared to subjects with normal hepatic function; however, dose adjustments are not considered necessary. The pharmacokinetics of avanafil in patients with severe hepatic disease have not been studied, therefore, avanafil should not be used in such patients.[3]

Renal Impairment

The pharmacokinetics of avanafil have been studied in patients with mild and moderate renal impairment. Avanafil exposure was similar after a single avanafil (200 mg) dose in patients with normal subjects compared to patients with mild to moderate renal impairment (CrCl 30—89 mL/min). The pharmacokinetics of avanafil in patients with severe renal disease or on renal dialysis have not been studied; therefore, avanafil should not be used in such patients.[3]

Geriatric

The pharmacokinetics of a single avanafil (200 mg) dose in elderly subjects (65—80 years) was compared to younger adult subjects (18—43 years). Drug exposure was not significantly affected by age in these patients: AUC increased by 6.8% and Cmax decreased by 2.1% in the elderly group, compared to the younger group.[3]

Dosing:
Oral dosage:

Adults: 100 mg PO once daily, approximately 15 minutes before sexual activity. The dose may be increased up to 200 mg PO, approximately 15 minutes before sexual activity or decreased to 50 mg PO, approximately 30 minutes before sexual activity, based on clinical response. Maximum dosing frequency is once daily.[3] PDE5 inhibitors are first line agents for ED according to guidelines. Although associated with high rates of success, approximately 35% of ED patients fail to respond to PDE5 inhibitor therapy. A course of an alternate PDE5 inhibitor may be considered if a patient does not respond to a PDE5 inhibitor trial; a treatment failure may be deemed after at least 4 unsuccessful trials.[4] Patients refractory to PDE5 inhibitors should be counseled on appropriate use, potentially modifiable factors (e.g. hormonal abnormalities, food or drug interactions, lack of adequate sexual stimulation, heavy alcohol use, and the patient's relationship with his partner), and the risks and benefits of other therapies. Second-line treatment options include intracavernous injection and intra-urethral therapy. Follow-up visits for ED patients, regardless of therapy, are necessary to determine whether therapy continues to be effective and whether cardiovascular health has significantly changed.[5]

Adults receiving potent CYP3A4 inhibitors: Do not use avanafil.[3]

Adults receiving moderate CYP3A4 inhibitors (e.g., erythromycin, amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, and verapamil) concomitantly: Do not exceed 50 mg PO once daily, approximately 30 minutes before sexual activity.[3]

Adults receiving alpha-blocker therapy concomitantly: Initiate treatment at lowest dose, 50 mg PO once daily, approximately 30 minutes

before sexual activity. Monitor for dose tolerance, due to potential additive effect on blood pressure. Patients should be stable on alpha-blocker therapy prior to initiating ED treatment.[3]

Maximum Dosage Limits

•Adults

200 mg/day PO; when given with moderate CYP3A4 inhibitors no more than 50 mg/day PO.

•Geriatric

200 mg/day PO; when given with moderate CYP3A4 inhibitors no more than 50 mg/day PO.

•Adolescents

Safety and efficacy have not been established.

•Children

Safety and efficacy have not been established.

•Infants

Safety and efficacy have not been established.

•Neonates

Safety and efficacy have not been established.

Patients with Hepatic Impairment Dosing

Mild to moderate hepatic impairment (Child Pugh Class A or B): No dose adjustments necessary.

Severe hepatic impairment (Child Pugh Class C): No data available; avoid use.

Patients with Renal Impairment Dosing

CrCl 30—89 mL/min: No dose adjustment is necessary for mild to moderate renal impairment.

CrCl < 30 mL/min: No data available; avoid use in patients with severe renal impairment or renal failure.

Contraindications/Precautions: Avanafil is contraindicated in patients who are currently on nitrate/nitrite therapy. Consistent with its known effects on the nitric oxide/cGMP pathway, avanafil may potentiate the hypotensive effects of organic nitrates and nitrites. Patients receiving

nitrates in any form are not to receive avanafil. This includes any patient who receives intermittent nitrate therapies. In a life-threatening situation, nitrate therapy should only be considered if at least 12 hours has elapsed since the last dose of avanafil; medical supervision is warranted.[3]

Avanafil troches are not recommended in patients with severe hepatic disease (Child-Pugh class C) or end stage renal disease requiring dialysis (severe renal impairment or renal failure). There are no controlled clinical studies on the safety and efficacy of avanafil in these patients. Patients with mild to moderate hepatic impairment or mild to moderate renal impairment do not require adjustments in the avanafil dosage. Do not use avanafil if a patient is taking a potent hepatic CYP3A4 inhibitor. The concomitant use of certain moderate hepatic cytochrome P450 3A4 inhibitors may result in a requirement to adjust the avanafil dosage.[3]

Use avanafil cautiously in patients with pre-existing visual disturbance. Post-marketing reports of sudden vision loss have occurred with phosphodiesterase inhibitors. Vision loss is attributed to a condition known as non-arteritic anterior ischemic optic neuropathy (NAION), where blood flow is blocked to the optic nerve. This can cause permanent loss of vision. Avanafil use should be discontinued in the event of sudden loss of vision in one or both eyes. Avanafil use is not recommended in patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa. A minority of patients with the inherited condition retinitis pigmentosa have genetic disorders of retinal phosphodiesterases. Avanafil use is not recommended in these patients until further information is available.[3]

Patients with a sudden decrease or loss of hearing (hearing impairment) should stop taking avanafil and seek prompt medical attention. Hearing loss, which may be accompanied by tinnitus and dizziness, has been reported in temporal association with the intake of PDE5 inhibitors; however, it is unknown if the hearing loss is directly related to PDE5 inhibitors or to other factors.[3]

There is a degree of cardiac risk associated with sexual activity; therefore, prescribers should evaluate the cardiovascular status of their patients prior to initiating any treatment for erectile dysfunction. Health care professionals should consider whether the individual would be adversely affected by vasodilatory events. In particular, avanafil use is not recommended in the following patient groups: patients who have suffered a myocardial infarction, stroke, or life-threatening cardiac arrhythmias in the last 6 months; patients with resting hypotension (BP < 90/50) or resting hypertension (BP > 170/110); patients with cardiac disease, New York Heart Association Class 2 or greater heart failure or coronary artery disease (CAD) which causes unstable angina including those with left ventricular outflow obstruction (e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis). Based on recommendations by the American College of Cardiology for similar medications for ED, it is recommended that avanafil be used with caution in the following: patients with active coronary ischemia who are not taking nitrates (e.g., positive exercise test for ischemia); patients with congestive heart failure and borderline low blood pressure and borderline low volume status; patients on a complicated, multidrug, antihypertensive program; and patients taking drugs that can prolong the half-life of avanafil. Avanafil is contraindicated in patients currently on nitrate/nitrite therapy. In addition, the systemic vasodilatory properties of avanafil may augment the hypotensive effects of other anti-hypertensive medications. In clinical evaluation, avanafil (200 mg) reduced the sitting blood pressure of healthy subjects by 8 mmHg systolic and 3.3 mmHg diastolic, with the maximum decrease observed at 1 hour after dosing. Patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity.[3]

Prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been associated with PDE5 inhibitor administration. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention. Use avanafil, and other agents for the treatment of erectile dysfunction, with caution in patients with penile structural abnormality (such as angulation, cavernosal fibrosis, or

Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell disease, leukemia, multiple myeloma, polycythemia, or history of priapism).[3][6]

Anafanil should be administered to patients with coagulopathy or significant active peptic ulcer disease only after careful benefit vs. risk assessment. In vitro studies with human platelets indicate that anafanil potentiates the anti-aggregatory effect of sodium nitroprusside (a nitric oxide [NO] donor). Anafanil has not been studied or administered to patients with bleeding disorders or significant active peptic ulceration.[3]

Avanafil is not indicated for use in females. Avanafil is classified as FDA pregnancy risk category C. There are no adequate and well-controlled trials of avanafil in humans during pregnancy.[3]

Avanafil is not indicated for use in females and is therefore not recommended during breast-feeding. It is not known if avanafil is excreted in human breast milk.[3]

There is no known indication for the use of avanafil in neonates, infants, or children. Avanafil should not be prescribed to these populations.[3]

How should I use this medicine? Take this medicine by mouth with a glass of water. Follow the directions on the prescription label. The dose is taken 15 to 30 minutes before sexual activity, depending on the dose you are being prescribed. You should not take the dose more than once per day. Do not take your medicine more often than directed.

Talk to your pediatrician regarding the use of this medicine in children. This medicine is not used in children for this condition.

Overdosage: If you think you've taken too much of this medicine contact a poison control center or emergency room at once.
NOTE: This medicine is only for you. Do not share this medicine with others.

What if I miss a dose? This does not apply. Do not take double or extra doses.

What may interact with this medicine? Do not take this medicine with any of the following medications:

- methscopolamine nitrate
- nitrates like amyl nitrite, isosorbide dinitrate, isosorbide mononitrate, nitroglycerin
- other medicines for erectile dysfunction like sildenafil, tadalafil, vardenafil
- riociguat

This medicine may also interact with the following medications:

- carbamazepine
- certain drugs for high blood pressure
- certain drugs for the treatment of HIV infection or AIDS
- certain drugs used for fungal or yeast infections, like fluconazole, itraconazole, ketoconazole, and voriconazole
- grapefruit juice
- macrolide antibiotics like clarithromycin, erythromycin, troleandomycin

- medicines for prostate problems
- phenobarbital
- phenytoin
- rifabutin, rifampin or rifapentine
- St. John's wort

This list may not describe all possible interactions. Give your health care provider a list of all the medicines, herbs, non-prescription drugs, or dietary supplements you use. Also tell them if you smoke, drink alcohol, or use illegal drugs. Some items may interact with your medicine.

What side effects may I notice from receiving this medicine? Side effects that you should report to your doctor or health care professional as soon as possible:

- allergic reactions like skin rash, itching or hives, swelling of the face, lips, or tongue
- breathing problems
- changes in hearing
- changes in vision
- chest pain
- fast, irregular heartbeat
- prolonged or painful erection
- seizures

Adverse Reactions: There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) associated with PDE5 inhibitors, such as avanafil. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention. Additional urogenital related adverse events reported in < 1% of patients receiving avanafil in clinical trials include: balanitis, increased erection, hematuria, nephrolithiasis, urinary urgency or increased urinary frequency, and urinary tract infection; a causal relationship to avanafil use could not be determined.[3]

Avanafil safety was evaluated in 3 placebo-controlled trials. Study patients received avanafil as needed for 3 months at varying doses, 50 mg (n=217), 100 mg (n=349), and 200 mg (n=352). Adverse reactions reported in >= 2% of patients, independent of dose and relative to placebo included: headache 5.1—10.5% vs. 1.7%. Headache was also reported among 5.6% of patients receiving avanafil (n=711) in an open-label extension trial. In an additional placebo-controlled study of men who underwent bilateral nerve-sparing radical prostatectomy, patients received avanafil at varying doses, 100 mg (n=99), and 200 mg (n=99); headache was reported in 8.1—12.1% vs. 1% of patients, independent of dose and relative to placebo. It appears headache may be a dose dependent adverse event; the incidence of headache increased with dose in clinical evaluation. Dizziness was also reported in prostatectomy patients at an incidence of 1—2% vs. 0% relative to placebo and was independent of dose. Additional central nervous system related adverse events reported in less than 1% of patients receiving avanafil in clinical trials include: depression, insomnia, drowsiness (somnolence), and vertigo; a causal relationship to avanafil use could not be determined.[3]

As with other PDE5 inhibitors, avanafil exhibits systemic vasodilatory proprieties and may result in subsequent hypotension. In clinical evaluation, avanafil (200 mg) reduced the sitting blood pressure of healthy subjects by 8 mmHg systolic and 3.3 mmHg diastolic, with the

maximum decrease in blood pressure observed at 1 hour after dosing. In most patients, this reduction in blood pressure is transient and is of little clinical consequence. However, patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity. Additional lowering of blood pressure by 3 to 5 mmHg can be expected when avanafil is combined with antihypertensive therapies. Hypertension was reported in 1—2% of patients in clinical evaluation of avanafil. Additional cardiovascular related adverse events reported in < 1% of patients receiving avanafil in clinical trials included: angina, unstable angina, deep vein thrombosis, and palpitations; a causal relationship to avanafil use could not be determined.[3] Syncope, orthostatic hypotension (decrease in standing blood pressure) and other forms of symptomatic hypotension (e.g., dizziness, lightheadedness) appear more likely occur in patients concomitantly using alpha-blockers or in those patients who consume substantial alcohol during dosing.

Single oral doses of phosphodiesterase type 5 (PDE5) inhibitors have demonstrated transient dose-related impairment of color discrimination (blue/green), using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. Across all trials with any avanafil dose, 1 patient reported a change in color vision. Post-marketing reports with other PDE5 inhibitors have included cases of visual disturbances including retinal vein occlusion, visual field defects, reduced visual acuity, and loss of vision (temporary or permanent). Non-arteritic anterior ischemic optic neuropathy (NAION) has also been reported rarely in patients using phosphodiesterase type 5 (PDE5) inhibitors.[7][8][9][10] It is thought that the vasoconstrictive effect of phosphodiesterase inhibitors may decrease blood flow to the optic nerve, especially in patients with a low cup to disk ratio. Symptoms, such as blurred vision (< 2%) and loss of visual field in one or both eyes, are usually reported within 24 hours of use. Most, but not all, of these patients who reported this adverse effect had underlying anatomic or vascular risk factors for development of NAION. These risk factors include, but are not limited to: low cup to disc ratio ('crowded disc'), age over 50 years, diabetes, high blood pressure, coronary artery disease, hyperlipidemia, and smoking. Additionally, two patients had retinal detachment and one patient had hypoplastic optic neuropathy.[7] It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Patients should be instructed to discontinue avanafil use and seek immediate medical attention if visual impairment including sudden loss of vision occurs in one or both eyes. Such an event may be a sign of NAION. Clinicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of avanafil.[3]

Use of PDE5 inhibitors has been associated with sudden decrease or loss of hearing. Twenty-nine reports of sudden changes in hearing including hearing loss or decrease in hearing, usually in 1 ear only, have been reported to the FDA during post-marketing surveillance in patients taking PDE5 inhibitors such as sildenafil, tadalafil, or vardenafil; the reports are associated with a strong temporal relationship to the dosing of these agents. Many times, the hearing changes are accompanied by vestibular effects including tinnitus and vertigo. Follow-up has been limited in many of the reports; however, in approximately one-third of the patients, the hearing loss was temporary. Concomitant medical conditions or patient factors may play a role, although risk factors for the onset of sudden hearing loss have not been identified. Patients should be instructed to contact their physician if they experience changes in hearing while taking avanafil.[3]

Gastrointestinal (GI) adverse events reported in 1—2% of patients in clinical evaluation of avanafil included: dyspepsia, nausea, constipation, and diarrhea. Other GI adverse events reported in less than 1% of patients receiving avanafil in clinical trials include: gastritis, gastroesophageal reflux disease, elevated hepatic enzymes (increased ALT), oropharyngeal pain, abdominal pain (stomach discomfort), and vomiting; a causal relationship to avanafil use could not be determined.[3]

Miscellaneous adverse events reported in less than 1% of patients receiving avanafil in clinical trials include: peripheral edema, fatigue,

hypoglycemia, and hyperglycemia. A causal relationship to avanafil use could not be determined.[3]

Side effects that usually do not require medical attention (report to your doctor or health care professional if they continue or are bothersome):

- back pain
- dizziness
- flushing
- headache
- indigestion
- muscle aches
- nausea
- stuffy or runny nose

What should I watch for while using this medicine? If you notice any changes in your vision while taking this drug, call your doctor or health care professional as soon as possible. Stop using this medicine and call your health care provider right away if you have a loss of sight in one or both eyes. Contact your doctor or health care professional right away if you have an erection that lasts longer than 4 hours or if it becomes painful. This may be a sign of a serious problem and must be treated right away to prevent permanent damage. If you experience symptoms of nausea, dizziness, chest pain or arm pain upon initiation of sexual activity after taking this medicine, you should refrain from further activity and call your doctor or health care professional as soon as possible. Do not drink alcohol to excess (examples, 5 glasses of wine or 5 shots of whiskey) when taking this medicine. When taken in excess, alcohol can increase your chances of getting a headache or getting dizzy, increasing your heart rate or lowering your blood pressure. Using this medicine does not protect you or your partner against HIV infection (the virus that causes AIDS) or other sexually transmitted diseases.

Where should I keep my medicine? Keep out of the reach of children. Store at room temperature between 20 and 30 degrees C (68 and 86 degrees F). Protect from light. Throw away any unused medicine after the expiration date.

1. Stendra (avanafil) package insert. Mountain View, CA: VIVUS, Inc.; 2014 Sep.
2. Montague DK, Jarow JP, Broderick GA, et al. Chapter 1: The management of erectile dysfunction: an AUA update. J Urol 2005;174:230-9.
3. Stendra (avanafil) package insert. Mountain View, CA: VIVUS, Inc.; 2014 Sep.
4. Shamloul R, Ghanem H. Erectile dysfunction. Lancet 2013;381:153-65.
5. Montague DK, Jarow JP, Broderick GA, et al. Chapter 1: The management of erectile dysfunction: an AUA update. J Urol 2005;174:230-9.
6. Burnett AL, Bivalacqua TJ. Priapism: current principles and practice. Urol Clin N Am 2007;34:631-642.
7. Pomeranz HD, Bhavsar AR. Nonarteritic ischemic optic neuropathy developing soon after use of sildenafil (Viagra): a report of seven new cases. J Neuroophthalmol 2005;25:9-13.
8. Escaravage GK Jr, Wright JD Jr, Givre SJ. Tadalafil associated with anterior ischemic optic neuropathy. Arch Ophthalmol 2005;123(3):399-400.
9. Bollinger K, Lee MS. Recurrent visual field defect and ischemic optic neuropathy associated with tadalafil rechallenge. Arch Ophthalmol 2005;123(3):400-1.
10. Peter NM, Singh MV, Fox PD. Tadalafil-associated anterior ischaemic optic neuropathy. Eye 2005;19(6):715-7.

EXHIBIT I

Empower on-line catalog page for avanafil oral tablets, highlighted portions copied or derived from the copyrighted STENDRA® package insert

AVANAFIL ODT: Fact Sheet - Uses, Side Effects, & Dosage

Pharmacologic Category: Anti-erectile dysfunction agent, phosphodiesterase type 5 (PDE5) inhibitor

What is this medicine? AVANAFIL (ah VA Na fil) is used to treat erection problems in men. Avanafil belongs to the phosphodiesterase type 5 (PDE5) inhibitors drug class, a class of drugs commonly indicated for treatment of erectile dysfunction (ED).1 PDE5 inhibitors do not inhibit prostaglandins as do some agents for treating impotence (e.g., alprostadil). The safety and efficacy of avanafil was studied in three clinical trials; compared to placebo, improved erections were recorded in patients with organic and/or psychogenic ED when avanafil was administered prior to visual sexual stimulation. Avanafil is taken prior to sexual activity without regard to food. Patients with preexisting cardiovascular disease should discuss the potential cardiac risks associated with sexual activity with their healthcare professional. As with other PDE5 inhibitors, avanafil has systemic vasodilatory proprieties. In clinical evaluation, avanafil (200 mg) reduced the sitting blood pressure of healthy subjects by 8 mmHg systolic and 3.3 mmHg diastolic, with the maximum decrease observed at 1 hour after dosing. Patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity. Avanafil should not be used by men who also take nitrates because the combination can cause a sudden drop in blood pressure that can be dangerous. According to ED treatment guidelines, oral phosphodiesterase type 5 inhibitors (PDE5 inhibitor) are considered first-line therapy.2

Mechanism of Action: Avanafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). The physiologic mechanism of erection of the penis involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. Nitric oxide then activates the enzyme guanylate cyclase, which results in increased levels of cGMP. Cyclic guanosine monophosphate causes smooth muscle relaxation in the corpus cavernosum thereby allowing inflow of blood; the exact mechanism by which cGMP stimulates relaxation of smooth muscles has not been determined. Phosphodiesterase type 5 is responsible for degradation of cGMP in the corpus cavernosum. Avanafil enhances the effect of NO by inhibiting PDE5 thereby raising concentrations of cGMP in the corpus cavernosum. Avanafil has no direct relaxant effect on isolated human corpus cavernosum and, at recommended doses, has no effect in the absence of sexual stimulation.3

In vitro studies show that avanafil is selective for PDE5, with a greater effect on PDE5 compared to other known phosphodiesterases (greater than 100-fold for PDE6; greater than 1,000-fold for PDE4, PDE8 and PDE10; greater than 5,000-fold for PDE2 and PDE7; greater than 10,000-fold for PDE1, PDE3, PDE9, and PDE11). Avanafil has a 100-fold greater affinity for PDE5 than PDE6, which is found in the retina and is responsible for phototransduction. PDE5 is also found in other tissues including platelets, vascular and visceral smooth muscle, and skeletal muscle, brain,

heart, liver, kidney, lung, pancreas, prostate, bladder, testis, and seminal vesicle. The inhibition of PDE5 in these tissues by avanafil may be the basis for the enhanced platelet anti-aggregatory activity of NO observed in vitro and peripheral vasodilatation in vivo.3

Pharmacokinetics: Avanafil is administered orally. The drug is approximately 99% bound to plasma proteins. It is predominately metabolized by hepatic cytochrome P450 (CYP) enzymes. CYP3A4 is the major metabolizing enzyme and CYP2C is a minor one. In vitro, an active metabolite (M4), has been found to have 18% of the inhibitory potency for PDE5 of that of the parent drug and accounts for approximately 4% of the pharmacologic activity of avanafil. Avanafil is excreted as metabolites; approximately 62% and 21% of the dose appears in the feces and urine, respectively. The half-life is approximately 5 hours.3

Affected cytochrome P450 isoenzymes and drug transporters: CYP2C2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4

Avanafil has weak inhibitory effects toward CYP2C8, 2C9, 2C19, 2D6, and 3A4 isoforms.

•Route-Specific Pharmacokinetics

Oral Route

Following oral administration, avanafil exhibits a median Tmax of 30 to 45 minutes in the fasted state. A high fat meal reduces avanafil drug exposure, delaying Tmax to 1.12—1.25 hours, reducing Cmax by 24%—39% (depending on dose), and decreasing AUC by approximately 3.8%. These changes are not considered clinically significant, thus, avanafil may be administered without regard to food.3

•Special Populations

Hepatic Impairment

The pharmacokinetics of avanafil have been studied in patients with mild and moderate hepatic impairment. Avanafil exposure was similar after a single avanafil (200 mg) dose in normal subjects compared to patients with mild hepatic impairment (Child-Pugh Class A). Avanafil Cmax was approximately 51% lower and AUC was 11% higher in patients with moderate hepatic impairment (Child Pugh Class B) compared to subjects with normal hepatic function; however, dose adjustments are not considered necessary. The pharmacokinetics of avanafil in patients with severe hepatic disease have not been studied, therefore, avanafil should not be used in such patients.3

Renal Impairment

The pharmacokinetics of avanafil have been studied in patients with mild and moderate renal impairment. Avanafil exposure was similar after a single avanafil (200 mg) dose in patients with normal subjects compared to patients with mild to moderate renal impairment (CrCl 30—89 mL/min). The pharmacokinetics of avanafil in patients with severe renal disease or on renal dialysis have not been studied;

therefore, avanafil should not be used in such patients.3

Geriatric

The pharmacokinetics of a single avanafil (200 mg) dose in elderly subjects (65—80 years) was compared to younger adult subjects (18—43 years). Drug exposure was not significantly affected by age in these patients: AUC increased by 6.8% and Cmax decreased by 2.1% in the elderly group, compared to the younger group.3

Dosing:
Oral dosage:

Adults: 100 mg PO once daily, approximately 15 minutes before sexual activity. The dose may be increased up to 200 mg PO, approximately 15 minutes before sexual activity or decreased to 50 mg PO, approximately 30 minutes before sexual activity, based on clinical response. Maximum dosing frequency is once daily.3 PDE5 inhibitors are first line agents for ED according to guidelines. Although associated with high rates of success, approximately 35% of ED patients fail to respond to PDE5 inhibitor therapy. A course of an alternate PDE5 inhibitor may be considered if a patient does not respond to a PDE5 inhibitor trial; a treatment failure may be deemed after at least 4 unsuccessful trials.4 Patients refractory to PDE5 inhibitors should be counseled on appropriate use, potentially modifiable factors (e.g. hormonal abnormalities, food or drug interactions, lack of adequate sexual stimulation, heavy alcohol use, and the patient's relationship with his partner), and the risks and benefits of other therapies. Second-line treatment options include intracavernous injection and intra-urethral therapy. Follow-up visits for ED patients, regardless of therapy, are necessary to determine whether therapy continues to be effective and whether cardiovascular health has significantly changed.5

Adults receiving potent CYP3A4 inhibitors: Do not use avanafil.3

Adults receiving moderate CYP3A4 inhibitors (e.g., erythromycin, amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, and verapamil) concomitantly: Do not exceed 50 mg PO once daily, approximately 30 minutes before sexual activity.3

Adults receiving alpha-blocker therapy concomitantly: Initiate treatment at lowest dose, 50 mg PO once daily, approximately 30 minutes before sexual activity. Monitor for dose tolerance, due to potential additive effect on blood pressure. Patients should be stable on alpha-blocker therapy prior to initiating ED treatment.3

Maximum Dosage Limits

•Adults

200 mg/day PO; when given with moderate CYP3A4 inhibitors no more than 50 mg/day PO.

•Geriatric

200 mg/day PO; when given with moderate CYP3A4 inhibitors no more than 50 mg/day PO.

•Adolescents

Safety and efficacy have not been established.

•Children

Safety and efficacy have not been established.

•Infants

Safety and efficacy have not been established.

•Neonates

Safety and efficacy have not been established.

Patients with Hepatic Impairment Dosing

Mild to moderate hepatic impairment (Child Pugh Class A or B): No dose adjustments necessary.

Severe hepatic impairment (Child Pugh Class C): No data available; avoid use.

Patients with Renal Impairment Dosing

CrCl 30—89 mL/min: No dose adjustment is necessary for mild to moderate renal impairment.

CrCl < 30 mL/min: No data available; avoid use in patients with severe renal impairment or renal failure.

Contraindications/Precautions: Avanafil is contraindicated in patients who are currently on nitrate/nitrite therapy. Consistent with its known effects on the nitric oxide/cGMP pathway, avanafil may potentiate the hypotensive effects of organic nitrates and nitrites. Patients receiving nitrates in any form are not to receive avanafil. This includes any patient who receives intermittent nitrate therapies. In a life-threatening situation, nitrate therapy should only be considered if at least 12 hours has elapsed since the last dose of avanafil; medical supervision is warranted.3

Avanafil troches are not recommended in patients with severe hepatic disease (Child-Pugh class C) or end stage renal disease requiring dialysis (severe renal impairment or renal failure). There are no controlled clinical studies on the safety and efficacy of avanafil in these patients. Patients with mild to moderate hepatic impairment or mild to moderate renal impairment do not require adjustments in the avanafil dosage. Do not use avanafil if a patient is taking a potent hepatic CYP3A4 inhibitor. The concomitant use of certain moderate hepatic cytochrome P450 3A4 inhibitors may result in a requirement to adjust the avanafil dosage.3

Use avanafil cautiously in patients with pre-existing visual disturbance. Post-marketing reports of sudden vision loss have occurred with phosphodiesterase inhibitors. Vision loss is attributed to a condition known as non-arteritic anterior ischemic optic neuropathy (NAION), where blood flow is blocked to the optic nerve.

This can cause permanent loss of vision. Avanafil use should be discontinued in the event of sudden loss of vision in one or both eyes. Avanafil use is not recommended in patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa. A minority of patients with the inherited condition retinitis pigmentosa have genetic disorders of retinal phosphodiesterases. Avanafil use is not recommended in these patients until further information is available.3

Patients with a sudden decrease or loss of hearing (hearing impairment) should stop taking avanafil and seek prompt medical attention. Hearing loss, which may be accompanied by tinnitus and dizziness, has been reported in temporal association with the intake of PDE5 inhibitors; however, it is unknown if the hearing loss is directly related to PDE5 inhibitors or to other factors.3

There is a degree of cardiac risk associated with sexual activity; therefore, prescribers should evaluate the cardiovascular status of their patients prior to initiating any treatment for erectile dysfunction. Health care professionals should consider whether the individual would be adversely affected by vasodilatory events. In particular, avanafil use is not recommended in the following patient groups: patients who have suffered a myocardial infarction, stroke, or life-threatening cardiac arrhythmias in the last 6 months; patients with resting hypotension (BP < 90/50) or resting hypertension (BP > 170/110); patients with cardiac disease, New York Heart Association Class 2 or greater heart failure or coronary artery disease (CAD) which causes unstable angina including those with left ventricular outflow obstruction (e.g., aortic stenosis and idiopathic hypertrophic subaortic stenosis). Based on recommendations by the American College of Cardiology for similar medications for ED, it is recommended that avanafil be used with caution in the following: patients with active coronary ischemia who are not taking nitrates (e.g., positive exercise test for ischemia); patients with congestive heart failure and borderline low blood pressure and borderline low volume status; patients on a complicated, multidrug, antihypertensive program; and patients taking drugs that can prolong the half-life of avanafil. Avanafil is contraindicated in patients currently on nitrate/nitrite therapy. In addition, the systemic vasodilatory properties of avanafil may augment the hypotensive effects of other anti-hypertensive medications. In clinical evaluation, avanafil (200 mg) reduced the sitting blood pressure of healthy subjects by 8 mmHg systolic and 3.3 mmHg diastolic, with the maximum decrease observed at 1 hour after dosing. Patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity.3

Prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been associated with PDE5 inhibitor administration. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention. Use avanafil, and other agents for the treatment of erectile dysfunction, with caution in patients with penile structural abnormality (such as angulation, cavernosal fibrosis, or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell disease, leukemia, multiple myeloma, polycythemia, or history of priapism).36

Anafanil should be administered to patients with coagulopathy or significant active peptic ulcer disease only after careful benefit vs. risk assessment. In vitro studies with

human platelets indicate that anafanil potentiates the anti-aggregatory effect of sodium nitroprusside (a nitric oxide [NO] donor). Anafanil has not been studied or administered to patients with bleeding disorders or significant active peptic ulceration.3

Avanafil is not indicated for use in females. Avanafil is classified as FDA pregnancy risk category C. There are no adequate and well-controlled trials of avanafil in humans during pregnancy.3

Avanafil is not indicated for use in females and is therefore not recommended during breast-feeding. It is not known if avanafil is excreted in human breast milk.3

There is no known indication for the use of avanafil in neonates, infants, or children. Avanafil should not be prescribed to these populations.3

How should I use this medicine? Take this medicine by mouth with a glass of water. Follow the directions on the prescription label. The dose is taken 15 to 30 minutes before sexual activity, depending on the dose you are being prescribed. You should not take the dose more than once per day. Do not take your medicine more often than directed.

Talk to your pediatrician regarding the use of this medicine in children. This medicine is not used in children for this condition.

Overdosage: If you think you've taken too much of this medicine contact a poison control center or emergency room at once.

NOTE: This medicine is only for you. Do not share this medicine with others.

What if I miss a dose? This does not apply. Do not take double or extra doses.

What may interact with this medicine? Do not take this medicine with any of the following medications:

- methscopolamine nitrate
- nitrates like amyl nitrite, isosorbide dinitrate, isosorbide mononitrate, nitroglycerin
- other medicines for erectile dysfunction like sildenafil, tadalafil, vardenafil
- riociguat

This medicine may also interact with the following medications:

- carbamazepine
- certain drugs for high blood pressure
- certain drugs for the treatment of HIV infection or AIDS
- certain drugs used for fungal or yeast infections, like fluconazole, itraconazole, ketoconazole, and voriconazole
- grapefruit juice
- macrolide antibiotics like clarithromycin, erythromycin, troleandomycin
- medicines for prostate problems

- phenobarbital
- phenytoin
- rifabutin, rifampin or rifapentine
- St. John's wort

This list may not describe all possible interactions. Give your health care provider a list of all the medicines, herbs, non-prescription drugs, or dietary supplements you use. Also tell them if you smoke, drink alcohol, or use illegal drugs. Some items may interact with your medicine.

What side effects may I notice from receiving this medicine? Side effects that you should report to your doctor or health care professional as soon as possible:

- allergic reactions like skin rash, itching or hives, swelling of the face, lips, or tongue
- breathing problems
- changes in hearing
- changes in vision
- chest pain
- fast, irregular heartbeat
- prolonged or painful erection
- seizures

Adverse Reactions: There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) associated with PDE5 inhibitors, such as avanafil. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention. Additional urogenital related adverse events reported in < 1% of patients receiving avanafil in clinical trials include: balanitis, increased erection, hematuria, nephrolithiasis, urinary urgency or increased urinary frequency, and urinary tract infection; a causal relationship to avanafil use could not be determined.3

Avanafil safety was evaluated in 3 placebo-controlled trials. Study patients received avanafil as needed for 3 months at varying doses, 50 mg (n=217), 100 mg (n=349), and 200 mg (n=352). Adverse reactions reported in >= 2% of patients, independent of dose and relative to placebo included: headache 5.1—10.5% vs. 1.7%. Headache was also reported among 5.6% of patients receiving avanafil (n=711) in an open-label extension trial. In an additional placebo-controlled study of men who underwent bilateral nerve-sparing radical prostatectomy, patients received avanafil at varying doses, 100 mg (n=99), and 200 mg (n=99); headache was reported in 8.1—12.1% vs. 1% of patients, independent of dose and relative to placebo. It appears headache may be a dose dependent adverse event; the incidence of headache increased with dose in clinical evaluation. Dizziness was also reported in prostatectomy patients at an incidence of 1—2% vs. 0% relative to placebo and was independent of dose. Additional central nervous system related adverse events reported in less than 1% of patients receiving avanafil in clinical trials include: depression, insomnia, drowsiness (somnolence), and vertigo; a causal relationship to avanafil use could not be determined.3

As with other PDE5 inhibitors, avanafil exhibits systemic vasodilatory proprieties and may result in subsequent hypotension. In clinical evaluation, avanafil (200 mg) reduced the sitting blood pressure of healthy subjects by 8 mmHg systolic and 3.3 mmHg diastolic, with the maximum decrease in blood pressure observed at 1 hour after dosing. In most patients, this reduction in blood pressure is transient and is of little clinical consequence. However, patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity. Additional lowering of blood pressure by 3 to 5 mmHg can be expected when avanafil is combined with antihypertensive therapies. Hypertension was reported in 1—2% of patients in clinical evaluation of avanafil. Additional cardiovascular related adverse events reported in < 1% of patients receiving avanafil in clinical trials included: angina, unstable angina, deep vein thrombosis, and palpitations; a causal relationship to avanafil use could not be determined.3 Syncope, orthostatic hypotension (decrease in standing blood pressure) and other forms of symptomatic hypotension (e.g., dizziness, lightheadedness) appear more likely occur in patients concomitantly using alpha-blockers or in those patients who consume substantial alcohol during dosing.

Single oral doses of phosphodiesterase type 5 (PDE5) inhibitors have demonstrated transient dose-related impairment of color discrimination (blue/green), using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. Across all trials with any avanafil dose, 1 patient reported a change in color vision. Post-marketing reports with other PDE5 inhibitors have included cases of visual disturbances including retinal vein occlusion, visual field defects, reduced visual acuity, and loss of vision (temporary or permanent). Non-arteritic anterior ischemic optic neuropathy (NAION) has also been reported rarely in patients using phosphodiesterase type 5 (PDE5) inhibitors.78910 It is thought that the vasoconstrictive effect of phosphodiesterase inhibitors may decrease blood flow to the optic nerve, especially in patients with a low cup to disk ratio. Symptoms, such as blurred vision (< 2%) and loss of visual field in one or both eyes, are usually reported within 24 hours of use. Most, but not all, of these patients who reported this adverse effect had underlying anatomic or vascular risk factors for development of NAION. These risk factors include, but are not limited to: low cup to disc ratio ('crowded disc'), age over 50 years, diabetes, high blood pressure, coronary artery disease, hyperlipidemia, and smoking. Additionally, two patients had retinal detachment and one patient had hypoplastic optic neuropathy.7 It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Patients should be instructed to discontinue avanafil use and seek immediate medical attention if visual impairment including sudden loss of vision occurs in one or both eyes. Such an event may be a sign of NAION. Clinicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of avanafil.3

Use of PDE5 inhibitors has been associated with sudden decrease or loss of hearing. Twenty-nine reports of sudden changes in hearing including hearing loss or decrease in hearing, usually in 1 ear only, have been reported to the FDA during post-marketing surveillance in patients taking PDE5 inhibitors such as sildenafil, tadalafil, or vardenafil; the reports are associated with a strong temporal relationship to the

dosing of these agents. Many times, the hearing changes are accompanied by vestibular effects including tinnitus and vertigo. Follow-up has been limited in many of the reports; however, in approximately one-third of the patients, the hearing loss was temporary. Concomitant medical conditions or patient factors may play a role, although risk factors for the onset of sudden hearing loss have not been identified. Patients should be instructed to contact their physician if they experience changes in hearing while taking avanafil.3

Gastrointestinal (GI) adverse events reported in 1—2% of patients in clinical evaluation of avanafil included: dyspepsia, nausea, constipation, and diarrhea. Other GI adverse events reported in less than 1% of patients receiving avanafil in clinical trials include: gastritis, gastroesophageal reflux disease, elevated hepatic enzymes (increased ALT), oropharyngeal pain, abdominal pain (stomach discomfort), and vomiting; a causal relationship to avanafil use could not be determined.3

Miscellaneous adverse events reported in less than 1% of patients receiving avanafil in clinical trials include: peripheral edema, fatigue, hypoglycemia, and hyperglycemia. A causal relationship to avanafil use could not be determined.3

Side effects that usually do not require medical attention (report to your doctor or health care professional if they continue or are bothersome):

- back pain
- dizziness
- flushing
- headache
- indigestion
- muscle aches
- nausea
- stuffy or runny nose

What should I watch for while using this medicine? If you notice any changes in your vision while taking this drug, call your doctor or health care professional as soon as possible. Stop using this medicine and call your health care provider right away if you have a loss of sight in one or both eyes. Contact your doctor or health care professional right away if you have an erection that lasts longer than 4 hours or if it becomes painful. This may be a sign of a serious problem and must be treated right away to prevent permanent damage. If you experience symptoms of nausea, dizziness, chest pain or arm pain upon initiation of sexual activity after taking this medicine, you should refrain from further activity and call your doctor or health care professional as soon as possible. Do not drink alcohol to excess (examples, 5 glasses of wine or 5 shots of whiskey) when taking this medicine. When taken in excess, alcohol can increase your chances of getting a headache or getting dizzy, increasing your heart rate or lowering your blood pressure. Using this medicine does not protect you or your partner against HIV infection (the virus that causes AIDS) or other sexually transmitted diseases.

Where should I keep my medicine? Keep out of the reach of children. Store at room temperature between 20 and 30 degrees C (68 and 86 degrees F). Protect from light. Throw away any unused medicine after the expiration date.

EXHIBIT J

Empower hard-copy catalog pages

Urology Product Catalog

EmpoweR PHARMACY

empowerpharmacy.com

5980 W Sam Houston Pkwy N, Suite 300
Houston, TX 77041

832.678.4417 Phone
832.678.4419 Fax
877.562.8577 Toll Free

Hours: M-F 8:30am - 5:30pm CT
Sat 8:30am - 1:30pm CT

Capsules & Tablets

PRODUCT NAME	STRENGTH	SIZE	PRICE
Anastrozole	0.125 mg	Each	$0.70
	0.25 mg	Each	$0.75
	0.5 mg	Each	$0.80
	0.75 mg	Each	$1.00
	1 mg	Each	$1.50
Armour Thyroid	0.5 Grain	Each	Market
	1 Grain	Each	Market
	1.5 Grain	Each	Market
	2 Grain	Each	Market
	3 Grain	Each	Market
Biotin / Finasteride	5/1 mg	Each	$1.50
Cabergoline	0.5 mg	Each	Market
Cialis	5 mg	Each	Market
	20 mg	Each	Market
Clomiphene Citrate	12.5 mg	Each	$1.50
	25 mg	Each	$1.70
	50 mg	Each	$2.00
Danazol	25 mg	Each	$1.75
	75 mg	Each	$2.00
Desiccated Thyroid	15 mg	Each	$0.50
	30 mg	Each	$0.50
	45 mg	Each	$0.55
	60 mg	Each	$0.65
	90 mg	Each	$0.85
	120 mg	Each	$1.05
DHEA (IR / SR)	5 mg	Each	$0.50
	10 mg	Each	$0.50
	25 mg	Each	$0.65
	50 mg	Each	$0.75
	100 mg	Each	$0.90
Finasteride	1 mg	Each	Market
	5 mg	Each	Market
Ibutamoren Mesylate	12.5 mg	Each	$3.04
	25 mg	Each	$4.83
Letrozole	2.5 mg	Each	$1.00
Levitra	20 mg	Each	Market
Oxandrolone	5 mg	Each	$1.00
	15 mg	Each	$1.00
	25 mg	Each	$1.00
	50 mg	Each	$1.00

Capsules & Tablets

PRODUCT NAME	STRENGTH	SIZE	PRICE
Sildenafil SR	36 mg	Each	$2.00
	75 mg	Each	$3.00
	110 mg	Each	$4.50
Sildenafil / Tadalafil	55/12.5 mg	Each	$3.83
Tadalafil SR	3 mg	Each	$1.35
	7 mg	Each	$2.35
	12 mg	Each	$3.50
	25 mg	Each	$5.00
Tamoxifen Citrate	10 mg	Each	$1.00
	20 mg	Each	$1.50
Viagra	100 mg	Each	Market
Yohimbine HCl	5.4 mg	Each	$1.25

Orally Disintegrating Tablets

PRODUCT NAME	STRENGTH	SIZE	PRICE
Avanafil	250 mg	Each	$5.50
Sildenafil	125 mg	Each	$5.50
Tadalafil	25 mg	Each	$5.50
Vardenafil	25 mg	Each	$5.50

Troches

PRODUCT NAME	STRENGTH	SIZE	PRICE
Avanafil	200 mg	Each	$6.10
Oxytocin	50 IU	Each	$2.70
Sildenafil	50 mg	Each	$4.30
	100 mg	Each	$6.10
Sildenafil / Testosterone Troche (Low Dose-Women)	20/20 mg	Each	$8.00
Sildenafil / Testosterone Troche (Men)	100/100 mg	Each	$12.00
Tadalafil	10 mg	Each	$4.30
	20 mg	Each	$6.10
Vardenafil	10 mg	Each	$4.30
	20 mg	Each	$6.10

EXHIBIT K

Plaintiff's cease and desist request

PHARMACEUTICAL PATENT ATTORNEYS, LLC
www.LicensingLaw.Net

55 Madison Avenue, 4th floor
Morristown, NJ 07960-7397 USA

Practice limited to Domestic & International
Pharmaceutical Patent law

01 June 2018

Mr. Shaun NOORIAN, Owner
Empower Rx Pharmaceuticals LLC
5980 Sam Houston Parkway N, Suite 300
Houston, TX 77041 USA
BY PRIORITY MAIL

Re: Avanafil 200 mg oral disintegrating tablets and troches
United States Letters Patent No. 6656935

Dear Shaun,

Congratulations on building a successful business. I write to ask your help to resolve an issue. Your *Urology Product Catalog* (copy attached) offers for sale avanafil. Avanafil, however, is patented. *See* United States Letters Patent No. 6656935 (copy attached). Selling avanafil infringes this patent.

Pharmaceutical patent litigation can easily cost you over five million dollars in legal fees. To avoid this expense, within seven (7) calendar days of receipt of this letter:

1. Confirm in writing that you no longer offer avanafil for sale.
2. Confirm in writing that you have removed avanafil products from your catalog, and provide a copy of your corrected catalog showing this.
3. Provide complete formulations for each of the captioned finished dosage forms.
4. Turn over all of your remaining inventory of avanafil (both as API and compounded into finished dosage form).
5. Provide records of each of your purchases of avanafil API, showing the dates, quantities and source of this API.
6. Provide an accounting of all of your sales of avanafil, showing the dates, quantities, prices, dosage forms and location (city and state) of the purchaser.

As an aside, before launching new products in the future, it might be useful for you to first review the FDA's *Orange Book* to see whether the product might be patented. The *Orange Book*, for example, lists the captioned patent. Reviewing the *Orange Book* before selling avanafil could have spared you this potentially-expensive legal headache.

If you have any questions, please let me know. I look forward to hearing from you within seven days.

Sincerely,

PHARMACEUTICAL PATENT ATTORNEYS, LLC

Mark Pohl, Esq.
☎ +1 (973) 984-6159 x304
✉ Mark.Pohl@LicensingLaw.Net

Enclosures
United States Letters Patent No. 6656935

Cc: Greg FORD
Regina MIRRA
Ms. Vi LI, Managing Member, Empower Rx Pharmacy LLC, 20018 Cypresswood Lake Drive, Spring, TX 77373 USA

EXHIBIT L

QSYMIA® (phentermine and topiramate) package insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use QSYMIA® safely and effectively. See full prescribing information for QSYMIA.

QSYMIA (phentermine and topiramate extended-release) capsules, for oral use, CIV
Initial U.S. Approval: 2012

----------INDICATIONS AND USAGE----------

Qsymia is a combination of phentermine, a sympathomimetic amine anorectic, and topiramate extended-release, an antiepileptic drug, indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obese) (1) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia (1)

Limitations of Use:

- The effect of Qsymia on cardiovascular morbidity and mortality has not been established (1).
- The safety and effectiveness of Qsymia in combination with other products intended for weight loss, including prescription and over-the-counter drugs, and herbal preparations, have not been established (1).

----------DOSAGE AND ADMINISTRATION----------

- Take once daily in morning. Avoid evening dose to prevent insomnia (2.1).
- Recommended dose: Qsymia 3.75 mg/23 mg (phentermine 3.75 mg/topiramate 23 mg extended-release) daily for 14 days; then increase to 7.5 mg/46 mg daily (2.1).
- Discontinue or escalate dose (as described) if 3% weight loss is not achieved after 12 weeks on 7.5 mg/46 mg dose (2.1).
- Discontinue Qsymia if 5% weight loss is not achieved after 12 weeks on maximum daily dose of 15 mg/92 mg (2.1).
- Discontinue 15 mg/92 mg dose gradually (as described) to prevent possible seizure (2.1).
- Do not exceed 7.5 mg/46 mg dose for patients with moderate or severe renal impairment or patients with moderate hepatic impairment (2.2, 2.3).

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: (phentermine mg/topiramate mg extended-release)

- 3.75 mg/23 mg (3)
- 7.5 mg/46 mg (3)
- 11.25 mg/69 mg (3)
- 15 mg/92 mg (3)

----------CONTRAINDICATIONS----------

- Pregnancy (4)
- Glaucoma (4)
- Hyperthyroidism (4)
- During or within 14 days of taking monoamine oxidase inhibitors (4)
- Known hypersensitivity or idiosyncrasy to sympathomimetic amines (4)

----------WARNINGS AND PRECAUTIONS----------

- Fetal Toxicity: Females of reproductive potential: Obtain negative pregnancy test before treatment and monthly thereafter; use effective contraception. Qsymia is available through a limited program under a Risk Evaluation and Mitigation Strategy (REMS) (5.1).
- Increase in Heart Rate: Monitor heart rate in all patients, especially those with cardiac or cerebrovascular disease (5.2).
- Suicidal Behavior and Ideation: Monitor for depression or suicidal thoughts. Discontinue Qsymia if symptoms develop (5.3).
- Acute Myopia and Secondary Angle Closure Glaucoma: Discontinue Qsymia (5.4).
- Mood and Sleep Disorders: Consider dose reduction or withdrawal for clinically significant or persistent symptoms (5.5).
- Cognitive Impairment: May cause disturbances in attention or memory. Caution patients about operating automobiles or hazardous machinery when starting treatment (5.6).
- Metabolic Acidosis: Measure electrolytes before/during treatment (5.7).
- Elevated Creatinine: Measure creatinine before/during treatment (5.8).
- Use of Antidiabetic Medications: Weight loss may cause hypoglycemia. Measure serum glucose before/during treatment (5.9).

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence greater than or equal to 5% and at a rate at least 1.5 times placebo) are: paraesthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact VIVUS, Inc., at 1-888-998-4887 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Oral contraceptives: Altered exposure may cause irregular bleeding but not increased risk of pregnancy. Advise patients not to discontinue oral contraceptives if spotting occurs (7.2).
- CNS depressants including alcohol: Potentiate CNS depressant effects. Avoid concomitant use of alcohol (7.3).
- Non-potassium sparing diuretics: May potentiate hypokalemia. Measure potassium before/during treatment (7.4).

----------USE IN SPECIFIC POPULATIONS----------

- Nursing Mothers: Discontinue drug or nursing (8.3).
- Pediatric Use: Safety and effectiveness not established and use not recommended (8.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 03/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Qsymia is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of

- 30 kg/m^2 or greater (obese), or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia

Limitations of Use

- The effect of Qsymia on cardiovascular morbidity and mortality has not been established.
- The safety and effectiveness of Qsymia in combination with other products intended for weight loss, including prescription and over-the-counter drugs and herbal preparations have not been established.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing and Administration

Determine the patient's BMI. BMI is calculated by dividing weight (in kilograms) by height (in meters) squared. A BMI conversion chart (Table 1) based on height [inches (in) or centimeters (cm)] and weight [pounds (lb) or kilograms (kg)] is provided below.

Table 1. BMI Conversion Chart

Weight	(lb)	125	130	135	140	145	150	155	160	165	170	175	180	185	190	195	200	205	210	215	220	225
	(kg)	56. 8	59. 1	61. 4	63. 6	65. 9	68. 2	70. 5	72. 7	75. 0	77. 3	79. 5	81. 8	84. 1	86. 4	88. 6	90. 9	93. 2	95. 5	97. 7	100. 0	102. 3
Height																						
(in)	(cm)																					
58	147. 3	26	27	28	29	30	31	32	34	35	36	37	38	39	40	41	42	43	44	45	46	47
59	149. 9	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	43	44	45	46
60	152. 4	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
61	154. 9	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43
62	157. 5	23	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	38	38	39	40	41
63	160. 0	22	23	24	25	26	27	28	28	29	30	31	32	33	34	35	36	36	37	38	39	40
64	162. 6	22	22	23	24	25	26	27	28	28	29	30	31	32	33	34	34	35	36	37	38	39
65	165. 1	21	22	23	23	24	25	26	27	28	28	29	30	31	32	33	33	34	35	36	37	38
66	167. 6	20	21	22	23	23	24	25	26	27	27	28	29	30	31	32	32	33	34	35	36	36
67	170. 2	20	20	21	22	23	24	24	25	26	27	27	28	29	30	31	31	32	33	34	35	35
68	172. 7	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32	33	34	34
69	175. 3	18	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32	33	33
70	177. 8	18	19	19	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31	32	32
71	180. 3	17	18	19	20	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31	31
72	182. 9	17	18	18	19	20	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31
73	185. 4	17	17	18	19	19	20	20	21	22	22	23	24	24	25	26	26	27	28	28	29	30
74	188. 0	16	17	17	18	19	19	20	21	21	22	23	23	24	24	25	26	26	27	28	28	29
75	190. 5	16	16	17	18	18	19	19	20	21	21	22	23	23	24	24	25	26	26	27	28	28
76	193. 0	15	16	16	17	18	18	19	20	20	21	21	22	23	23	24	24	25	26	26	27	27

In adults with an initial BMI of 30 kg/m2 or greater or 27 kg/m2 or greater when accompanied by weight-related co-morbidities such as hypertension, type 2 diabetes mellitus, or dyslipidemia prescribe Qsymia as follows:

- Take Qsymia once daily in the morning with or without food. Avoid dosing with Qsymia in the evening due to the possibility of insomnia.
- Start treatment with Qsymia 3.75 mg/23 mg (phentermine 3.75 mg/topiramate 23 mg extended-release) daily for 14 days; after 14 days increase to the recommended dose of Qsymia 7.5 mg/46 mg (phentermine 7.5 mg/topiramate 46 mg extended-release) once daily.
- Evaluate weight loss after 12 weeks of treatment with Qsymia 7.5 mg/46 mg.

  If a patient has not lost at least 3% of baseline body weight on Qsymia 7.5 mg/46 mg, discontinue Qsymia or escalate the dose, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss at the Qsymia 7.5 mg/46 mg dose.

  To escalate the dose: Increase to Qsymia 11.25 mg/69 mg (phentermine 11.25 mg/topiramate 69 mg extended-release) daily for 14 days; followed by dosing Qsymia 15 mg/92 mg (phentermine 15 mg/topiramate 92 mg extended-release) once daily.
- Evaluate weight loss following dose escalation to Qsymia 15 mg/92 mg after an additional 12 weeks of treatment.

  If a patient has not lost at least 5% of baseline body weight on Qsymia 15 mg/92 mg, discontinue Qsymia as directed, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.
- Qsymia 3.75 mg/23 mg and Qsymia 11.25 mg/69 mg are for titration purposes only.

Discontinuing Qsymia

- Discontinue Qsymia 15 mg/92 mg gradually by taking a dose every other day for at least 1 week prior to stopping treatment altogether, due to the possibility of precipitating a seizure *[see Warnings and Precautions (5.12)]*.

2.2 Dosing in Patients with Renal Impairment

In patients with moderate (creatinine clearance [CrCl] greater than or equal to 30 and less than 50 mL/min) or severe (CrCl less than 30 mL/min) renal impairment dosing should not exceed Qsymia 7.5 mg/46 mg once daily. Renal impairment is determined by calculating CrCl using the Cockcroft-Gault equation with actual body weight *[see Warnings and Precautions (5.13) and Clinical Pharmacology (12.3)]*.

2.3 Dosing in Patients with Hepatic Impairment

In patients with moderate hepatic impairment (Child-Pugh score 7 - 9), dosing should not exceed Qsymia 7.5 mg/46 mg once daily [see *Warnings and Precautions (5.14)* and *Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

Qsymia capsules are formulated in the following four strength combinations (phentermine mg/topiramate mg extended-release):

- 3.75 mg/23 mg [Purple cap imprinted with VIVUS, Purple body imprinted with 3.75/23]
- 7.5 mg/46 mg [Purple cap imprinted with VIVUS, Yellow body imprinted with 7.5/46]
- 11.25 mg/69 mg [Yellow cap imprinted with VIVUS, Yellow body imprinted with 11.25/69]

- 15 mg/92 mg [Yellow cap imprinted with VIVUS, White body imprinted with 15/92]

4 CONTRAINDICATIONS

Qsymia is contraindicated in the following conditions:

- Pregnancy *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*
- Glaucoma *[see Warnings and Precautions (5.4)]*
- Hyperthyroidism
- During or within 14 days following the administration of monoamine oxidase inhibitors *[see Drug Interactions (7.1)]*
- Known hypersensitivity or idiosyncrasy to the sympathomimetic amines *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

Qsymia can cause fetal harm. Data from pregnancy registries and epidemiology studies indicate that a fetus exposed to topiramate, a component of Qsymia, in the first trimester of pregnancy has an increased risk of oral clefts (cleft lip with or without cleft palate). If Qsymia is used during pregnancy or if a patient becomes pregnant while taking Qsymia, treatment should be discontinued immediately, and the patient should be apprised of the potential hazard to a fetus. Females of reproductive potential should have a negative pregnancy test before starting Qsymia and monthly thereafter during Qsymia therapy. Females of reproductive potential should use effective contraception during Qsymia therapy *[see Use in Specific Populations (8.1) and (8.6)]*.

Qsymia Risk Evaluation and Mitigation Strategy (REMS)
Because of the teratogenic risk associated with Qsymia therapy, Qsymia is available through a limited program under the REMS. Under the Qsymia REMS, only certified pharmacies may distribute Qsymia. Further information, is available at www.QsymiaREMS.com or by telephone at 1-888-998-4887.

5.2 Increase in Heart Rate

Qsymia can cause an increase in resting heart rate.

A higher percentage of Qsymia-treated overweight and obese adults experienced heart rate increases from baseline of more than 5, 10, 15, and 20 beats per minute (bpm) compared to placebo-treated overweight and obese adults. Table 2 provides the numbers and percentages of patients with elevations in heart rate in clinical studies of up to one year.

Table 2. Number and Percentage of Patients with an Increase in Heart Rate at a Single Time Point from Baseline

	Placebo N=1561 n (%)	Qsymia 3.75 mg/23 mg N=240 n (%)	Qsymia 7.5 mg/46 mg N=498 n (%)	Qsymia 15 mg/92 mg N=1580 n (%)
Greater than 5 bpm	1021 (65.4)	168 (70.0)	372 (74.7)	1228 (77.7)
Greater than 10 bpm	657 (42.1)	120 (50.0)	251 (50.4)	887 (56.1)
Greater than 15 bpm	410 (26.3)	79 (32.9)	165 (33.1)	590 (37.3)
Greater than 20 bpm	186 (11.9)	36 (15.0)	67 (13.5)	309 (19.6)

The clinical significance of a heart rate elevation with Qsymia treatment is unclear, especially for patients with cardiac and cerebrovascular disease (such as patients with a history of myocardial infarction or stroke in the previous 6 months, life-threatening arrhythmias, or congestive heart failure).

Regular measurement of resting heart rate is recommended for all patients taking Qsymia, especially patients with cardiac or cerebrovascular disease or when initiating or increasing the dose of Qsymia. Qsymia has not been studied in patients with recent or unstable cardiac or cerebrovascular disease and therefore use is not recommended.

Patients should inform healthcare providers of palpitations or feelings of a racing heartbeat while at rest during Qsymia treatment. For patients who experience a sustained increase in resting heart rate while taking Qsymia, the dose should be reduced or Qsymia discontinued.

5.3 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including topiramate, a component of Qsymia, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with Qsymia should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue Qsymia in patients who experience suicidal thoughts or behaviors.

Avoid Qsymia in patients with a history of suicidal attempts or active suicidal ideation.

Pooled analyses of 199 placebo-controlled clinical studies (monotherapy and adjunctive therapy, median treatment duration 12 weeks) of 11 different AEDs across several indications showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% Confidence Interval [CI] 1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. The estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in AED-treated patients in the trials and none in placebo treated patients, but the number is too small to allow any conclusion about AED effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1 week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed.

5.4 Acute Myopia and Secondary Angle Closure Glaucoma

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients treated with topiramate, a component of Qsymia. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness), and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating treatment with topiramate but may occur at any time during therapy. The primary treatment to reverse symptoms is immediate discontinuation of Qsymia. Elevated intraocular pressure of any etiology, if left untreated, can lead to serious adverse events including permanent loss of vision.

5.5 Mood and Sleep Disorders

Qsymia can cause mood disorders, including depression, and anxiety, as well as insomnia. Patients with a history of depression may be at increased risk of recurrent depression or other mood disorders while taking Qsymia. The majority of these mood and sleep disorders resolved spontaneously, or resolved upon discontinuation of dosing *[see Adverse Reactions (6.1)]*.

For clinically significant or persistent symptoms consider dose reduction or withdrawal of Qsymia. If patients have symptoms of suicidal ideation or behavior, discontinue Qsymia.

5.6 Cognitive Impairment

Qsymia can cause cognitive dysfunction (e.g., impairment of concentration/attention, difficulty with memory, and speech or language problems, particularly word-finding difficulties). Rapid titration or high initial doses of Qsymia may be associated with higher rates of cognitive events such as attention, memory, and language/word-finding difficulties *[see Adverse Reactions (6.1)]*.

Since Qsymia has the potential to impair cognitive function, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain Qsymia therapy does not affect them adversely. If cognitive dysfunction persists consider dose reduction or withdrawal of Qsymia for symptoms that are moderate to severe, bothersome, or those which fail to resolve with dose reduction.

5.7 Metabolic Acidosis

Hyperchloremic, non-anion gap, metabolic acidosis (decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) has been reported in patients treated with Qsymia *[see Adverse Reactions (6.1)]*.

Conditions or therapies that predispose to acidosis (i.e., renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery or ketogenic diet) may be additive to the bicarbonate lowering effects of topiramate. Concomitant use of Qsymia and a carbonic anhydrase inhibitor (e.g., zonisamide, acetazolamide, or dichlorphenamide) may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. Therefore, if Qsymia is given concomitantly with another carbonic anhydrase inhibitor to a patient with a predisposing condition for metabolic acidosis the patient should be monitored for the appearance or worsening of metabolic acidosis.

Some manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fractures. The effect of Qsymia on growth and bone-related sequelae has not been systematically investigated in long-term, placebo-controlled trials.

Measurement of electrolytes including serum bicarbonate prior to starting Qsymia and during Qsymia treatment is recommended. In Qsymia clinical trials, the peak reduction in serum bicarbonate occurred by week 4, and in most subjects there was a correction of bicarbonate by week 56, without any change to study drug. However, if persistent metabolic acidosis develops while taking Qsymia, reduce the dose or discontinue Qsymia.

5.8 Elevation in Creatinine

Qsymia can cause an increase in serum creatinine that reflects a decrease in renal function (glomerular filtration rate). In phase 3 trials, peak increases in serum creatinine were observed after 4 to 8 weeks of treatment. On average, serum creatinine gradually declined but remained elevated over baseline creatinine values The changes in serum creatinine (and measured GFR) with short-term Qsymia treatment appear reversible with treatment discontinuation, but the effect of chronic treatment on renal function is not known. Therefore, measurement of

serum creatinine prior to starting Qsymia and during Qsymia treatment is recommended. If persistent elevations in creatinine occur while taking Qsymia, reduce the dose or discontinue Qsymia *[see Adverse Reactions (6.1), Pharmacodynamics (12.2)]*.

5.9 Potential Risk of Hypoglycemia in Patients with Type 2 Diabetes Mellitus on Anti-Diabetic Therapy

Weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus treated with insulin and/or insulin secretagogues (e.g., sulfonylureas). Qsymia has not been studied in combination with insulin. Measurement of blood glucose levels prior to starting Qsymia and during Qsymia treatment is recommended in patients with type 2 diabetes. Decreases in medication doses for antidiabetic medications which are non-glucose-dependent should be considered to mitigate the risk of hypoglycemia. If a patient develops hypoglycemia after starting Qsymia, appropriate changes should be made to the antidiabetic drug regimen.

5.10 Potential Risk of Hypotension in Patients Treated with Antihypertensive Medications

In hypertensive patients being treated with antihypertensive medications, weight loss may increase the risk of hypotension, and associated symptoms including dizziness, lightheadedness, and syncope. Measurement of blood pressure prior to starting Qsymia and during Qsymia treatment is recommended in patients being treated for hypertension. If a patient develops symptoms associated with low blood pressure after starting Qsymia, appropriate changes should be made to the antihypertensive drug regimen.

5.11 CNS Depression with Concomitant CNS Depressants Including Alcohol

The concomitant use of alcohol or central nervous system (CNS) depressant drugs (e.g., barbiturates, benzodiazepines, and sleep medications) with phentermine or topiramate may potentiate CNS depression or other centrally mediated effects of these agents, such as dizziness, cognitive adverse reactions, drowsiness, light-headedness, impaired coordination and somnolence. Therefore, avoid concomitant use of alcohol with Qsymia.

5.12 Potential Seizures with Abrupt Withdrawal of Qsymia

Abrupt withdrawal of topiramate, a component of Qsymia, has been associated with seizures in individuals without a history of seizures or epilepsy. In situations where immediate termination of Qsymia is medically required, appropriate monitoring is recommended. Patients discontinuing Qsymia 15 mg/92 mg should be gradually tapered as recommended to reduce the possibility of precipitating a seizure *[see Dosage and Administration (2.1)]*.

5.13 Patients with Renal Impairment

Phentermine and topiramate, the components of Qsymia, are cleared by renal excretion. Therefore, exposure to phentermine and topiramate is higher in patients with moderate (creatinine clearance [CrCl] greater than or equal to 30 and less than 50 mL/min) or severe (CrCl less than 30 mL/min) renal impairment. Adjust dose of Qsymia for both patient populations.

Qsymia has not been studied in patients with end-stage renal disease on dialysis. Avoid use of Qsymia in this patient population *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

5.14 Patients with Hepatic Impairment

In patients with mild (Child-Pugh score 5 - 6) or moderate (Child-Pugh score 7 - 9) hepatic impairment, exposure to phentermine was higher compared to healthy volunteers. Adjust dose of Qsymia for patients with moderate hepatic impairment.

Qsymia has not been studied in patients with severe hepatic impairment (Child-Pugh score 10 - 15). Avoid use of Qsymia in this patient population *[see Dosage and Administration (2.3), and Clinical Pharmacology (12.3)]*.

5.15 Kidney Stones

Use of Qsymia has been associated with kidney stone formation. Topiramate, a component of Qsymia, inhibits carbonic anhydrase activity and promotes kidney stone formation by reducing urinary citrate excretion and increasing urine pH.

Avoid the use of Qsymia with other drugs that inhibit carbonic anhydrase (e.g., zonisamide, acetazolamide, or methazolamide).

Use of topiramate by patients on a ketogenic diet may also result in a physiological environment that increases the likelihood of kidney stone formation.

Increase fluid intake to increase urinary output which can decrease the concentration of substances involved in kidney stone formation *[see Adverse Reactions (6.1)]*.

5.16 Oligohidrosis and Hyperthermia

Oligohidrosis (decreased sweating), infrequently resulting in hospitalization, has been reported in association with the use of topiramate, a component of Qsymia. Decreased sweating and an elevation in body temperature above normal characterized these cases. Some of the cases have been reported with topiramate after exposure to elevated environmental temperatures.

Patients treated with Qsymia should be advised to monitor for decreased sweating and increased body temperature during physical activity, especially in hot weather. Caution should be used when Qsymia is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity.

5.17 Hypokalemia

Qsymia can increase the risk of hypokalemia through its inhibition of carbonic anhydrase activity. In addition, when Qsymia is used in conjunction with non-potassium sparing diuretics such as furosemide (loop diuretic) or hydrochlorothiazide (thiazide-like diuretic) this may further potentiate potassium-wasting. When prescribing Qsymia, patients should be monitored for hypokalemia *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*.

5.18 Monitoring: Laboratory Tests

Qsymia was associated with changes in several clinical laboratory analytes in randomized, double-blind, placebo-controlled studies.

Obtain a blood chemistry profile that includes bicarbonate, creatinine, potassium, and glucose at baseline and periodically during treatment [s*ee Warnings and Precautions (5.7), (5.8), (5.9), and (5.17)]*.

6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Fetal Toxicity: *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1), (8.6)]*
- Elevation in Heart Rate [*see Warnings and Precautions (5.2)*]
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.3)]*
- Acute Angle Closure Glaucoma *[see Warnings and Precautions (5.4)]*
- Mood and Sleep Disorders *[see Warnings and Precautions (5.5)]*
- Cognitive Impairment *[see Warnings and Precautions (5.6)]*
- Metabolic Acidosis *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The data described herein reflects exposure to Qsymia in two, 1-year, randomized, double-blind, placebo-controlled, multicenter clinical trials, and two Phase 2 supportive trials in 2318 adult patients (936 [40.4%] patients with hypertension, 309 [13.3%] patients with type 2 diabetes, 808 [34.9%] patients with BMI greater than 40 kg/m^2) exposed for a mean duration of 298 days.

Common Adverse Reactions: Adverse reactions occurring at a rate of greater than or equal to 5% and at a rate at least 1.5 times placebo include paraesthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth.

Adverse reactions reported in greater than or equal to 2% of Qsymia-treated patients and more frequently than in the placebo group are shown in Table 3.

Table 3. Adverse Reactions Reported in Greater Than or Equal to 2% of Patients and More Frequently than Placebo during 1 Year of Treatment – Overall Study Population

System Organ Class Preferred Term	Placebo (N = 1561) %	Qsymia 3.75 mg/23 mg (N = 240) %	Qsymia 7.5 mg/46 mg (N = 498) %	Qsymia 15 mg/92 mg (N = 1580) %
Nervous System Disorders				
Paraesthesia	1.9	4.2	13.7	19.9
Headache	9.3	10.4	7.0	10.6
Dizziness	3.4	2.9	7.2	8.6
Dysgeusia	1.1	1.3	7.4	9.4
Hypoesthesia	1.2	0.8	3.6	3.7
Disturbance in Attention	0.6	0.4	2.0	3.5
Psychiatric Disorders				
Insomnia	4.7	5.0	5.8	9.4
Depression	2.2	3.3	2.8	4.3
Anxiety	1.9	2.9	1.8	4.1
Gastrointestinal Disorders				
Constipation	6.1	7.9	15.1	16.1
Dry Mouth	2.8	6.7	13.5	19.1
Nausea	4.4	5.8	3.6	7.2
Diarrhea	4.9	5.0	6.4	5.6
Dyspepsia	1.7	2.1	2.2	2.8
Gastroesophageal Reflux Disease	1.3	0.8	3.2	2.6
Paraesthesia Oral	0.3	0.4	0.6	2.2
General Disorders and Administration Site Conditions				
Fatigue	4.3	5.0	4.4	5.9
Irritability	0.7	1.7	2.6	3.7
Thirst	0.7	2.1	1.8	2.0
Chest Discomfort	0.4	2.1	0.2	0.9
Eye Disorders				
Vision Blurred	3.5	6.3	4.0	5.4
Eye Pain	1.4	2.1	2.2	2.2
Dry Eye	0.8	0.8	1.4	2.5
Cardiac Disorders				
Palpitations	0.8	0.8	2.4	1.7
Skin and Subcutaneous Tissue Disorders				
Rash	2.2	1.7	2.0	2.6
Alopecia	0.7	2.1	2.6	3.7
Metabolism and Nutrition Disorders				
Hypokalemia	0.4	0.4	1.4	2.5
Decreased Appetite	0.6	2.1	1.8	1.5
Reproductive System and Breast Disorders				
Dysmenorrhea	0.2	2.1	0.4	0.8
Infections and Infestations				
Upper Respiratory Tract Infection	12.8	15.8	12.2	13.5
Nasopharyngitis	8.0	12.5	10.6	9.4
Sinusitis	6.3	7.5	6.8	7.8
Bronchitis	4.2	6.7	4.4	5.4
Influenza	4.4	7.5	4.6	4.4
Urinary Tract Infection	3.6	3.3	5.2	5.2
Gastroenteritis	2.2	0.8	2.2	2.5
Musculoskeletal and Connective Tissue Disorders				
Back Pain	5.1	5.4	5.6	6.6
Pain in Extremity	2.8	2.1	3.0	3.0

Muscle Spasms	2.2	2.9	2.8	2.9
Musculoskeletal Pain	1.2	0.8	3.0	1.6
Neck Pain	1.3	1.3	2.2	1.2
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	3.5	3.3	3.8	4.8
Sinus Congestion	2.0	2.5	2.6	2.0
Pharyngolaryngeal Pain	2.0	2.5	1.2	2.3
Nasal Congestion	1.4	1.7	1.2	2.0
Injury, Poisoning, and Procedural Complications				
Procedural Pain	1.7	2.1	2.4	1.9

Paraesthesia/Dysgeusia

Reports of paraesthesia, characterized as tingling in hands, feet, or face, occurred in 4.2%, 13.7%, and 19.9% of patients treated with Qsymia 3.75 mg/23 mg, 7.5 mg/46 mg, and 15 mg/92 mg, respectively, compared to 1.9% of patients treated with placebo. Dysgeusia was characterized as a metallic taste, and occurred in 1.3%, 7.4%, and 9.4% of patients treated with Qsymia 3.75 mg/23 mg, 7.5 mg/46 mg, and 15 mg/92 mg, respectively, compared to 1.1% of patients treated with placebo. The majority of these events first occurred within the initial 12 weeks of drug therapy; however, in some patients, events were reported later in the course of treatment. Only Qsymia-treated patients discontinued treatment due to these events (1% for paraesthesia and 0.6% for dysgeusia).

Mood and Sleep Disorders

The proportion of patients in 1-year controlled trials of Qsymia reporting one or more adverse reactions related to mood and sleep disorders was 15.8%, 14.5%, and 20.6% with Qsymia 3.75 mg/23 mg, 7.5 mg/46 mg, and 15 mg/92 mg, respectively, compared to 10.3% with placebo. These events were further categorized into sleep disorders, anxiety, and depression. Reports of sleep disorders were typically characterized as insomnia, and occurred in 6.7%, 8.1%, and 11.1% of patients treated with Qsymia 3.75 mg/23 mg, 7.5 mg/46 mg, and 15 mg/92 mg, respectively, compared to 5.8% of patients treated with placebo. Reports of anxiety occurred in 4.6%, 4.8%, and 7.9% of patients treated with Qsymia 3.75 mg/23 mg, 7.5 mg/46 mg, and 15 mg/92 mg, respectively, compared to 2.6% of patients treated with placebo. Reports of depression/mood problems occurred in 5.0%, 3.8%, and 7.6% of patients treated with Qsymia 3.75 mg/23 mg, 7.5 mg/46 mg, and 15 mg/92 mg, respectively, compared to 3.4% of patients treated with placebo. The majority of these events first occurred within the initial 12 weeks of drug therapy; however, in some patients, events were reported later in the course of treatments. In the Qsymia clinical trials, the overall prevalence of mood and sleep adverse reactions was approximately twice as great in patients with a history of depression compared to patients without a history of depression; however, the proportion of patients on active treatment versus placebo who reported mood and sleep adverse reactions was similar in these two subgroups. Occurrence of depression-related events was more frequent in patients with a past history of depression across all treatment groups. However, the placebo-adjusted difference in incidence of these events remained constant between groups regardless of previous depression history.

Cognitive Disorders

In the 1-year controlled trials of Qsymia, the proportion of patients who experienced one or more cognitive-related adverse reactions was 2.1% for Qsymia 3.75 mg/23 mg, 5.0% for Qsymia 7.5 mg/46 mg, and 7.6% for Qsymia 15 mg/92 mg, compared to 1.5% for placebo. These adverse reactions were comprised primarily of reports of problems with attention/concentration, memory, and language (word finding). These events typically began within the first 4 weeks of treatment, had a median duration of approximately 28 days or less, and were reversible upon discontinuation of treatment; however, individual patients did experience events later in treatment, and events of longer duration.

Laboratory Abnormalities

Serum Bicarbonate

In the 1-year controlled trials of Qsymia, the incidence of persistent treatment-emergent decreases in serum bicarbonate below the normal range (levels of less than 21 mEq/L at 2 consecutive visits or at the final visit) was 8.8% for Qsymia 3.75 mg/23 mg, 6.4% for Qsymia 7.5 mg/46 mg, and 12.8% for Qsymia 15 mg/92 mg, compared to 2.1% for placebo. The incidence of persistent, markedly low serum bicarbonate values (levels of less than 17 mEq/L on 2 consecutive visits or at the final visit) was 1.3% for Qsymia 3.75 mg/23 mg, 0.2% for Qsymia 7.5 mg/46 mg dose, and 0.7% for Qsymia 15 mg/92 mg dose, compared to 0.1% for placebo. Generally, decreases in serum bicarbonate levels were mild (average 1-3 mEq/L) and occurred early in treatment (4-week visit), however severe decreases and decreases later in treatment occurred.

Serum Potassium

In the 1-year controlled trials of Qsymia, the incidence of persistent low serum potassium values (less than 3.5 mEq/L at two consecutive visits or at the final visit) during the trial was 0.4% for Qsymia 3.75 mg/23 mg, 3.6% for Qsymia 7.5 mg/46 mg dose, and 4.9% for Qsymia 15 mg/92 mg, compared to 1.1% for placebo. Of the subjects who experienced persistent low serum potassium, 88% were receiving treatment with a non-potassium sparing diuretic.

The incidence of markedly low serum potassium (less than 3 mEq/L, and a reduction from pre-treatment of greater than 0.5 mEq/L) at any time during the trial was 0.0% for Qsymia 3.75 mg/23 mg, 0.2% for Qsymia 7.5 mg/46 mg dose, and 0.7% for Qsymia 15 mg/92 mg dose, compared to 0.0% for placebo. Persistent markedly low serum potassium (less than 3 mEq/L, and a reduction from pre-treatment of greater than 0.5 mEq/L at two consecutive visits or at the final visit) occurred in 0.0% of subjects receiving Qsymia 3.75 mg/23 mg, 0.2% receiving Qsymia 7.5 mg/46 mg dose, and 0.1% receiving Qsymia 15 mg/92 mg dose, compared to 0.0% receiving placebo.

Hypokalemia was reported by 0.4% of subjects treated with Qsymia 3.75 mg/23 mg, 1.4% of subjects treated with Qsymia 7.5 mg/46 mg, and 2.5% of subjects treated with Qsymia 15 mg/92 mg compared to 0.4% of subjects treated with placebo. “Blood potassium decreased” was reported by 0.4% of subjects treated with Qsymia 3.75 mg/23 mg, 0.4% of subjects treated with Qsymia 7.5 mg/46 mg, 1.0% of subjects treated with Qsymia 15 mg/92 mg, and 0.0% of subjects treated with placebo.

Serum Creatinine

In the 1-year controlled trials of Qsymia, there was a dose-related increase from baseline, peaking between Week 4 to 8, which declined but remained elevated over baseline over 1 year of treatment. The incidence of increases in serum creatinine of greater than or equal to 0.3 mg/dL at any time during treatment was 2.1% for Qsymia 3.75 mg/23 mg, 7.2% for Qsymia 7.5 mg/46 mg, and 8.4% for Qsymia 15 mg/92 mg, compared to 2.0% for placebo. Increases in serum creatinine of greater than or equal to 50% over baseline occurred in 0.8% of subjects receiving Qsymia 3.75 mg/23 mg, 2.0% receiving Qsymia 7.5 mg/46 mg, and 2.8% receiving Qsymia 15 mg/92 mg, compared to 0.6% receiving placebo.

Nephrolithiasis

In the 1-year controlled trials of Qsymia, the incidence of nephrolithiasis was 0.4% for Qsymia 3.75 mg/23 mg, 0.2% for Qsymia 7.5 mg/46 mg, and 1.2% for Qsymia 15 mg/92 mg, compared to 0.3% for placebo.

Drug Discontinuation Due to Adverse Reactions

In the 1-year placebo-controlled clinical studies, 11.6% of Qsymia 3.75 mg/23 mg, 11.6% of Qsymia 7.5 mg/46 mg, 17.4% of Qsymia 15 mg/92 mg, and 8.4% of placebo-treated patients discontinued treatment due to reported adverse reactions. The most common adverse reactions that led to discontinuation of treatment are shown in Table 4.

Table 4. Adverse Reactions Greater Than or Equal To 1% Leading to Treatment Discontinuation (1-Year Clinical Trials)

Adverse Reaction Leading to Treatment Discontinuation[a]	Placebo (N=1561) %	Qsymia 3.75 mg/23 mg (N=240) %	Qsymia 7.5 mg/46 mg (N=498) %	Qsymia 15 mg/92 mg (N=1580) %
Vision blurred	0.5	2.1	0.8	0.7
Headache	0.6	1.7	0.2	0.8
Irritability	0.1	0.8	0.8	1.1
Dizziness	0.2	0.4	1.2	0.8
Paraesthesia	0.0	0.4	1.0	1.1
Insomnia	0.4	0.0	0.4	1.6
Depression	0.2	0.0	0.8	1.3
Anxiety	0.3	0.0	0.2	1.1

[a] greater than or equal to 1% in any treatment group

6.2 Postmarketing Experience

The following adverse reactions have been reported during post approval use of phentermine and topiramate, the components of Qsymia. Because these reactions are reported voluntarily from a population of uncertain size it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Qsymia

Psychiatric Disorders
Suicidal ideation, Suicidal behavior

Ophthalmic disorders

Acute angle closure glaucoma
Increased intraocular pressure

Phentermine

Allergic adverse reactions
Urticaria
Cardiovascular adverse reactions
Elevation of blood pressure, Ischemic events
Central nervous system adverse reactions
Euphoria, Psychosis, Tremor
Reproductive adverse reactions
Changes in libido, Impotence

Topiramate

Dermatologic disorders
Bullous skin reactions (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), Pemphigus
Gastrointestinal disorders
Pancreatitis
Hepatic disorders
Hepatic failure (including fatalities), Hepatitis
Metabolic disorders
Hyperammonemia
Hypothermia
Ophthalmic disorders
Maculopathy

7 DRUG INTERACTIONS

7.1 Monoamine Oxidase Inhibitors

Use of phentermine is contraindicated during or within 14 days following the administration of monoamine oxidase inhibitors because of the risk of hypertensive crisis.

7.2 Oral Contraceptives

Co-administration of multiple-dose Qsymia 15 mg/92 mg once daily with a single dose of oral contraceptive containing 35 µg ethinyl estradiol (estrogen component) and 1 mg norethindrone (progestin component), in obese otherwise healthy volunteers, decreased the exposure of ethinyl estradiol by 16% and increased the exposure of norethindrone by 22% *[see Clinical Pharmacology (12.3)]*.

Although this study did not specifically address the impact of the interaction on contraceptive efficacy, an increased risk of pregnancy is not anticipated. The primary determinant of contraceptive efficacy is the progestin component of the combination oral contraceptive, so higher exposure to the progestin would not be expected to be deleterious.

However, irregular bleeding (spotting) may occur more frequently due to both the increased exposure to the progestin and lower exposure to the estrogen, which tends to stabilize the endometrium. Patients should be informed not to discontinue their combination oral contraceptive if spotting occurs, but to notify their healthcare provider if the spotting is troubling to them.

7.3 CNS Depressants Including Alcohol

Specific drug interaction studies of Qsymia and alcohol or other CNS depressant drugs have not been performed. The concomitant use of alcohol or CNS depressant drugs (e.g., barbiturates, benzodiazepines, and sleep medications) with phentermine or topiramate may potentiate CNS depression such as dizziness or cognitive adverse reactions, or other centrally mediated effects of these agents. Therefore, if Qsymia is used with alcohol or other CNS depressants, the patient should be counseled regarding possible increased risk of CNS depression or side effects.

7.4 Non-Potassium Sparing Diuretics

Concurrent use of Qsymia with non-potassium sparing diuretics may potentiate the potassium-wasting action of these diuretics. Concomitant administration of hydrochlorothiazide alone with topiramate alone has been shown to increase the C_{max} and AUC of topiramate by 27% and 29%, respectively. When prescribing Qsymia in the

presence of non-potassium-sparing medicinal products, patients should be monitored for hypokalemia *[see Warnings and Precautions (5.17) and Clinical Pharmacology (12.3)]*.

7.5 Antiepileptic Drugs

Concomitant administration of phenytoin or carbamazepine with topiramate in patients with epilepsy, decreased plasma concentrations of topiramate by 48% and 40%, respectively, when compared to topiramate given alone *[see Clinical Pharmacology (12.3)]*.

Concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy. Concomitant administration of topiramate with valproic acid in patients has also been associated with hypothermia (with and without hyperammonemia). It may be prudent to examine blood ammonia in patients in whom the onset of hypothermia or encephalopathy has been reported *[see Clinical Pharmacology (12.3)]*.

7.6 Carbonic Anhydrase Inhibitors

Concomitant use of topiramate, a component of Qsymia, with any other carbonic anhydrase inhibitor (e.g., zonisamide, acetazolamide, or dichlorphenamide) may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. Avoid the use of Qsymia with other drugs that inhibit carbonic anhydrase *[see Warnings and Precautions (5.7)]*.

7.7 Pioglitazone

A decrease in the exposure of pioglitazone and its active metabolites were noted with the concurrent use of pioglitazone and topiramate in a clinical trial. The clinical relevance of these observations is unknown; however, when Qsymia is added to pioglitazone therapy or pioglitazone is added to Qsymia therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Risk Summary

Qsymia is contraindicated in pregnant women. The use of Qsymia can cause fetal harm and weight loss offers no potential benefit to a pregnant woman. Available epidemiologic data indicate an increased risk in oral clefts (cleft lip with or without cleft palate) with first trimester exposure to topiramate, a component of Qsymia. When multiple species of pregnant animals received topiramate at clinically relevant doses, structural malformations, including craniofacial defects, and reduced fetal weights occurred in offspring.

If this drug is used during pregnancy, or if a patient becomes pregnant while taking this drug, treatment should be discontinued immediately and the patient should be apprised of the potential hazard to a fetus.

There is a Qsymia Pregnancy Surveillance Program to monitor maternal-fetal outcomes of pregnancies that occur during Qsymia therapy. Healthcare providers and patients are encouraged to report pregnancies by calling 1-888-998-4887.

Clinical Considerations

Oral clefts occur from the fifth through the ninth week of gestation. The lip is formed between the beginning of the fifth week to the seventh week of gestation, and the palate is formed between the beginning of the sixth week through the ninth week of gestation.

A minimum weight gain, and no weight loss, is currently recommended for all pregnant women, including those who are already overweight or obese, due to the obligatory weight gain that occurs in maternal tissues during pregnancy.

Qsymia can cause metabolic acidosis. The effect of topiramate-induced metabolic acidosis has not been studied in pregnancy; however, metabolic acidosis in pregnancy (due to other causes) can cause decreased fetal growth, decreased fetal oxygenation, and fetal death, and may affect the fetus' ability to tolerate labor *[see Warnings and Precautions (5.7)]*.

Human Data

Data evaluating the risk of major congenital malformations and oral clefts with topiramate (a component of Qsymia) exposure during pregnancy is available from the North American Anti-Epileptic Drug (NAAED) Pregnancy Registry and from several larger retrospective epidemiologic studies. The NAAED Pregnancy Registry suggested an estimated increase in risk for oral clefts of 9.60 (95% CI 3.60 - 25.70). Larger retrospective epidemiology studies showed that topiramate monotherapy exposure in pregnancy is associated with an approximately two to five-fold increased risk of oral clefts (Table 5). The FORTRESS study, sponsored by the maker of Qsymia, found an excess risk of 1.5 (95% CI = -1.1 to 4.1) oral cleft cases per 1,000 infants exposed to topiramate during the first trimester.

Table 5. Summary of Studies Evaluating the Association of Topiramate in Utero Exposure and Oral Clefts and Major Congenital Malformations

	Oral clefts		Major Congenital Malformations	
Epidemiology Study	**Estimated Increase in Risk**	**95% CI**	**Estimated Increase in Risk**	**95% CI**
Wolters Kluwer[a]	1.47	0.36 – 6.06	1.12	0.81 – 1.55
FORTRESS[a]	2.22	0.78 – 6.36	1.21	0.99 – 1.47
Slone/CDC	5.36	1.49 – 20.07	1.01	0.37 – 3.22

[a] Sponsored by the maker of Qsymia
CI = confidence interval

Animal Data

Phentermine/Topiramate

Embryo-fetal development studies have been conducted in rats and rabbits with combination phentermine and topiramate treatment. Phentermine and topiramate co-administered to rats during the period of organogenesis caused reduced fetal body weights but did not cause fetal malformations at the maximum dose of 3.75 mg/kg phentermine and 25 mg/kg topiramate [approximately 2 times the maximum recommended human dose (MRHD) based on area under the curve (AUC) estimates for each active ingredient]. In a similar study in rabbits, no effects on embryo-fetal development were observed at approximately 0.1 times (phentermine) and 1 time (topiramate) clinical exposures at the MRHD based on AUC. Significantly lower maternal body weight gain was recorded at these doses in rats and rabbits.

A pre- and post-natal development study was conducted in rats with combination phentermine and topiramate treatment. There were no adverse maternal or offspring effects in rats treated throughout organogenesis and lactation with 1.5 mg/kg/day phentermine and 10 mg/kg/day topiramate (approximately 2 and 3 times clinical exposures at the MRHD, respectively, based on AUC). Treatment with higher doses of 11.25 mg/kg/day phentermine and 75 mg/kg/day topiramate (approximately 5 and 6 times maximum clinical doses based on AUC, respectively) caused reduced maternal body weight gain and offspring toxicity. Offspring effects included lower pup survival after birth, increased limb and tail malformations, reduced pup body weight and delayed growth, development, and sexual maturation without affecting learning, memory, or fertility and

reproduction. The limb and tail malformations were consistent with results of animal studies conducted with topiramate alone *[see Nonclinical Toxicology (13.3)]*.

Phentermine

Animal reproduction studies have not been conducted with phentermine. Limited data from studies conducted with the phentermine/topiramate combination indicate that phentermine alone was not teratogenic but resulted in lower body weight and reduced survival of offspring in rats at 5-fold the MRHD of Qsymia, based on AUC.

Topiramate

Topiramate causes developmental toxicity, including teratogenicity, at clinically relevant doses *[see Nonclinical Toxicology (13.3)]*.

8.2 Labor and Delivery

The effect of Qsymia on labor and delivery in humans is unknown. The development of Qsymia-induced metabolic acidosis in the mother and/or in the fetus might affect the fetus's ability to tolerate labor.

8.3 Nursing Mothers

Qsymia may be present in human milk because topiramate and amphetamines (phentermine has pharmacologic activity and a chemical structure similar to amphetamines) are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of Qsymia in pediatric patients below the age of 18 years have not been established and the use of Qsymia is not recommended in pediatric patients. Serious adverse reactions seen in pediatric patients using topiramate, a component of Qsymia, include acute angle glaucoma, oligohidrosis and hyperthermia, metabolic acidosis, cognitive and neuropsychiatric reactions, hyperammonemia and encephalopathy, and kidney stones.

Juvenile Animal Studies

Juvenile animal studies have not been conducted with Qsymia. When topiramate (30, 90, or 300 mg/kg/day) was administered orally to rats during the juvenile period of development (postnatal days 12 to 50), bone growth plate thickness was reduced in males at the highest dose.

8.5 Geriatric Use

In the Qsymia clinical trials, a total of 254 (7%) of the patients were 65 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Clinical studies of Qsymia did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Females of Reproductive Potential

Qsymia can cause fetal harm. Data from pregnancy registries and epidemiology studies indicate that a fetus exposed to topiramate, a component of Qsymia, in the first trimester of pregnancy has an increased risk of oral clefts (cleft lip with or without cleft palate).

Females who become pregnant during Qsymia therapy should stop Qsymia treatment immediately and notify their healthcare provider.

Pregnancy Testing

Females of reproductive potential should have a negative pregnancy test before starting Qsymia and monthly thereafter during Qsymia therapy.

Contraception

Females of reproductive potential should use effective contraception during Qsymia therapy.

8.7 Renal Impairment

Compared to healthy volunteers, patients with moderate and severe renal impairment as estimated by the Cockcroft-Gault equation had higher phentermine and topiramate exposures.

No dose adjustments are necessary in patients with mild renal impairment. In patients with moderate (CrCl greater than or equal to 30 to less than 50 mL/min) and severe (CrCl less than 30 mL/min) renal impairment, the dose should not exceed Qsymia 7.5 mg/46 mg once daily.

Qsymia has not been studied in patients with end-stage renal disease on dialysis. Avoid Qsymia in this patient population *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

8.8 Hepatic Impairment

In patients with mild (Child-Pugh 5 - 6) and moderate (Child-Pugh 7 - 9) hepatic impairment, exposure to phentermine was higher compared to healthy volunteers. Exposure to topiramate, a component of Qsymia, was similar among patients with mild and moderate hepatic impairment and healthy volunteers.

No dose adjustments are necessary in patients with mild hepatic impairment. In patients with moderate hepatic impairment, the dose should not exceed Qsymia 7.5 mg/46 mg once daily.

Qsymia has not been studied in patients with severe hepatic impairment (Child-Pugh score 10 - 15). Avoid Qsymia in this patient population *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Qsymia is controlled in Schedule IV of the Controlled Substances Act because it contains phentermine a Schedule IV drug. Any material, compound, mixture, or preparation that contains any quantity of phentermine is controlled as a Schedule IV drug.

Topiramate is not controlled in the Controlled Substances Act.

9.2 Abuse

Phentermine, a component of Qsymia, has a known potential for abuse.

Phentermine, a component of Qsymia, is related chemically and pharmacologically to the amphetamines. Amphetamines and other stimulant drugs have been extensively abused and the possibility of abuse of phentermine should be kept in mind when evaluating the desirability of including Qsymia as part of a weight reduction program. Abuse of amphetamines and related drugs (e.g., phentermine) may be associated with impaired control over drug use and severe social dysfunction. There are reports of patients who have increased the dosage of these drugs to many times than recommended.

9.3 Dependence

Qsymia has not been systematically studied for its potential to produce physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use. Physical dependence manifests by drug-class-specific withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Limited information on the potential for physical dependence for the individual components of Qsymia is available. For topiramate, abrupt discontinuation has been associated with seizures in patients without a history of seizures or epilepsy. For phentermine, abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on a sleep electroencephalogram. Thus, in situations where rapid withdrawal of Qsymia is required, appropriate medical monitoring is recommended.

10 OVERDOSAGE

In the event of a significant overdose with Qsymia, if the ingestion is recent, the stomach should be emptied immediately by gastric lavage or by induction of emesis. Appropriate supportive treatment should be provided according to the patient's clinical signs and symptoms.

Acute overdose of phentermine may be associated with restlessness, tremor, hyperreflexia, rapid respiration, confusion, aggressiveness, hallucinations, and panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmia, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. A severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

Management of acute phentermine intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Acidification of the urine increases phentermine excretion. Intravenous phentolamine has been suggested for possible acute, severe hypertension, if this complicates phentermine overdosage.

Topiramate overdose has resulted in severe metabolic acidosis. Other signs and symptoms include convulsions, drowsiness, speech disturbance, blurred vision, diplopia, mentation impaired, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness, and depression. The clinical consequences were not severe in most cases, but deaths have been reported after poly-drug overdoses involving gram amounts of topiramate. A patient who ingested a dose between 96 and 110 grams topiramate was admitted to hospital with coma lasting 20 to 24 hours followed by full recovery after 3 to 4 days.

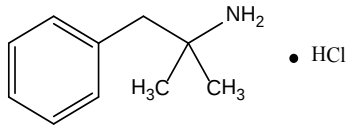
Activated charcoal has been shown to adsorb topiramate *in vitro*. Hemodialysis is an effective means of removing topiramate from the body.

11 DESCRIPTION

Qsymia capsule is a combination oral product comprised of immediate-release phentermine hydrochloride (expressed as the weight of the free base) and extended-release topiramate. Qsymia contains phentermine hydrochloride, a sympathomimetic amine anorectic, and topiramate, a sulfamate-substituted monosaccharide related to fructose antiepileptic drug.

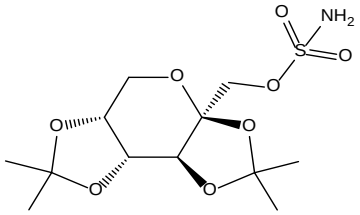
Phentermine Hydrochloride

The chemical name of phentermine hydrochloride is α,α-dimethylphenethylamine hydrochloride. The molecular formula is $C_{10}H_{15}N$ • HCl and its molecular weight is 185.7 (hydrochloride salt) or 149.2 (free base). Phentermine hydrochloride is a white, odorless, hygroscopic, crystalline powder that is soluble in water, methanol, and ethanol. Its structural formula is:



Topiramate

Topiramate is 2,3:4,5-di-O-isopropylidene-β-D-fructopyranose sulfamate. The molecular formula is $C_{12}H_{21}NO_8S$ and its molecular weight is 339.4. Topiramate is a white to off-white crystalline powder with a bitter taste. It is freely soluble in methanol and acetone, sparingly soluble in pH 9 to pH 12 aqueous solutions and slightly soluble in pH 1 to pH 8 aqueous solutions. Its structural formula is:



Qsymia

Qsymia is available in four dosage strengths:

- Qsymia 3.75 mg/23 mg (phentermine 3.75 mg and topiramate 23 mg extended-release) capsules;
- Qsymia 7.5 mg/46 mg (phentermine 7.5 mg and topiramate 46 mg extended-release) capsules;
- Qsymia 11.25 mg/69 mg (phentermine 11.25 mg and topiramate 69 mg extended-release) capsules;
- Qsymia 15 mg/92 mg (phentermine 15 mg and topiramate 92 mg extended-release) capsules.

Each capsule contains the following inactive ingredients: methylcellulose, sucrose, starch, microcrystalline cellulose, ethylcellulose, povidone, gelatin, talc, titanium dioxide, FD&C Blue #1, FD&C Red #3, FD&C Yellow #5 and #6, and pharmaceutical black and white inks.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Phentermine is a sympathomimetic amine with pharmacologic activity similar to the prototype drugs of this class used in obesity, amphetamine (d- and d/l-amphetamine). Drugs of this class used in obesity are commonly known as "anorectics" or "anorexigenics." The effect of phentermine on chronic weight management is likely mediated by release of catecholamines in the hypothalamus, resulting in reduced appetite and decreased food consumption, but other metabolic effects may also be involved. The exact mechanism of action is not known.

The precise mechanism of action of topiramate on chronic weight management is not known. Topiramate's effect on chronic weight management may be due to its effects on both appetite suppression and satiety enhancement, induced by a combination of pharmacologic effects including augmenting the activity of the neurotransmitter gamma-aminobutyrate, modulation of voltage-gated ion channels, inhibition of AMPA/kainite excitatory glutamate receptors, or inhibition of carbonic anhydrase.

12.2 Pharmacodynamics

Typical actions of amphetamines include central nervous system stimulation and elevation of blood pressure. Tachyphylaxis and tolerance have been demonstrated with all drugs of this class in which these phenomena have been looked for.

Cardiac Electrophysiology

The effect of Qsymia on the QTc interval was evaluated in a randomized, double-blind, placebo- and active-controlled (400 mg moxifloxacin), and parallel group/crossover thorough QT/QTc study. A total of 54 healthy subjects were administered Qsymia 7.5 mg/46 mg at steady state and then titrated to Qsymia 22.5 mg/138 mg at steady state. Qsymia 22.5 mg/138 mg [a supra-therapeutic dose resulting in a phentermine and topiramate maximum concentration (C_{max}) of 4- and 3- times higher than those at Qsymia 7.5 mg/46 mg, respectively] did not affect cardiac repolarization as measured by the change from baseline in QTc.

Glomerular Filtration Rate (GFR)

Healthy obese men and women received Qsymia daily for 4 weeks (3.75 mg/23 mg on Days 1 to 3, 7.5 mg/46 mg on Days 4 to 6, 11.25 mg/69 mg on Days 7 to 9, and 15 mg/92 mg on Days 10 to 28). The glomerular filtration rate (GFR) of these participants was assessed via iohexol clearance. On average, GFR decreased during Qsymia treatment and returned to baseline within 4 weeks after discontinuing Qsymia *[See* Warnings and Precautions (5.8)*]*

12.3 Pharmacokinetics

Phentermine

Upon oral administration of a single Qsymia 15 mg/92 mg, the resulting mean plasma phentermine maximum concentration (C_{max}), time to C_{max} (T_{max}), area under the concentration curve from time zero to the last time with measureable concentration (AUC_{0-t}), and area under the concentration curve from time zero to infinity ($AUC_{0-\infty}$) are 49.1 ng/mL, 6 hr, 1990 ng·hr/mL, and 2000 ng·hr/mL, respectively. A high fat meal does not affect phentermine pharmacokinetics for Qsymia 15 mg/92 mg. Phentermine pharmacokinetics is approximately dose-proportional from Qsymia 3.75 mg/23 mg to phentermine 15 mg/topiramate 100 mg. Upon dosing phentermine/topiramate 15/100 mg fixed dose combination capsule to steady state, the mean phentermine accumulation ratios for AUC and C_{max} are both approximately 2.5.

Topiramate

Upon oral administration of a single Qsymia 15 mg/92 mg, the resulting mean plasma topiramate C_{max}, T_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, are 1020 ng/mL, 9 hr, 61600 ng·hr/mL, and 68000 ng·hr/mL, respectively. A high fat meal does not affect topiramate pharmacokinetics for Qsymia 15 mg/92 mg. Topiramate pharmacokinetics is approximately dose-proportional from Qsymia 3.75 mg/23 mg to phentermine 15 mg/topiramate 100 mg. Upon dosing phentermine 15 mg/topiramate 100 mg fixed dose combination capsule to steady state, the mean topiramate accumulation ratios for AUC and C_{max} are both approximately 4.0.

Distribution

Phentermine

Phentermine is 17.5% plasma protein bound. The estimated phentermine apparent volume of distribution (Vd/F) is 348 L via population pharmacokinetic analysis.

Topiramate

Topiramate is 15 - 41% plasma protein bound over the blood concentration range of 0.5 to 250 µg/mL. The fraction bound decreased as blood topiramate increased. The estimated topiramate Vc/F (volume of the central compartment), and Vp/F (volume of the peripheral compartment) are 50.8 L, and 13.1 L, respectively, via population pharmacokinetic analysis.

Metabolism and Excretion

Phentermine

Phentermine has two metabolic pathways, namely p-hydroxylation on the aromatic ring and N-oxidation on the aliphatic side chain. Cytochrome P450 (CYP) 3A4 primarily metabolizes phentermine but does not show extensive metabolism. Monoamine oxidase (MAO)-A and MAO-B do not metabolize phentermine. Seventy to 80% of a dose exists as unchanged phentermine in urine when administered alone. The mean phentermine terminal half-life is about 20 hours. The estimated phentermine oral clearance (CL/F) is 8.79 L/h via population pharmacokinetic analysis.

Topiramate

Topiramate does not show extensive metabolism. Six topiramate metabolites (via hydroxylation, hydrolysis, and glucuronidation) exist, none of which constitutes more than 5% of an administered dose. About 70% of a dose exists as unchanged topiramate in urine when administered alone. The mean topiramate terminal half-life is about 65 hours. The estimated topiramate CL/F is 1.17 L/h via population pharmacokinetic analysis.

Specific Populations

Renal Impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of Qsymia 15 mg/92 mg in patients with varying degrees of chronic renal impairment compared to healthy volunteers with normal renal function. The study included patients with renal impairment classified on the basis of creatinine clearance as mild (greater or equal to 50 and less than 80 mL/min), moderate (greater than or equal to 30 and less than 50 mL/min), and severe (less than 30 mL/min). Creatinine clearance was estimated from serum creatinine based on the Cockcroft-Gault equation.

Compared to healthy volunteers, phentermine $AUC_{0\text{-}inf}$ was 91%, 45%, and 22% higher in patients with severe, moderate, and mild renal impairment, respectively; phentermine C_{max} was 2% to 15% higher. Compared to healthy volunteers, topiramate $AUC_{0\text{-}inf}$ was 126%, 85%, and 25% higher for patients with severe, moderate, and mild renal impairment, respectively; topiramate C_{max} was 6% to 17% higher. An inverse relationship between phentermine or topiramate C_{max} or AUC and creatinine clearance was observed.

Qsymia has not been studied in patients with end-stage renal disease on dialysis *[see Dosage and Administration (2.2), Warnings and Precautions (5.13), and Use in Specific Populations (8.7)]*.

Hepatic Impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of Qsymia 15 mg/92 mg in healthy volunteers with normal hepatic function compared with patients with mild (Child-Pugh score 5 - 6) and moderate (Child-Pugh score 7 - 9) hepatic impairment. In patients with mild and moderate hepatic impairment, phentermine AUC was 37% and 60% higher compared to healthy volunteers. Pharmacokinetics of topiramate was not affected in patients with mild and moderate hepatic impairment when compared with healthy volunteers. Qsymia has not been studied in patients with severe hepatic impairment (Child-Pugh score 10 - 15) *[see Dosage and Administration (2.3), Warnings and Precautions (5.14), and Use in Specific Populations (8.8)]*.

Drug Interactions

In Vitro Assessment of Drug Interactions

Phentermine
Phentermine is not an inhibitor of CYP isozymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4, and is not an inhibitor of monoamine oxidases. Phentermine is not an inducer of CYP1A2, CYP2B6, and CYP3A4. Phentermine is not a P-glycoprotein substrate.

Topiramate
Topiramate is not an inhibitor of CYP isozymes CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4/5. However, topiramate is a mild inhibitor of CYP2C19. Topiramate is a mild inducer of CYP3A4. Topiramate is not a P-glycoprotein substrate.

Effects of Phentermine/Topiramate on Other Drugs

Table 6. Effect of Phentermine/Topiramate on the Pharmacokinetics of Co-administered Drugs

Phentermine/Topiramate	Co-administered Drug and Dosing Regimen		
	Drug and Dose (mg)	Change in AUC	Change in C_{max}
*15 mg/92 mg dose QD for 16 days	Metformin 500 mg BID for 5 days	↑ 23%	↑ 16%
*15 mg/92 mg dose QD for 21 days	Sitagliptin 100 mg QD for 5 days	↓ 3%	↓ 9%
15 mg/92 mg dose QD for 15 days	Oral contraceptive single dose norethindrone 1 mg ethinyl estradiol 35 mcg	 ↑ 16% ↓ 16%	 ↑ 22% ↓ 8%

*A single study examined the effect of multiple-dose Qsymia 15 mg/92 mg once daily on the pharmacokinetics of multiple-dose 500 mg metformin twice daily and multiple-dose 100 mg sitagliptin once daily in 10 men and 10 women (mean BMI of 27.1 kg/m^2 and range of 22.2 – 32.7 kg/m^2). The study participants received metformin, sitagliptin, phentermine/topiramate only, phentermine/topiramate plus probenecid, phentermine/topiramate plus metformin, and phentermine/topiramate plus sitagliptin on Days 1 – 5, 6 – 10, 11 – 28, 29, 30 – 34, and 35 – 39, respectively.

Effect of Other Drugs on Phentermine/Topiramate

Table 7. Effect of Co-administered Drugs on the Pharmacokinetics of Phentermine/Topiramate

Co-administered Drug and Dosing Regimen	Phentermine/Topiramate		
	Dose (mg)	Change in AUC	Change in C_{max}
Topiramate 92 mg single dose	15 mg phentermine single dose	↑ 42%	↑ 13%
Phentermine 15 mg single dose	92 mg topiramate single dose	↑ 6%	↑ 2%
*Metformin 500 mg BID for 5 days	15 mg/92 mg dose QD for 16 days phentermine topiramate	 ↑ 5% ↓ 5%	 ↑ 7% ↓ 4%
*Sitagliptin 100 mg QD for 5 days	15 mg/92 mg dose QD for 21 days phentermine topiramate	 ↑ 9% ↓ 2%	 ↑ 10% ↓ 2%
*Probenecid 2 g QD	15 mg/92 mg dose QD for 11 days phentermine topiramate	 ↓ 0.3% ↑ 0.7%	 ↑ 4% ↑ 3%

*The same single study examined the effect of multiple-dose 500 mg metformin twice daily, a single-dose 2 g probenecid, and multiple-dose 100 mg sitagliptin once daily on the pharmacokinetics of multiple-dose phentermine/topiramate 15 mg/92 mg once daily in 10 men and 10 women (mean BMI of 27.1 kg/m^2 and range of 22.2 – 32.7 kg/m^2). The study participants received metformin, sitagliptin, phentermine/topiramate only, phentermine/topiramate plus probenecid, phentermine/topiramate plus metformin, and phentermine/topiramate plus sitagliptin on Days 1 – 5, 6 – 10, 11 – 28, 29, 30 – 34, and 35 – 39, respectively.

Effects of Topiramate Alone on Other Drugs and Effects of Other Drugs on Topiramate

Antiepileptic Drugs

Potential interactions between topiramate and standard antiepileptic (AED) drugs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effects of these interactions on mean plasma AUCs are summarized in Table 8.

In Table 8, the second column (AED concentration) describes what happens to the concentration of the AED listed in the first column when topiramate is added. The third column (topiramate concentration) describes how the co-administration of a drug listed in the first column modifies the concentration of topiramate in experimental settings when topiramate was given alone.

Table 8. Summary of AED Interactions with Topiramate

AED Co-administered	AED Concentration	Topiramate Concentration
Phenytoin	NC or 25% increase[a]	48% decrease
Carbamazepine (CBZ)	NC	40% decrease
CBZ epoxide[b]	NC	NE
Valproic acid	11% decrease	14% decrease
Phenobarbital	NC	NE
Primidone	NC	NE
Lamotrigine	NC at TPM doses up to 400 mg/day	13% decrease

[a] Plasma concentration increased 25% in some patients, generally those on a twice a day dosing regimen of phenytoin.
[b] Is not administered but is an active metabolite of carbamazepine.
NC = Less than 10% change in plasma concentration; NE = Not Evaluated; TPM = topiramate

Digoxin

In a single-dose study, serum digoxin AUC was decreased by 12% with concomitant topiramate administration. The clinical relevance of this observation has not been established.

Hydrochlorothiazide

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of hydrochlorothiazide (HCTZ) (25 mg q24h) and topiramate (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that topiramate C_{max} increased by 27% and AUC increased by 29% when HCTZ was added to topiramate. The clinical significance of this change is unknown. The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicated decreases in serum potassium after topiramate or HCTZ administration, which were greater when HCTZ and topiramate were administered in combination.

Pioglitazone

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of topiramate (96 mg twice daily) and pioglitazone (30 mg daily) when administered alone and concomitantly for 7 days. A 15% decrease in the area under the concentration-time curve during a dosage interval at steady state ($AUC_{\tau,ss}$) of pioglitazone with no alteration in maximum steady-state plasma drug concentration during a dosage interval ($C_{max,ss}$) was observed. This finding was not statistically significant. In addition, a 13% and 16% decrease in $C_{max,ss}$ and $AUC_{\tau,ss}$ respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in $C_{max,ss}$ and $AUC_{\tau,ss}$ of the active keto-metabolite. The clinical significance of these findings is not known.

Glyburide

A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glyburide (5 mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 22% decrease in C_{max} and a 25% reduction in AUC_{24} for glyburide during topiramate administration. Systemic exposure (AUC) of the active metabolites, 4-*trans*-hydroxyglyburide (M1), and 3-*cis*-hydroxyglyburide (M2),

was reduced by 13% and 15%, and C_{max} was reduced by 18% and 25%, respectively. The steady-state pharmacokinetics of topiramate were unaffected by concomitant administration of glyburide.

Lithium
In patients, the pharmacokinetics of lithium were unaffected during treatment with topiramate at doses of 200 mg/day; however, there was an observed increase in systemic exposure of lithium (27% for C_{max} and 26% for AUC) following topiramate doses up to 600 mg/day. Lithium levels should be monitored when co-administered with high-dose topiramate.

Haloperidol
The pharmacokinetics of a single dose of haloperidol (5 mg) were not affected following multiple dosing of topiramate (100 mg every 12 hours) in 13 healthy adults (6 males, 7 females).

Amitriptyline
There was a 12% increase in AUC and C_{max} for amitriptyline (25 mg per day) in 18 normal subjects (9 males, 9 females) receiving 200 mg/day of topiramate. Some subjects may experience a large increase in amitriptyline concentration in the presence of topiramate and any adjustments in amitriptyline dose should be made according to the patient's clinical response and not on the basis of plasma levels.

Sumatriptan
Multiple dosing of topiramate (100 mg every 12 hrs) in 24 healthy volunteers (14 males, 10 females) did not affect the pharmacokinetics of single-dose sumatriptan either orally (100 mg) or subcutaneously (6 mg).

Risperidone
When administered concomitantly with topiramate at escalating doses of 100, 250, and 400 mg/day, there was a reduction in risperidone systemic exposure (16% and 33% for steady-state AUC at the 250 and 400 mg/day doses of topiramate). No alterations of 9-hydroxyrisperidone levels were observed. Co-administration of topiramate 400 mg/day with risperidone resulted in a 14% increase in C_{max} and a 12% increase in AUC_{12} of topiramate. There were no clinically significant changes in the systemic exposure of risperidone plus 9-hydroxyrisperidone or of topiramate; therefore, this interaction is not likely to be of clinical significance.

Propranolol
Multiple dosing of topiramate (200 mg/day) in 34 healthy volunteers (17 males, 17 females) did not affect the pharmacokinetics of propranolol following daily 160 mg doses. Propranolol doses of 160 mg/day in 39 volunteers (27 males, 12 females) had no effect on the exposure to topiramate, at a dose of 200 mg/day of topiramate.

Dihydroergotamine
Multiple dosing of topiramate (200 mg/day) in 24 healthy volunteers (12 males, 12 females) did not affect the pharmacokinetics of a 1 mg subcutaneous dose of dihydroergotamine. Similarly, a 1 mg subcutaneous dose of dihydroergotamine did not affect the pharmacokinetics of a 200 mg/day dose of topiramate in the same study.

Diltiazem
Co-administration of diltiazem (240 mg Cardizem CD®) with topiramate (150 mg/day) resulted in a 10% decrease in C_{max} and a 25% decrease in diltiazem AUC, a 27% decrease in C_{max} and an 18% decrease in des-acetyl diltiazem AUC, and no effect on N-desmethyl diltiazem. Co-administration of topiramate with diltiazem resulted in a 16% increase in C_{max} and a 19% increase in AUC_{12} of topiramate.

Venlafaxine
Multiple dosing of topiramate (150 mg/day) in healthy volunteers did not affect the pharmacokinetics of venlafaxine or O-desmethyl venlafaxine. Multiple dosing of venlafaxine (150 mg extended release) did not affect the pharmacokinetics of topiramate.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Phentermine/Topiramate

No animal studies have been conducted with phentermine/topiramate, the combined products in Qsymia, to evaluate carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on findings in studies performed individually with phentermine or topiramate, Qsymia's two active ingredients.

Phentermine

Phentermine was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a chromosomal aberration test in Chinese hamster lung (CHL-K1) cells, or an *in vivo* micronucleus assay.

Rats were administered oral doses of 3, 10, and 30 mg/kg/day phentermine for 2 years. There was no evidence of carcinogenicity at the highest dose of phentermine (30 mg/kg) which is approximately 11 to 15 times the maximum recommended clinical dose of Qsymia 15 mg/92 mg based on AUC exposure.

No animal studies have been conducted with phentermine to determine the potential for impairment of fertility.

Topiramate

Topiramate did not demonstrate genotoxic potential when tested in a battery of *in vitro* and *in vivo* assays. Topiramate was not mutagenic in the Ames test or the *in vitro* mouse lymphoma assay; it did not increase unscheduled DNA synthesis in rat hepatocytes *in vitro*; and it did not increase chromosomal aberrations in human lymphocytes *in vitro* or in rat bone marrow *in vivo*.

An increase in urinary bladder tumors was observed in mice given topiramate (20, 75, and 300 mg/kg) in the diet for 21 months. The elevated bladder tumor incidence, which was statistically significant in males and females receiving 300 mg/kg, was primarily due to the increased occurrence of a smooth muscle tumor considered histomorphologically unique to mice. Plasma exposures in mice receiving 300 mg/kg were approximately 2 to 4 times steady-state exposures measured in patients receiving topiramate monotherapy at the MRHD of Qsymia 15 mg/92 mg. The relevance of this finding to human carcinogenic risk is uncertain. No evidence of carcinogenicity was seen in rats following oral administration of topiramate for 2 years at doses up to 120 mg/kg (approximately 4 to 10 times the MRHD of Qsymia based on AUC estimates).

No adverse effects on male or female fertility were observed in rats at doses up to 100 mg/kg or approximately 4 to 8 times male and female MRHD exposures of Qsymia based on AUC.

13.3 Reproductive and Developmental Toxicology

Topiramate

Topiramate, a component of Qsymia, causes developmental toxicity, including teratogenicity, in multiple animal species at clinically relevant doses.

When oral doses of 20, 100, or 500 mg/kg were administered to pregnant mice during the period of organogenesis, the incidence of fetal malformations (primarily craniofacial defects) was increased at all doses. The low dose of topiramate in this study (20 mg/kg) is approximately 2 times the MRHD of topiramate in Qsymia 15 mg/92 mg on a mg/m^2 basis. Fetal body weights and skeletal ossification were reduced at 500 mg/kg in conjunction with decreased maternal body weight gain.

In rat studies (oral doses of 20, 100, and 500 mg/kg or 0.2, 2.5, 30, and 400 mg/kg), the frequency of limb malformations (ectrodactyly, micromelia, and amelia) was increased among the offspring of dams treated with

400 mg/kg (34 times the MRHD of Qsymia based on AUC estimates) or greater during the organogenesis period of pregnancy. Embryotoxicity (reduced fetal body weights, increased incidence of structural variations) was observed at doses as low as 20 mg/kg (2 times the MRHD of Qsymia based on estimated AUC). Clinical signs of maternal toxicity were seen at 400 mg/kg and above, and maternal body weight gain was reduced during treatment with 100 mg/kg or greater.

In rabbit studies (20, 60, and 180 mg/kg or 10, 35, and 120 mg/kg orally during organogenesis), embryo/fetal mortality was increased at 35 mg/kg (2 times the MRHD based on estimated AUC) or greater, and teratogenic effects (primarily rib and vertebral malformations) were observed at 120 mg/kg (6 times the MRHD of Qsymia based on estimated AUC). Evidence of maternal toxicity (decreased body weight gain, clinical signs, and/or mortality) was seen at 35 mg/kg and above.

When female rats were treated during the latter part of gestation and throughout lactation (0.2, 4, 20, and 100 mg/kg or 2, 20, and 200 mg/kg), offspring exhibited decreased viability and delayed physical development at 200 mg/kg (16 times the MRHD of Qsymia based on estimated AUC) and reductions in pre-and/or post-weaning body weight gain at 2 mg/kg (2 times the MRHD of Qsymia based on estimated AUC) and above. Maternal toxicity (decreased body weight gain, clinical signs) was evident at 100 mg/kg or greater.

In a rat embryo/fetal development study with a postnatal component (0.2, 2.5, 30, or 400 mg/kg during organogenesis; noted above), pups exhibited delayed physical development at 400 mg/kg (34 times the MRHD of Qsymia based on estimated AUC) and persistent reductions in body weight gain at 30 mg/kg (2 times the MRHD of Qsymia based on estimated AUC) and higher.

14 CLINICAL STUDIES

The effect of Qsymia on weight loss in conjunction with reduced caloric intake and increased physical activity was studied in 2 randomized, double-blind, placebo-controlled studies in obese patients (Study 1) and in obese and overweight patients with two or more significant co-morbidities (Study 2). Both studies had a 4-week titration period, followed by 52 weeks of treatment. There were 2 co-primary efficacy outcomes measured after 1 year of treatment (Week 56): 1) the percent weight loss from baseline; and 2) treatment response defined as achieving at least 5% weight loss from baseline.

In Study 1, obese patients (BMI greater than or equal to 35 kg/m^2) were randomized to receive 1 year of treatment with placebo (N=514), Qsymia 3.75 mg/23 mg (N=241), or Qsymia 15 mg/92 mg (N=512) in a 2:1:2 ratio. Patients ranged in age from 18-71 years old (mean age 43) and 83% were female. Approximately 80% were Caucasian, 18% were African American, and 15% were Hispanic/Latino. At the beginning of the study the average weight and BMI of patients was 116 kg and 42 kg/m^2, respectively. Patients with type 2 diabetes were excluded from participating in Study 1. During the study, a well-balanced, reduced-calorie diet to result in an approximate 500 kcal/day decrease in caloric intake was recommended to all patients and patients were offered nutritional and lifestyle modification counseling.

In Study 2, overweight and obese patients were randomized to receive 1 year of treatment with placebo (N=994), Qsymia 7.5 mg/46 mg (N=498), or Qsymia 15 mg/92 mg (N=995) in a 2:1:2 ratio. Eligible patients had to have a BMI greater than or equal to 27 kg/m^2 and less than or equal to 45 kg/m^2 (no lower limit on BMI for patients with type 2 diabetes) and two or more of the following obesity-related co-morbid conditions:

- Elevated blood pressure (greater than or equal to 140/90 mmHg, or greater than or equal to 130/85 mmHg for diabetics) or requirement for greater than or equal to 2 antihypertensive medications;
- Triglycerides greater than 200-400 mg/dL or were receiving treatment with 2 or more lipid-lowering agents;
- Elevated fasting blood glucose (greater than 100 mg/dL) or diabetes; and/or

- Waist circumference greater than or equal to 102 cm for men or greater than or equal to 88 cm for women.

Patients ranged in age from 19-71 years old (mean age 51) and 70% were female. Approximately 86% were Caucasian, 12% were African American, and 13% were Hispanic/Latino. The average weight and BMI of patients at the start of the study was 103 kg and 36.6 kg/m^2, respectively. Approximately half (53%) of patients had hypertension at the start of the study. There were 388 (16%) patients with type 2 diabetes at the start of the study. During the study, a well-balanced, reduced-calorie diet to result in an approximate 500 kcal/day decrease in caloric intake was recommended to all patients and patients were offered nutritional and lifestyle modification counseling.

A substantial percentage of randomized patients withdrew from each study prior to week 56, 40% in Study 1, and 31% in Study 2.

Table 9 provides the results for the weight loss at 1 year in Studies 1 and 2. After 1 year of treatment with Qsymia, all dose levels resulted in statistically significant weight loss compared to placebo (Table 9, Figures 1 and 2). A statistically significant greater proportion of the patients randomized to Qsymia than placebo achieved 5% and 10% weight loss.

Table 9. Weight Loss at One Year in Study 1 and 2

	Study 1 (Obesity)			Study 2 (Overweight and Obese with Co-morbidities)		
Analysis Method	**Placebo**	**Qsymia 3.75 mg/23 mg**	**Qsymia 15 mg/92 mg**	**Placebo**	**Qsymia 7.5 mg/46 mg**	**Qsymia 15 mg/92 mg**
ITT-LOCF (Primary)*	n = 498	n = 234	n = 498	n = 979	n = 488	n = 981
Weight (kg)						
Baseline mean (SD)	115.7 (21.4)	118.6 (21.9)	115.2 (20.8)	103.3 (18.1)	102.8 (18.2)	103.1 (17.6)
% LS Mean Change from baseline (SE)**	-1.6 (0.4)	-5.1 (0.5)†	-10.9 (0.4)†‡	-1.2 (0.3)	-7.8 (0.4)†	-9.8 (0.3)†‡
Difference from placebo (95% CI)		3.5 (2.4-4.7)	9.4 (8.4-10.3)		6.6 (5.8-7.4)	8.6 (8.0-9.3)
Percentage of patients losing greater than or equal to 5% body weight	17%	45%†	67%†‡	21%	62%†	70%†‡
Risk Difference vs. placebo (95% CI)		27.6 (20.4-34.8)	49.4 (44.1-54.7)		41.3 (36.3-46.3)	49.2 (45.4-53.0)
Percentage of patients losing greater than or equal to 10% body weight	7%	19%†	47%†‡	7%	37%†	48%†‡
Risk Difference vs. placebo (95% CI)		11.4 (5.9-16.9)	39.8 (34.8-44.7)		29.9 (25.3-34.5)	40.3 (36.7-43.8)

SD=standard deviation; LS=least-squares; SE=standard error; CI=confidence interval

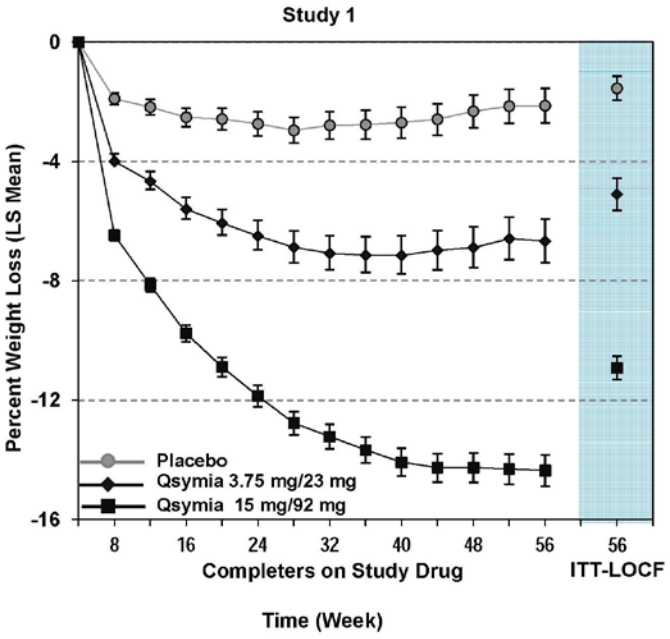
* Uses all available data from subjects in ITT population, including data collected from subjects who discontinued drug but remained on study. Last Observation Carried Forward (LOCF) method used to impute missing data.

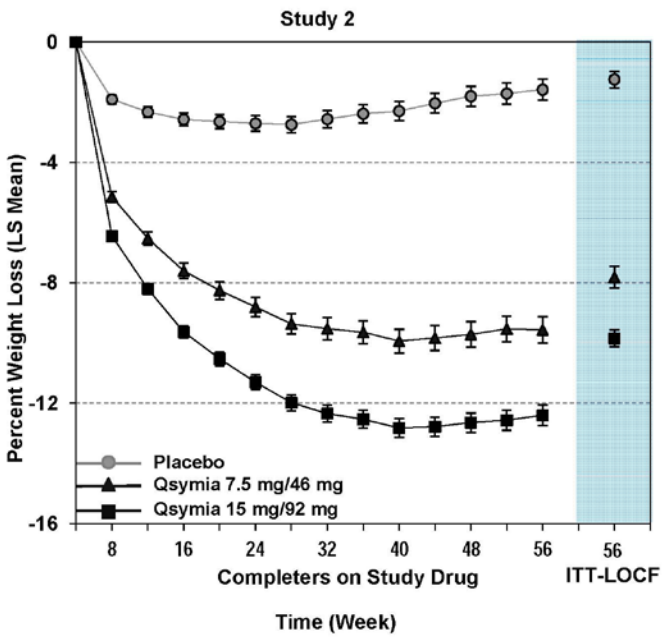
† $p < 0.0001$ vs. placebo based on least-squares (LS) mean from an analysis of covariance.

‡ $p < 0.01$ vs. 3.75 mg/23 mg (Study 1) or 7.5 mg/46 mg (Study 2) dose.

Type 1 error was controlled across all pairwise treatment comparisons.

** Adjusted for baseline bodyweight (Study 1) and baseline bodyweight and diabetic status (Study 2).





p<0.0001 for all three Qsymia doses vs placebo, and 15 mg/92 mg vs 7.5 mg/46 mg or 3.75 mg/23 mg at all time points for both completers and ITT-LOCF

Figure 1. Study 1 Percent Weight Change

Figure 2. Study 2 Percent Weight Change

The changes in cardiovascular, metabolic, and anthropometric risk factors associated with obesity from Study 1 and 2 are presented in Table 10 and 11. One year of therapy with Qsymia resulted in relative improvement over placebo in several risk factors associated with obesity with the exception of heart rate *[see Warnings and Precautions (5.2)]*.

Table 10. Least-Squares (LS) Mean† Change from Baseline and Treatment Difference from Placebo in Risk Factors Following One Year of Treatment in Study 1 (Obesity)

Study 1 (Obesity)	Placebo (N=498)	Qsymia 3.75 mg/23 mg (N=234)	Qsymia 15 mg/92 mg (N=498)	Qsymia – Placebo: LS Mean	
				Qsymia 3.75 mg/23 mg	Qsymia 15 mg/92 mg
Heart rate, bpm					
Baseline mean (SD)	73.2 (8.8)	72.3 (9.2)	73.1 (9.6)	+1.1	+1.8
LS Mean Change (SE)	-0.8 (0.5)	+0.3 (0.6)	+1.0 (0.5)		
Systolic blood pressure, mmHg					
Baseline mean (SD)	121.9 (11.5)	122.5 (11.1)	121.9 (11.6)	-2.8	-3.8
LS Mean Change (SE)	+0.9 (0.6)	-1.8 (0.8)	-2.9 (0.6)		
Diastolic blood pressure, mmHg					
Baseline mean (SD)	77.2 (7.9)	77.8 (7.5)	77.4 (7.7)	-0.5	-1.9
LS Mean Change (SE)	+0.4 (0.4)	-0.1 (0.6)	-1.5 (0.4)		
Total Cholesterol, %					
Baseline mean (SD)	194.3 (36.7)	196.3 (36.5)	192.7 (33.8)	-1.9	-2.5
LS Mean Change (SE)	-3.5 (0.6)	-5.4 (0.9)	-6.0 (0.6)		
LDL-Cholesterol, %					
Baseline mean (SD)	120.9 (32.2)	122.8 (33.4)	120.0 (30.1)	-2.2	-2.8
LS Mean Change (SE)	-5.5 (1.0)	-7.7 (1.3)	-8.4 (0.9)		
HDL-Cholesterol, %					
Baseline mean (SD)	49.5 (13.3)	50.0 (11.1)	49.7 (11.7)	+0.5	+3.5
LS Mean Change (SE)	+0.0 (0.8)	+0.5 (1.1)	+3.5 (0.8)		
Triglycerides, %					
Baseline mean (SD)	119.0 (39.3)	117.5 (40.3)	114.6 (37.1)	-3.9	-14.3
LS Mean Change (SE)	+9.1 (2.3)	+5.2 (3.1)	-5.2 (2.2)		
Fasting glucose, mg/dL					
Baseline mean (SD)	93.1 (8.7)	93.9 (9.2)	93.0 (9.5)	-1.2	-2.5
LS Mean Change (SE)	+1.9 (0.5)	+0.8 (0.7)	-0.6 (0.5)		
Waist Circumference, cm					
Baseline mean (SD)	120.5 (14.0)	121.5 (15.2)	120.0 (14.7)	-2.5*	-7.8*
LS Mean Change (SE)	-3.1 (0.5)	-5.6 (0.6)	-10.9 (0.5)		

SD=standard deviation; SE=standard error

* Statistically significant versus placebo based on the pre-specified method for controlling Type I error across multiple doses

† Study 1 adjusted for baseline bodyweight

Table 11. Least-Squares (LS) Mean† Change from Baseline and Treatment Difference from Placebo in Risk Factors Following One Year of Treatment in Study 2 (Overweight and Obese with Comorbidities)

Study 2 (Overweight and Obese with Comorbidities)	Placebo (N=979)	Qsymia 7.5 mg/46 mg (N=488)	Qsymia 15 mg/92 mg (N=981)	Qsymia – Placebo: LS Mean	
				Qsymia 7.5 mg/46 mg	Qsymia 15 mg/92 mg
Heart rate, bpm					
Baseline mean (SD)	72.1 (9.9)	72.2 (10.1)	72.6 (10.1)	+0.6	+1.7
LS Mean Change (SE)	-0.3 (0.3)	+0.3 (0.4)	+1.4 (0.3)		
Systolic Blood Pressure, mmHg					
Baseline mean (SD)	128.9 (13.5)	128.5 (13.6)	127.9 (13.4)	-2.3	-3.2
LS Mean Change (SE)	-2.4 (0.48)	-4.7 (0.63)	-5.6 (0.5)		
Diastolic Blood Pressure, mmHg					
Baseline mean (SD)	81.1 (9.2)	80.6 (8.7)	80.2 (9.1)	-0.7	-1.1
LS Mean Change (SE)	-2.7 (0.3)	-3.4 (0.4)	-3.8 (0.3)		
Total Cholesterol, %					
Baseline mean (SD)	205.8 (41.7)	201.0 (37.9)	205.4 (40.4)	-1.6	-3.0
LS Mean Change (SE)	-3.3 (0.5)	-4.9 (0.7)	-6.3 (0.5)		
LDL-Cholesterol, %					
Baseline mean (SD)	124.2 (36.2)	120.3 (33.7)	123.9 (35.6)	+0.4	-2.8
LS Mean Change (SE)	-4.1 (0.9)	-3.7 (1.1)	-6.9 (0.9)		
HDL-Cholesterol, %					
Baseline mean (SD)	48.9 (13.8)	48.5 (12.8)	49.1 (13.8)	+4.0	+5.6
LS Mean Change (SE)	+1.2 (0.7)	+5.2 (0.9)	+6.8 (0.7)		
Triglycerides, %					
Baseline mean (SD)	163.5 (76.3)	161.1 (72.2)	161.9 (73.4)	-13.3	-15.3
LS Mean Change (SE)	+4.7 (1.7)	-8.6 (2.2)	-10.6 (1.7)		
Fasting Insulin, (µIU/mL)					
Baseline mean (SD)	17.8 (13.2)	18.0 (12.9)	18.4 (17.5)	-4.2	-4.7
LS Mean Change (SE)	+0.7 (0.8)	-3.5 (1.1)	-4.0 (0.8)		
Fasting glucose, mg/dL					
Baseline mean (SD)	106.6 (23.7)	106.2 (21.0)	105.7 (21.4)	-2.4	-3.6
LS Mean Change (SE)	+2.3 (0.6)	-0.1 (0.8)	-1.3 (0.6)		
Waist Circumference, cm					
Baseline mean (SD)	113.4 (12.2)	112.7 (12.4)	113.2 (12.2)	-5.2*	-6.8*
LS Mean Change (SE)	-2.4 (0.3)	-7.6 (0.4)	-9.2 (0.3)		

SD=standard deviation; SE=standard error
* Statistically significant versus placebo based on the pre-specified method for controlling Type I error across multiple doses
† Study 2 adjusted for baseline bodyweight and diabetic status

Among the 388 subjects with type 2 diabetes treated in study 2, reductions in HbA1c from baseline (6.8%) were 0.1% for placebo compared to 0.4% and 0.4% with Qsymia 7.5 mg/46 mg and Qsymia 15 mg/92 mg, respectively *[see Warnings and Precautions (5.9)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

Qsymia is available as phentermine hydrochloride (expressed as the weight of the free base)/topiramate extended-release gelatin capsules in the following strengths and colors:

- 3.75 mg/23 mg [Purple cap imprinted with VIVUS, Purple body imprinted with 3.75/23]
- 7.5 mg/46 mg [Purple cap imprinted with VIVUS, Yellow body imprinted with 7.5/46]
- 11.25 mg/69 mg [Yellow cap imprinted with VIVUS, Yellow body imprinted with 11.25/69]
- 15 mg/92 mg [Yellow cap imprinted with VIVUS, White body imprinted with 15/92]

The capsules are supplied as follows:

Strength		NDC Code
Unit of Use Bottle (14 capsules)	3.75 mg/23 mg capsules	62541-201-14
Pharmacy Bottle (30 capsules)	3.75 mg/23 mg capsules	62541-201-30
Unit of Use Bottle (30 capsules)	7.5 mg/46 mg capsules	62541-202-30
Unit of Use Bottle (30 capsules)	15 mg/92 mg capsules	62541-204-30
Pharmacy Bottle (30 capsules)	11.25 mg/69 mg capsules	62541-203-30
Starter Pack - Blister Configuration (28 Capsules)	3.75 mg/23 mg and 7.5 mg/46 mg capsules	62541-210-28
Dose Escalation Pack – Blister Configuration (28 Capsules)	11.25 mg/69 mg and 15 mg/92 mg capsules	62541-220-28

Store at controlled room temperature, 15°C to 25°C (59°F to 77°F). Keep container tightly closed and protect from moisture.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

Adjunctive Treatment
Qsymia is indicated for chronic weight management in conjunction with a reduced-calorie diet and increased physical activity.

Access to Qsymia
Qsymia is only available through certified pharmacies that are enrolled in the Qsymia certified pharmacy network. Advise patients on how to access Qsymia through certified pharmacies. Additional information may be obtained via the website www.QsymiaREMS.com or by telephone at 1-888-998-4887.

Concomitant Use with Other Products
Advise patients to tell healthcare provider(s) about all medications, nutritional supplements, and vitamins (including any weight loss products) that are being taken or may be taken while on Qsymia.

How to take Qsymia

Advise patients to take Qsymia in the morning with or without food.

Advise patients to start treatment with Qsymia as follows:

- Take one Qsymia 3.75 mg/23 mg capsule once daily – in the morning - for the first 14 days

- After the first 14 days is complete, take one Qsymia 7.5 mg/46 mg capsule once daily – in the morning
- Do not take Qsymia 3.75 mg/23 mg and Qsymia 7.5/46 mg capsules together

If an increase in Qsymia dose is prescribed after medical evaluation, advise patients to increase the dose of Qsymia as follows:

- Take one Qsymia 11.25 mg/69 mg capsule once daily – in the morning - for 14 days
- After the 14 days is complete, take one Qsymia 15 mg/92 mg capsule once daily – in the morning
- Do not take Qsymia 11.25/69 mg and Qsymia 15 mg/92 mg capsules together

Advise patients to discontinue the Qsymia 15 mg/92 mg dose gradually by taking one Qsymia 15 mg/92 mg capsule every other day for at least one week before stopping in order to avoid a seizure.

Females of Reproductive Potential

Qsymia can cause fetal harm and patients should avoid getting pregnant while taking Qsymia *[see Warnings and Precautions (5.1)]*

- Pregnancy testing is recommended before starting Qsymia and monthly thereafter during therapy.
- Advise patients about effective methods of contraception, as well as the importance of using effective contraception consistently during Qsymia therapy. Advise females who become pregnant during Qsymia therapy to stop Qsymia immediately and tell their healthcare provider(s).

Nursing Mothers

Either discontinue nursing or discontinue Qsymia *[see Use in Specific Populations (8.3)]*.

Elevation in Heart Rate

- Qsymia can increase resting heart rate *[see Warnings and Precautions (5.2)]*.
- Advise patients to report symptoms of sustained periods of heart pounding or racing while at rest to their healthcare provider(s).

Suicidal Behavior and Ideation; Changes in Mood or Depression

Qsymia can increase the risk of mood changes, depression, and suicidal ideation *[see Warnings and Precautions (5.5)]*.

- Advise patients to tell their healthcare provider(s) immediately if mood changes, depression, and suicidal ideation occur.

Acute Angle Closure Glaucoma

Qsymia can increase the risk of acute myopia and secondary angle closure glaucoma *[see Warnings and Precautions (5.4)]*.

- Advise patients to report symptoms of severe and persistent eye pain or significant changes in their vision to their healthcare provider(s).

Cognitive Adverse Reactions

Qsymia can cause dizziness, confusion, concentration, and word-finding difficulties, or visual changes *[see Warnings and Precautions (5.6)]*.

- Advise patients to tell their healthcare provider(s) about any changes in attention, concentration, memory, and/or difficulty finding words.

- Advise patients not to drive or operate machinery until they have gained sufficient experience on Qsymia to gauge whether it adversely affects their mental performance, motor performance, and/or vision.

Metabolic Acidosis

Qsymia can increase the risk of metabolic acidosis *[see Warnings and Precautions (5.7)]*.

- Advise patients to tell their healthcare provider(s) about any factors that can increase the risk of acidosis (e.g. prolonged diarrhea, surgery, and high protein/low carbohydrate diet, and/or concomitant medications such as carbonic anhydrase inhibitors).

Hypoglycemia in Patients with Type 2 Diabetes Mellitus on Anti-diabetic Therapy

Weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus treated with insulin and/or insulin secretagogues (e.g., sulfonylureas) *[see Warnings and Precautions (5.9)]*.

- Advise patients with type 2 diabetes mellitus on anti-diabetic therapy to monitor their blood glucose levels and report symptoms of hypoglycemia to their healthcare provider(s)

CNS Depression with Concomitant CNS Depressants including Alcohol

The concomitant use of alcohol or central nervous system (CNS) depressant drugs (e.g., barbiturates, benzodiazepines, and sleep medications) with phentermine or topiramate may potentiate CNS depression or other centrally mediated effects of these agents, such as dizziness, cognitive adverse reactions, drowsiness, light-headedness, impaired coordination and somnolence *[see Warnings and Precautions (5.11)]*.

- Advise patients not to drink alcohol while taking Qsymia.

Potential Seizures with Abrupt Withdrawal of Qsymia

Abrupt withdrawal of topiramate, a component of Qsymia, has been associated with seizures in individuals without a history of seizures or epilepsy.

- Advise patients not to abruptly stop Qsymia without first talking to their healthcare provider(s) *[see Dosage and Administration (2.1)]*

Kidney stones

Use of Qsymia has been associated with kidney stone formation *[see Warnings and Precautions (5.15) and Adverse Reactions (6.1)]*.

- Advise patients to increase fluid intake to increase urinary output which can decrease the concentration of substances involved in kidney stone formation.
- Advise patients to report symptoms of severe side or back pain, and/or blood in their urine to their healthcare provider(s).

Oligohidrosis and Hyperthermia

Oligohidrosis (decreased sweating) has been reported in association with the use of topiramate, a component of Qsymia. Decreased sweating and an elevation in body temperature above normal characterized these cases.

- Advise patients to monitor for decreased sweating and increased body temperature during physical activity, especially in hot weather.

Manufactured for VIVUS, Inc. by Catalent Pharma Solutions, LLC
1100 Enterprise Drive
Winchester, KY 40391

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US Patent Numbers: 7,056,890; 7,553,818; 7,659,256; 7,674,776; 8,580,298; 8,580,299; 8,895,057; 8,895,058, 9,011,905; and 9,011,906

MEDICATION GUIDE

QSYMIA® (Kyoo sim ee' uh)

(phentermine and topiramate extended-release)

Capsules CIV

Read this Medication Guide before you start taking Qsymia and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. If you have any questions about Qsymia, talk to your healthcare provider or pharmacist.

What is the most important information I should know about Qsymia?

(For other side effects, also see **"What are the possible side effects of Qsymia?"**)

Qsymia can cause serious side effects, including:

- **Birth defects (cleft lip/cleft palate).** If you take Qsymia during pregnancy, your baby has a higher risk for birth defects called cleft lip and cleft palate. These defects can begin early in pregnancy, even before you know you are pregnant.

  Women who are pregnant must not take Qsymia.

  Women who can become pregnant should:

  1. Have a negative pregnancy test before taking Qsymia and every month while taking Qsymia.
  2. Use effective birth control (contraception) consistently while taking Qsymia. Talk to your healthcare provider about how to prevent pregnancy.

  If you become pregnant while taking Qsymia, stop taking Qsymia immediately, and tell your healthcare provider right away. Healthcare providers and patients should report all cases of pregnancy to:

  - FDA MedWatch at 1-800-FDA-1088, and
  - The Qsymia Pregnancy Surveillance Program at 1-888-998-4887

- **Increases in heart rate.** Qsymia can increase your heart rate at rest. Your healthcare provider should check your heart rate while you take Qsymia. Tell your healthcare provider if you experience, while at rest, a racing or pounding feeling in your chest lasting several minutes when taking Qsymia.
- **Suicidal thoughts or actions.** Topiramate, an ingredient in Qsymia, may cause you to have suicidal thoughts or actions.

Call your healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

- **Serious eye problems** which include:
  - any sudden decrease in vision, with or without eye pain and redness,
  - a blockage of fluid in the eye causing increased pressure in the eye (secondary angle closure glaucoma).

These problems can lead to permanent vision loss if not treated. Tell your healthcare provider right away if you have any new eye symptoms.

What is Qsymia?

Qsymia is a prescription medicine that contains phentermine and topiramate extended-release that may help some obese adults or some overweight adults who also have weight-related medical problems lose weight and keep the weight off.

Qsymia should be used with a reduced calorie diet and increased physical activity.

It is not known if Qsymia changes your risk of heart problems or stroke or of death due to heart problems or stroke.

It is not known if Qsymia is safe and effective when taken with other prescription, over-the-counter, or herbal weight loss products.

It is not known if Qsymia is safe and effective in children under 18 years old.

Qsymia is a federally controlled substance (CIV) because it contains phentermine and can be abused or lead to drug dependence. Keep Qsymia in a safe place, to protect it from theft. Never give your Qsymia to anyone else, because it may cause death or harm them. Selling or giving away this medicine is against the law.

Who should not take Qsymia?

Do not take Qsymia if you:

- are pregnant, planning to become pregnant, or become pregnant during Qsymia treatment.
- have glaucoma
- have thyroid problems (hyperthyroidism)
- are taking certain medicines called monoamine oxidase inhibitors (MAOIs) or have taken MAOIs in the past 14 days.
- are allergic to topiramate, sympathomimetic amines such as phentermine, or any of the ingredients in Qsymia. See the end of this Medication Guide for a complete list of ingredients in Qsymia.

What should I tell my healthcare provider before taking Qsymia?

Tell your healthcare provider if you:

- are pregnant or planning to become pregnant
- have had a heart attack or stroke
- have or have had an abnormal heart rhythm
- have or have had depression, mood problems, or suicidal thoughts or behavior
- have eye problems, especially glaucoma
- have a history of metabolic acidosis (too much acid in the blood) or a condition that puts you at higher risk for metabolic acidosis such as
    - chronic diarrhea, surgery, a diet high in fat and low in carbohydrates (ketogenic diet), weak, brittle, or soft bones (osteomalacia, osteoporosis, osteopenia), or decreased bone density
- have kidney problems, have kidney stones, or are getting kidney dialysis
- have liver problems
- have seizures or convulsions (epilepsy)
- are breastfeeding. It is not known if Qsymia passes into your breast milk. You and your healthcare provider should decide if you will take Qsymia or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Qsymia taken with other medicines may affect how each medicine works and may cause side effects.

Especially tell your healthcare provider if you take:

- **Birth control pills**. Tell your healthcare provider if your menstrual bleeding changes while you are taking birth control pills and Qsymia.
- **Water pills** (diuretics) such as hydrochlorothiazide (HCTZ)

- **Any medicines that impair or decrease your thinking, concentration, or muscle coordination**
- **Carbonic anhydrase inhibitors** [such as ZONEGRAN® (zonisamide), DIAMOX® (acetazolamide) or NEPTAZANE® (methazolamide)]
- **Seizure medicines** such as Valproic acid (DEPAKENE® or DEPAKOTE®)

Ask your healthcare provider or pharmacist for a list of these medicines, if you are not sure.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist each time you get a new medicine. Do not start a new medicine without talking to your healthcare provider.

How should I take Qsymia?

- Your healthcare provider should start you on a diet and exercise program when you start taking Qsymia. Stay on this program while you are taking Qsymia.
- **Do not** change your dose without talking to your healthcare provider.
- Qsymia can be taken with or without food.
- If you miss a dose of Qsymia, wait until the next morning to take your usual dose of Qsymia. **Do not** double your dose.
- **To start treatment with Qsymia**
    - Take one Qsymia 3.75 mg/23 mg capsule (Figure A) once each morning for the first 14 days
    - After taking Qsymia 3.75 mg/23 mg capsule for 14 days, then take one Qsymia 7.5 mg/46 mg capsule (Figure B) once each morning
- **After taking Qsymia for 12 weeks**
    - Your healthcare provider should either (1) tell you to stop taking Qsymia or (2) increase your dose of Qsymia if you do not lose a certain amount of weight within the first 12 weeks of treatment at the recommended dose.
- **If your healthcare provider increases the dose of Qsymia**
    - Take one Qsymia 11.25 mg/69 mg capsule (Figure C) once each morning for 14 days
    - After taking 14 days of Qsymia 11.25 mg/69 mg capsule, then take one Qsymia 15 mg/92 mg capsule (Figure D) once each morning
- **Stopping Qsymia treatment**

Your healthcare provider should tell you to stop taking Qsymia if you have not lost a certain amount of weight after an additional 12 weeks of treatment on the higher dose.

Do not stop taking Qsymia without talking to your healthcare provider. Stopping Qsymia suddenly can cause serious problems, such as seizures. Your healthcare provider will tell you how to stop taking Qsymia slowly.

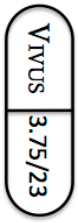


Figure A
Qsymia (3.75 mg/23 mg)
Cap and body are purple with white printing

Figure B
Qsymia (7.5 mg/46 mg)
Cap is purple with white printing and the body is yellow with black printing

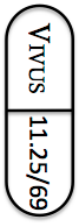


Figure C
Qsymia (11.25 mg/69 mg)
Cap and body are yellow with black printing

Figure D
Qsymia (15 mg/92 mg)
Cap is yellow with black printing and the body is white with black printing

If you take too much Qsymia, call your healthcare provider or go to the nearest emergency room right away.

What should I avoid while taking Qsymia?

- **Do not get pregnant while taking Qsymia.** See **"What is the most important information I should know about Qsymia."**
- **Do not drink alcohol while taking Qsymia**. Qsymia and alcohol can affect each other causing side effects such as sleepiness or dizziness.
- **Do not drive a car or operate heavy machinery, or do other dangerous activities until you know how Qsymia affects you.** Qsymia can slow your thinking and motor skills, and may affect vision.

What are the possible side effects of Qsymia?

- See **"What is the most important information I should know about Qsymia?"** at the beginning of this Medication Guide
- **Mood changes and trouble sleeping.** Qsymia may cause depression or mood problems, and trouble sleeping. Tell your healthcare provider if symptoms occur.
- **Concentration, memory, and speech difficulties.** Qsymia may affect how you think and cause confusion, problems with concentration, attention, memory, or speech. Tell your healthcare provider if symptoms occur.
- **Increases of acid in bloodstream (metabolic acidosis).** If left untreated, metabolic acidosis can cause brittle or soft bones (osteoporosis, osteomalacia, osteopenia), kidney stones, can slow the rate of growth in children, and may possibly harm your baby if you are pregnant. Metabolic acidosis can happen with or without symptoms. Sometimes people with metabolic acidosis will:
  - feel tired
  - not feel hungry (loss of appetite)
  - feel changes in heartbeat
  - have trouble thinking clearly

  Your healthcare provider should do a blood test to measure the level of acid in your blood before and during your treatment with Qsymia.

- **Low blood sugar (hypoglycemia) in people with type 2 diabetes mellitus who also take medicines used to treat type 2 diabetes mellitus.** Weight loss can cause low blood sugar in people with type 2 diabetes mellitus who also take medicines used to treat type 2 diabetes mellitus (such as insulin or sulfonylureas). You should check your blood sugar before you start taking Qsymia and while you take Qsymia.
- **Possible seizures if you stop taking Qsymia too fast.** Seizures may happen in people who may or may not have had seizures in the past if you stop Qsymia too fast. Your healthcare provider will tell you how to stop taking Qsymia slowly.
- **Kidney stones.** Drinking plenty of fluids when taking Qsymia to help decrease your chances of getting kidney stones. If you get severe side or back pain, and/or blood in your urine, call your healthcare provider
- **Decreased sweating and increased body temperature (fever).** People should be watched for signs of decreased sweating and fever, especially in hot temperatures. Some people may need to be hospitalized for this condition.

Common side effects of Qsymia include:

- numbness or tingling in the hands, arms, feet, or face (paraesthesia)
- dizziness
- change in the way foods taste or loss of taste (dysgeusia)
- trouble sleeping (insomnia)
- constipation
- dry mouth

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

These are not all of the possible side effects of Qsymia. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to VIVUS at 1-888-998-4887 or FDA at 1-800-FDA-1088.

How should I store Qsymia?

- Store Qsymia at room temperature between 59°F to 77°F (15°C to 25°C).

Keep Qsymia and all medicines out of the reach of children.

General Information about Qsymia

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Qsymia for a condition for which it was not prescribed. Do not give Qsymia to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes important information about Qsymia. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Qsymia that is written for healthcare professionals.

For more information, go to www.QsymiaREMS.com or call 1-888-998-4887.

What are the ingredients in Qsymia?

Active Ingredient: phentermine hydrochloride and topiramate extended-release

Inactive Ingredients: methylcellulose, sucrose, starch, microcrystalline cellulose, ethylcellulose, povidone, gelatin, talc, titanium dioxide, FD&C Blue #1, FD&C Red #3, FD&C Yellow #5 and #6, and pharmaceutical black and white inks.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

VIVUS, Inc
900 E. Hamilton Ave., Suite 550
Campbell, CA 95008 USA

US Patent Numbers: 7,056,890; 7,553,818; 7,659,256; 7,674,776; 8,580,298; 8,580,299; 8,895,057; 8,895,058; 9,011,905; and 9,011,906

Qsymia is a registered trademark of VIVUS, Inc.

PH-03-002-09

EXHIBIT M

Vivus Therapeutics' cease and desist request

VIVUS, Inc.
900 E. Hamilton Ave., Suite 550, Campbell, California 95008 | TEL (650) 934-5200

WRITER'S DIRECT DIAL NO.
(650) 934-5306

WRITER'S EMAIL ADDRESS
wells@vivus.com

March 30, 2018

VIA UPS

Shaun Noorian, CEO
Empower Clinical Services, LLC
dba Empower Pharmacy
5980 W Sam Houston Pkwy N
Suite 300
Houston, TX 77041

Re: U.S. Patents Covering Pharmaceutical Compositions Comprising Phentermine HCl and Topiramate

Dear Mr. Noorian:

I represent VIVUS, Inc. ("VIVUS") as intellectual property counsel. It has come to our attention that you are compounding and offering for sale, through EmpowerRX, a pharmaceutical composition comprised of phentermine HCl and topiramate for weight management. Based on your "Patient Product Catalog" (02.19) as well as your "Clinic Product Catalog" (02.19.3) on pages 5 and 3, respectively, you are offering for sale products you refer to as "Phentermine HCl/Topiramate" at the following strengths 15/12.5, 15/25, 30/25, 30/50, 45/25 and 45/50 mg.

VIVUS is the owner of U.S. Patent Nos 7,553,818 ("the '818 patent"), 7,659,256 ("the '256 patent") and 7,674,776 ("the '776 patent") covering, among other things, pharmaceutical compositions comprised of phentermine in combination with topiramate. Copies of the '818 patent, the '256 patent and the '776 patent are enclosed for your reference.

We believe that by your activity, you have infringed, and continue to infringe, the '818 patent, the '256 patent and the '776 patent pursuant to 35 U.S.C. § 271. Accordingly, you should immediately cease and desist from offering your "Phentermine HCl/Topiramate" combinations for sale and provide to me via email a copy of your revised patient and clinic product catalogs once these products have been removed.

I would also like to take this opportunity to make sure that you are aware that QSYMIA® (phentermine and topiramate extended-release) is subject to a risk evaluation and mitigation strategy (REMS) with the goal of informing prescribers and female patients of reproductive

potential about (i) the increased risk of congenital malformation in infants exposed to QSYMIA during the first trimester of pregnancy, (ii) the importance of pregnancy prevention for females of reproductive potential receiving QSYMIA and (iii) the need to discontinue QSYMIA immediately if pregnancy occurs. The REMS program has been put in place to mitigate the risk of birth defects and includes elements to assure safe use that limit dispensing of QSYMIA to only certified pharmacies that agree to distribute the QSYMIA Medication Guide and the *Risk of Birth Defects with Qsymia* patient brochure each time QSYMIA is dispensed and to maintain a list of QSYMIA prescribers. The FDA made the determination that a REMS was required for safe distribution of QSYMIA and in the event a generic equivalent to QSYMIA is approved in the future the generic manufacturer would also be required to provide a comparable REMS program.

The QSYMIA REMS program, like many REMS, is a complex program that is specifically designed to ensure patient safety with respect to a drug that poses a heightened safety risk. VIVUS has worked diligently to establish an appropriate risk management plan to address these heightened risks and to allow patients to safely receive the benefits of QSYMIA and mitigate VIVUS's liability risks. Your distribution of "Phentermine HCl/Topiramate" subverts the QSYMIA REMS program and potentially exposes patients to safety risks.

We hope that this matter can be resolved amicably without resorting to any of the legal and equitable remedies that are available to VIVUS to protect our intellectual property rights relating to pharmaceutical compositions comprised of phentermine in combination with topiramate. Please contact me immediately so that we can discuss the resolution of this matter.

Very truly yours,

Sandra Wells

Sandra Wells
VP Patents & Assistant General Counsel

Enclosures:

U.S. Patent Nos. 7,553,818, 7,659,256 and 7,674,776

EXHIBIT N

Chemical Abstracts™ abstract for avanafil

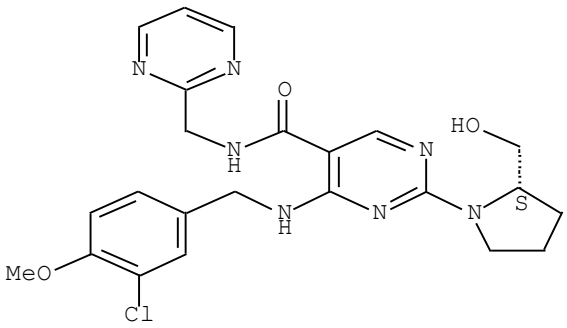
Detailed Results

```
L1    ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2018 ACS on STN
RN    330784-47-9  REGISTRY
ED    Entered STN:  11 Apr 2001
CN    5-Pyrimidinecarboxamide, 4-[[(3-chloro-4-methoxyphenyl)methyl]amino]-2-
      [(2S)-2-(hydroxymethyl)-1-pyrrolidinyl]-N-(2-pyrimidinylmethyl)-  (CA
      INDEX NAME)
OTHER CA INDEX NAMES:
CN    4-[[(3-Chloro-4-methoxyphenyl)methyl]amino]-2-[(2S)-2-(hydroxymethyl)-1-
      pyrrolidinyl]-N-(2-pyrimidinylmethyl)-5-pyrimidinecarboxamide
OTHER NAMES:
CN    (S)-2-(2-Hydroxymethyl-1-pyrrolidinyl)-4-(3-chloro-4-methoxybenzylamino)-5-
      [N-(2-pyrimidinylmethyl)carbamoyl]pyrimidine
CN    Avanafil
CN    TA 1790
FS    STEREOSEARCH
DR    330785-17-6, 647841-09-6
MF    C23 H26 Cl N7 O3
CI    COM
SR    CA
LC    STN Files:   ADISINSIGHT, CA, CAPLUS, CASREACT, CHEMCATS, CHEMLIST,
        EMBASE, IMSRESEARCH, IPA, MEDLINE, TOXCENTER, USPAT2, USPATFULL
DT.CA  CAplus document type:  Journal; Patent
```

Ring System Data

Elemental Analysis EA	Elemental Sequence ES	Size of the Rings SZ	Ring System Formula RF	Ring Identifier RID	RID Occurrence Count
C4N	NC4	5	C4N	16.136.1	1
C6	C6	6	C6	46.150.18	1
C4N2	NCNC3	6	C4N2	46.195.39	2

Absolute stereochemistry.




```
See HELP PROPERTIES for information about property data sources in REGISTRY.
             269 REFERENCES IN FILE CA (1907 TO DATE)
               1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             272 REFERENCES IN FILE CAPLUS (1907 TO DATE)
```

EXHIBIT O

Product identity discussion from www.PeakTestosteroneForum.com

Peak Testosterone Forum first.

This is NOT medical advice. Talk to your doctor

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Peak Testosterone Forum » General Category » Testosterone, Hormones and General Men's Health » Search » Search Results

Search results for: avanafil

Pages: [**1**]

1 **Testosterone, Hormones and General Men's Health / Re: AVANAFIL(Stendra) TROCHES**
« Message by **Balderdasher** on *March 23, 2017, 05:38:29 pm* »

Quote from: mikezz on March 23, 2017, 03:56:46 pm

Has anyone tried these? I'm interested in AVANAFIL because by what I've read it appears to have less affect on vision then any other PDE5 inhibitor.
If I have this wrong please correct me.

I see empower pharmacy have them, but only in 200mg.
How much should I expect to pay? And, will I be able to cut the 200mg trouche?

Please provide any feed back.

Thanks

Mike

Yep, I've used them in the past. I forget what empower's prices are, but much more affordable than paying cash at your local drug store from what I can tell. Had a great experience with them, though they seemed to last a shorter period of time than pills. Yes, you can cut them.

2 **Testosterone, Hormones and General Men's Health / AVANAFIL(Stendra) TROCHES**
« Message by **mikezz** on *March 23, 2017, 03:56:46 pm* »

Has anyone tried these? I'm interested in **AVANAFIL** because by what I've read it appears to have less affect on vision then any other PDE5 inhibitor. If I have this wrong please correct me.

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Thanks
Mike

Pages: [**1**]

Jump to: => Please select a destination Go!

EXHIBIT P

Product failure discussion from www.PeakTestosteroneForum.com

Peak Testosterone Forum first.

This is NOT medical advice. Talk to your doctor

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Peak Testosterone Forum » General Category »
Testosterone, Hormones and General Men's Health (Moderators: Cronos, Kierkegaard, Hydranted, euphorixx1, Cataceous) »
Avanafil/Sildenfail/Tadalafil Troches

« previous next »

Pages: [**1**]

PRINT

Author

Topic: Avanafil/Sildenfail/Tadalafil Troches (Read 1502 times)

Balderdasher
Sr. Member
Posts: 382

Avanafil / Sildenfail / Tadalafil Troches
« **on:** November 07, 2016, 05:10:00 pm »

Just curious if anyone here has had experience using compounded sublingual troches for their PDE5 inhibitor meds (Viagra/Stendra/Cialis/etc.)? Just received my first order and have had mixed success relative to the pills so far. Curious specifically if people have better results putting the troche between their cheek and gums, or under the tongue?

Logged

I am not a medical doctor. All suggestions are meant to be discussed with your doctor.

Age: 30 | Height: 6ft 1in | Weight: 175

Protocol: 40mg T Cyp 2x/week + 400u HCG 2x/week.

Original Results - 9-2012:
TT: 387 ng/dl
FT: 11.2 pg/ml

Varicocele repair -> on TRT for 1 year -> tapered off T for 1 year -> back to TRT

PeakT

Administrator
Hero Member

Posts: 38447

Re: Avanafil/Sildenfail/Tadalafil Troches

« **Reply #1 on:** November 07, 2016, 06:38:21 pm »

Quote from: Balderdasher on November 07, 2016, 05:10:00 pm

> Just curious if anyone here has had experience using compounded sublingual troches for their PDE5 inhibitor meds (Viagra/Stendra/Cialis/etc.)? Just received my first order and have had mixed success relative to the pills so far. Curious specifically if people have better results putting the troche between their cheek and gums, or under the tongue?

I had sublingual tadalafil (Cialis) from Empower Pharmacy (a site sponsor). This was better for me, because apparently much of it was indeed absorbed under the tongue which meant less stomach upset. At the time I was doing about 3-3.5 mg/daily which normally would cause me heartburn. (Now I am doing 2 mg/day, so I don't really need the troches from what I can tell.)

 Logged

THE MOST COMPREHENSIVE BOOK ON TRT/TESTOSTERONE:
https://www.amazon.com/Natural-Versus-Testosterone-Therapy-Myer/dp/1523210532/ref=sr_1_1?ie=UTF8&qid=1499116128&sr=8-1&keywords=natural+versus+testosterone+therapy
And check out my **New Peak Testosterone Program: http://www.peaktestosterone.com/peak_testosterone_program.aspx**
If you are on medications or have a medical condition, always check with your doctor first before making any lifestyle changes or taking new supplements. And low testosterone is a medical condition.

Peak Testosterone Forum

Re: Avanafil/Sildenfail/Tadalafil Troches

« **Reply #1 on:** November 07, 2016, 06:38:21 pm »

Balderdasher

Sr. Member

Posts: 382

Re: Avanafil / Sildenfail / Tadalafil Troches

« **Reply #2 on:** November 07, 2016, 09:11:22 pm »

Quote from: PeakT on November 07, 2016, 06:38:21 pm

Quote from: Balderdasher on November 07, 2016, 05:10:00 pm

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Yeah, I'm loving the delivery - no upset stomach on my end either. Effectiveness seems to wax and wane though - sort of odd considering I respond well to the pills. Thought maybe I was just placing it in the wrong location, but that doesn't seem to be the case.

Logged

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PeakT

Administrator
Hero Member

Posts: 38447

Re: Avanafil / Sildenfail / Tadalafil Troches

« **Reply #3 on:** November 09, 2016, 07:56:53 am »

> **Quote from: Balderdasher on November 07, 2016, 09:11:22 pm**
>
> > **Quote from: PeakT on November 07, 2016, 06:38:21 pm**
> >
> > > **Quote from: Balderdasher on November 07, 2016, 05:10:00 pm**
> > >
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>
> Yeah, I'm loving the delivery - no upset stomach on my end either. Effectiveness seems to wax and wane though - sort of odd considering I respond well to the pills. Thought maybe I was just placing it in the wrong location, but that doesn't seem to be the case.

Hmm. You eating or taking other medications that could affect those cytochrome enzymes? Grapefruit and pomegrate will improve for example. Did u stop those by any chance?

Logged

THE MOST COMPREHENSIVE BOOK ON TRT / TESTOSTERONE:
https://www.amazon.com/Natural-Versus-Testosterone-Therapy-Myer/dp/1523210532/ref=sr_1_1?ie=UTF8&qid=1499116128&sr=8-1&keywords=natural+versus+testosterone+therapy
And check out my **New Peak Testosterone Program: http://www.peaktestosterone.com/peak_testosterone_program.aspx**
If you are on medications or have a medical condition, always check with your doctor first before making any lifestyle changes or taking new supplements. And low testosterone is a medical condition.

Peak Testosterone Forum

Re: Avanafil / Sildenfail / Tadalafil Troches

« **Reply #3 on:** November 09, 2016, 07:56:53 am »

Balderdasher

Sr. Member

Posts: 382

Re: Avanafil / Sildenfail / Tadalafil Troches

« **Reply #4 on:** November 09, 2016, 12:37:34 pm »

Quote from: PeakT on November 09, 2016, 07:56:53 am

Quote from: Balderdasher on November 07, 2016, 09:11:22 pm

Quote from: PeakT on November 07, 2016, 06:38:21 pm

Quote from: Balderdasher on November 07, 2016, 05:10:00 pm

Just curious if anyone here has had experience using compounded sublingual troches for their PDE5 inhibitor meds (Viagra/Stendra/Cialis/etc.)? Just received my first order and have had mixed success relative to the pills so far. Curious specifically if people have better results putting the troche between their cheek and gums, or under the tongue?

I had sublingual tadalafil (Cialis) from Empower Pharmacy (a site sponsor). This was better for me,

> because apparently much of it was indeed absorbed under the tongue which meant less stomach upset. At the time I was doing about 3-3.5 mg/daily which normally would cause me heartburn. (Now I am doing 2 mg/day, so I don't really need the troches from what I can tell.)

> Yeah, I'm loving the delivery - no upset stomach on my end either. Effectiveness seems to wax and wane though - sort of odd considering I respond well to the pills. Thought maybe I was just placing it in the wrong location, but that doesn't seem to be the case.

> Hmm. You eating or taking other medications that could affect those cytochrome enzymes? Grapefruit and pomegrate will improve for example. Did u stop those by any chance?

I'm on a course of antibiotics right now (Cephalaxin) for bronchitis, but other than that nothing that I can think of. Really weird - first time I took them I had a great response, but ever since I'm seeing essentially zero results. Kind of regretting dropping a wad of cash on this stash, only to find that they're not working at all :/

Interestingly enough, Dr. Saya mentioned to me that you can actually take troches as you would pills, and that this might extend out the medicine's effects for those who metabolize faster when taking sublingual troches.

Logged

I am not a medical doctor. All suggestions are meant to be discussed with your doctor.

Age: 30 | Height: 6ft 1in | Weight: 175

Protocol: 40mg T Cyp 2x/week + 400u HCG 2x/week.

Original Results - 9-2012:
TT: 387 ng/dl
FT: 11.2 pg/ml

Varicocele repair -> on TRT for 1 year -> tapered off T for 1 year -> back to TRT

PeakT

Administrator
Hero Member

Posts: 38447

Re: Avanafil / Sildenfail / Tadalafil Troches

« **Reply #5 on:** November 11, 2016, 07:33:01 am »

Quote from: Balderdasher on November 09, 2016, 12:37:34 pm

Quote from: PeakT on November 09, 2016, 07:56:53 am

Quote from: Balderdasher on November 07, 2016, 09:11:22 pm

> **Quote from: PeakT on November 07, 2016, 06:38:21 pm**
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> > **Quote from: Balderdasher on November 07, 2016, 05:10:00 pm**
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> Interestingly enough, Dr. Saya mentioned to me that you can actually take troches as you would pills, and that this might extend out the medicine's effects for those who metabolize faster when taking sublingual troches.

I tried the Cialis troches from them and they worked for me, so I dont know what to say. I can't imagine it's the troches as they they should be absorbed downstream even if it doesnt make it sublingually. But I hear ya, and youre doing the right thing by talking to Dr Saya.

Logged

THE MOST COMPREHENSIVE BOOK ON TRT/TESTOSTERONE:
https://www.amazon.com/Natural-Versus-Testosterone-Therapy-Myer/dp/1523210532/ref=sr_1_1?ie=UTF8&qid=1499116128&sr=8-1&keywords=natural+versus+testosterone+therapy
And check out my **New Peak Testosterone Program: http://www.peaktestosterone.com/peak_testosterone_program.aspx**
If you are on medications or have a medical condition, always check with your doctor first before making any lifestyle changes or taking new supplements. And low testosterone is a medical condition.

Peak Testosterone Forum

Re: Avanafil/Sildenfail/Tadalafil Troches
« **Reply #5 on:** November 11, 2016, 07:33:01 am »

Pages: [**1**]

PRINT

« previous next »

Peak Testosterone Forum » General Category »
Testosterone, Hormones and General Men's Health (Moderators: Cronos, Kierkegaard, Hydranted, euphorixx1, Cataceous) »
Avanafil/Sildenfail/Tadalafil Troches

Jump to: => Testosterone, Hormones and General Men's Health go

EXHIBIT Q

STENDRA® Federal trademark registration

United States of America
United States Patent and Trademark Office

STENDRA

Reg. No. 4,526,269

Registered May 6, 2014

Int. Cl.: 5

TRADEMARK

PRINCIPAL REGISTER

VIVUS, INC. (DELAWARE CORPORATION)
351 EAST EVELYN AVENUE
MOUNTAIN VIEW, CA 94041

FOR: PHARMACEUTICALS FOR THE TREATMENT OF ERECTILE DYSFUNCTION AND SEXUAL DYSFUNCTIONS AND DISORDERS, AND FOR THE MAINTENANCE OF SEXUAL HEALTH, FOR USE IN THE TREATMENT AND PREVENTION OF INCONTINENCE, FOR TREATMENT OF PROSTATE AND URINARY TRACT DISEASES AND DISORDERS, FOR TREATMENT OF CARDIOVASCULAR OR ENDOTHELIAL DISEASE, DISORDERS OR DYSFUNCTION, FOR TREATMENT OF NEURODEGENERATIVE DISEASES, AND FOR MEMORY ENHANCEMENT, IN CLASS 5 (U.S. CLS. 6, 18, 44, 46, 51 AND 52).

FIRST USE 12-27-2013; IN COMMERCE 12-27-2013.

THE MARK CONSISTS OF STANDARD CHARACTERS WITHOUT CLAIM TO ANY PARTICULAR FONT, STYLE, SIZE, OR COLOR.

SN 85-565,411, FILED 3-9-2012.

DAVID C. REIHNER, EXAMINING ATTORNEY

UNITED STATES PATENT AND TRADEMARK OFFICE · DEPARTMENT OF COMMERCE

Michelle K. Lee

Deputy Director of the United States Patent and Trademark Office

Assignment

For good consideration, the receipt and adequacy of which are acknowledged by the parties, the undersigned assignor, owner of the trademarks listed on Exhibit A, effective as of 30 September 2016, hereby assigns to the undersigned assignee all right, title and interest in the trademarks listed on Exhibit A together with: (a) that part of the good will of the assignor's business connected with the use of and symbolized by the mark, and (b) any of the assignor's unregistered and common law rights in the forgoing, and (c) any recovery or damages for past infringement of the forgoing. This assignment is, for each trademark, limited to the territory(ies) for that trademark specified on Exhibit A; assignor retains all its rights in such trademark outside the specified territory(ies).

ASSIGNOR
Vivus, Inc.
a Delaware corporation

Sandra Wells, Esq.
Assistant General Counsel
March 28, 2018

ASSIGNEE
Metuchen Pharmaceuticals, LLC
a Delaware limited liability company

J. Gregory Ford
Chief Executive Officer

State of _____
County of _____
The foregoing instrument was acknowledged before me this ____ day of _____, 2018 by Sandra Wells, Esq. of Vivus, Inc., a Delaware corporation, on behalf of the corporation.

SEE ATTACHED

_____
Notary's official signature
My commission expires _____

SEAL

State of _____
County of _____
The foregoing instrument was acknowledged before me this ____ day of _____, 2018 by J. Gregory Ford of Metuchen Pharmaceuticals, LLC, a Delaware limited liability company, on behalf of the corporation.

_____
Notary's official signature
My commission expires _____

SEAL

EXHIBIT A
ASSIGNED TRADEMARKS

Mark	Country	App. No. / Reg. No.	Date Filed	Reg. Date	Status
STENDRA	US	85-565411/4526269	09-MAR-2012	06-MAY-2014	Registered
STENDRA	Canada CA	1592942	05-SEP-2012		Allowed
STENDRA	India IN	2390407	05-SEP-2012		Pending
STENDRA	Argentina AR	3189354/2613896	06-SEP-2012	05-DEC-2013	Registered
STENDRA	Brazil BR	8400259441/40259441	10-SEP-2012	11-AUG-2015	Registered
STENDRA	Chile CL	1052848/1139476	05-APR-2013	04-NOV-2014	Registered
STENDRA	Columbia CO	1131863/489813	26-OCT-2012	26-MAR-2014	Registered
STENDRA	Peru	502951/00199499	06-AUG-2012	06-MAY-2013	Registered
STENDRA	Venezuela VE	2013-015411	09-AUG-2013		Pending
SPEDRA	Canada CA	1574172	19-APR-2012		Pending
SPEDRA	India IN	2319226	20-APR-2012		Published
SPEDRA	Argentina AR	3408270	08-MAY-2015		Published
SPEDRA	Brazil BR	909363250	12-MAY-2015		Published
SPEDRA	Columbia CO	15106101	08-MAY-2015		Published
	US	86-304551/4918812	09-JUN-2014	13-JAN-2015	Registered
	Canada	1703669	20-NOV-2014		Allowed
	Brazil	908728875	09-DEC-2014		Published