JS 44 (Rev. 3/99)

CIVIL COVER SHEET

APPENDIX B

The JS-44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS

PFIZER INC., WARNER-LAMBERT COMPANY and GÖDECKE AKTIENGESELLSCHAFT

(b) County of Residence of First Listed Plaintiff Suffolk
(EXCEPT IN U.S. PLAINTIFF CASES)

DEFENDANTS

PHARMACEUTICAL HOLDINGS CORP., UNITED RESEARCH LABORATORIES, INC. and MUTUAL PHARMACEUTICAL COMPANY

County of Residence of First Listed Philadelphia
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED.

(c) Attorney's (Firm Name, Address, and Telephone Number)
Gregory J. Lavorgna, PA I.D. #34874
Drinker Biddle & Reath LLP
One Logan Square, 18th & Cherry Streets
Philadelphia, PA 19103-6996

Attorneys (If Known)
Robert F. Green
Leydig, Voit & Mayer, Ltd.
Two Prudential Plaza, Suite 4900
Chicago, IL 60601-6780

II. BASIS OF JURISDICTION (Place an "X" in One Box Only)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" in One Box for Plaintiff and One Box for Defendant)
(For Diversity Cases Only)

	DEF		DEF
Citizen of This State	☐ 1 ☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4 ☒ 4
Citizen of Another State	☐ 2 ☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5 ☐ 5
Citizen or Subject of a Foreign Country	☐ 3 ☐ 3	Foreign Nation	☐ 6 ☐ 6

IV. NATURE OF SUIT (Place an "X" in One Box Only)

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury—Med. Malpractice
- ☐ 365 Personal Injury — Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence
- Habeas Corpus:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt.Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl Ret. Inc. Security Act

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce/ICC Rates/etc.
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900 Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes
- ☐ 890 Other Statutory Actions

V. ORIGIN (PLACE AN "X" IN ONE BOX ONLY)

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from another district (specify) ☐ 6 Multidistrict Litigation ☐ 7 Appeal to District Judge from Magistrate Judgment

VI. CAUSE OF ACTION (Cite the U.S. Civil Statute under which you are filing and write brief statement of cause. Do not cite jurisdictional statutes unless diversity.)

Patent Infringement

VII. REQUESTED IN COMPLAINT: ☐ CHECK IF THIS IS A CLASS ACTION UNDER F.R.C.P. 23 DEMAND $ CHECK YES only if demanded in complaint: JURY DEMAND: ☐ Yes ☐ No

VIII. RELATED CASE(S) IF ANY (See instructions): JUDGE The Honorable John C. Lifland DOCKET NUMBER

MDL 1384 (D.N.J.)
98-2749 (D.N.J.)
99-3057 (D.N.J.)
99-5948 (D.N.J.)
01-0577 (D.N.J.)
01-1538 (D.N.J.)

DATE 05 February 2003 SIGNATURE OF ATTORNEY OF RECORD PA 34,874

FOR OFFICE USE ONLY

RECEIPT # AMOUN APPLYING IFP JUDGE MAG. JUDGE

IN THE UNITED STATES DISTRICT COURT **APPENDIX C**
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

CASE MANAGEMENT TRACK DESIGNATION FORM

PFIZER INC., WARNER-LAMBERT COMPANY and GÖDECKE AKTIENGESELLSCHAFT	:	CIVIL ACTION
Plaintiffs,	:	
V.	:	
PHARMACEUTICAL HOLDINGS CORP., UNITED RESEARCH LABORATORIES, INC. and MUTUAL PHARMACEUTICAL COMPANY	:	NO.
Defendants.	:	

In accordance with the Civil Justice Expense and Delay Reduction Plan of this court, counsel for plaintiff shall complete a case Management Track Designation Form in all civil cases at the time of filing the complaint and serve a copy on all defendants. (See § 1:03 of the plan set forth on the reverse side of this form.) In the event that a defendant does not agree with the plaintiff regarding said designation, that defendant shall, with its first appearance, submit to the clerk of court and serve on the plaintiff and all other parties, a case management track designation form specifying the track to which that defendant believes the case should be assigned.

SELECT ONE OF THE FOLLOWING CASE MANAGEMENT TRACKS:

(a)	Habeas Corpus -- Cases brought under 28 U.S.C. §2241 through §2255.	( )
(b)	Social Security -- Cases requesting review of a decision of the Secretary of Health and Human Services denying plaintiff Social Security Benefits.	( )
(c)	Arbitration -- Cases required to be designated for arbitration under Local Civil Rule 53.2.	( )
(d)	Asbestos -- Cases involving claims for personal injury or property damage from exposure to asbestos.	( )
(e)	Special Management -- Cases that do not fall into tracks (a) through (d) that are commonly referred to as complex and that need special or intense management by the court. (See reverse side of this form for a detailed explanation of special management cases.)	(X)
(f)	Standard Management -- Cases that do not fall into any one of the other tracks.	( )

2/5/03
Date

Attorney-at-law

Gregory J. Lavorgna PA I.D. #34,874
Attorney for PFIZER INC., WARNER-LAMBERT COMPANY and GODECKE AKTIENGESELLSCHAFT

(Civ. 660) 7/95

UNITED STATES DISTRICT COURT

APPENDIX A

FOR THE EASTERN DISTRICT OF PENNSYLVANIA — DESIGNATION FORM to be used by counsel to indicate the category of the case for the purpose of assignment to appropriate calendar.

Address of Plaintiff: Pfizer, Inc.: 235 E. 42 St., NY, NY 10017; Warner-Lambert Company: 201 Tabor Rd., Morris Plains, NJ 07950 and Gödecke Aktiengesellschaft: Berlin, Germany.

Address of Defendant: 1100 Orthodox St., Philadelphia, PA 19124

Place of Accident, Incident or Transaction: Philadelphia

(Use Reverse Side For Additional Space)

Does this case involve multidistrict litigation possibilities? Yes☐ No☒

RELATED CASE, IF ANY:

Case Number: _____ Judge _____ Date Terminated: _____

Civil cases are deemed related when yes is answered to any of the following questions:

1. Is this case related to property included in an earlier numbered suit pending or within one year previously terminated action in this court? Yes☐ No☒

2. Does this case involve the same issue of fact or grow out of the same transaction as a prior suit pending or within one year previously terminated action in this court? Yes☐ No☒

3. Does this case involve the validity or infringement of a patent already in suit or any earlier numbered case pending or within one year previously terminated action in this court? Yes☐ No☒

CIVIL: (Place ✔ in ONE CATEGORY ONLY)

A. *Federal Question Cases:*

1. ☐ Indemnity Contract, Marine Contract, and All Other Contracts
2. ☐ FELA
3. ☐ Jones Act-Personal Injury
4. ☐ Antitrust
5. ☒ **Patent**
6. ☐ Labor-Management Relations
7. ☐ Civil Rights
8. ☐ Habeas Corpus
9. ☐ Securities Act(s) Cases
10. ☐ Social Security Review Cases
11. ☐ All other Federal Question Cases (Please specify)

B. *Diversity Jurisdiction Cases:*

1. ☐ Insurance Contract and Other Contracts
2. ☐ Airplane Personal Injury
3. ☐ Assault, Defamation
4. ☐ Marine Personal Injury
5. ☐ Motor Vehicle Personal Injury
6. ☐ Other Personal Injury (Please specify)
7. ☐ Products Liability
8. ☐ Products Liability — Asbestos
9. ☐ All other Diversity Cases (Please specify)

ARBITRATION CERTIFICATION

(Check appropriate Category)

I, Gregory J. Lavorgna, counsel of record do hereby certify:

☐ Pursuant to Local Civil Rule 53.2, Section 3(c)(2), that to the best of my knowledge and belief, the damages recoverable in this civil action case exceed the sum of $150,000.00 exclusive of interest and costs;

☒ Relief other than monetary damages is sought.

DATE: 2/5/03 _____ Attorney-at-Law 34,874 Attorney I.D.#

NOTE: A trial de novo will be a trial by jury only if there has been compliance with F.R.C.P. 38.

I certify that, to my knowledge, the within case is not related to any case now pending or within one year previously terminated action in this court except as noted above.

DATE: 2/5/03 _____ Attorney-at-Law 34,874 Attorney I.D.#

CIV. 609 (9/99)

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

PFIZER INC., WARNER-LAMBERT COMPANY and GÖDECKE AKTIENGESELLSCHAFT	:	
Plaintiffs,	:	**Civil Action No.**
v.	:	03-740
PHARMACEUTICAL HOLDINGS CORP., UNITED RESEARCH LABORATORIES, INC. and MUTUAL PHARMACEUTICAL COMPANY	:	
Defendants.	:	

COMPLAINT FOR PATENT INFRINGEMENT

For their complaint herein, Plaintiffs allege as follows:

THE PARTIES

1. Plaintiff Pfizer Inc. is a corporation incorporated under the laws of the State of Delaware, having its principal place of business at 235 East 42nd Street, New York, New York 10017.

2. Plaintiff Warner-Lambert Company is a corporation incorporated under the laws of the State of Delaware, having its principal place of business at 201 Tabor Road, Morris Plains, New Jersey 07950.

3. Warner-Lambert Company became a wholly owned subsidiary of Pfizer Inc. as of June 19, 2000.

4. Plaintiff Gödecke Aktiengesellschaft is a corporation incorporated under the laws of Germany, having its principal place of business in Berlin, Germany.

5. Gödecke Aktiengesellschaft is an indirect wholly owned subsidiary of Warner-Lambert Company.

6. Hereinafter, Pfizer Inc., Warner-Lambert Company and Gödecke Aktiengesellschaft are collectively referred to as "Warner-Lambert".

7. On information and belief, Defendants United Research Laboratories, Inc. and Mutual Pharmaceutical Co. are corporations incorporated under the laws of the State of Pennsylvania and having their principal places of business at 1100 Orthodox Street, Philadelphia, Pennsylvania 19124.

8. On information and belief, Defendant Pharmaceutical Holdings Corp. is a corporation incorporated under the laws of the State of Delaware and having its principal place of business at 1100 Orthodox Street, Philadelphia, Pennsylvania 19124.

9. On information and belief, United Research Laboratories, Inc. and Mutual Pharmaceutical Co. are wholly owned subsidiaries of Pharmaceutical Holdings Corp. On information and belief, United Research Laboratories, Inc., Mutual Pharmaceutical Co. and Pharmaceutical Holdings Corp. have common officers and directors. On information and belief, the acts of United Research Laboratories, Inc. and Mutual Pharmaceutical Co. complained of herein were done at the direction of, with the authorization of and with the cooperation, participation and assistance of Pharmaceutical Holdings Corp.

10. Hereinafter, United Research Laboratories, Inc., Mutual Pharmaceutical Co. and Pharmaceutical Holdings Corp. will be collectively referred to as "Mutual".

JURISDICTION AND VENUE

11. This action arises under the patent laws of the United States of America. Jurisdiction is founded on Title 28, United States Code §§ 1331, 1338(a).

12. Venue is proper in this Court under Title 28, United States Code §§ 1391(b), 1391(c) and 1400(b).

FIRST CLAIM FOR PATENT INFRINGEMENT

13. United States Patent No. 6,054,482 ("the '482 patent") discloses and claims pharmaceutical compositions of and processes for making the drug gabapentin. The '482 patent was duly and legally issued on April 25, 2000 and expires on April 25, 2017. Plaintiff Gödecke Aktiengesellschaft is the assignee of the '482 patent. A copy of the '482 patent is attached as Exhibit A.

14. Gabapentin under certain conditions converts to a form called lactam. Lactam presents a toxicity problem and must therefore be avoided in gabapentin compositions. The '482 patent discloses and claims pharmaceutical compositions of and processes for making gabapentin that are substantially lactam-free.

15. On information and belief, the formulation of Mutual's gabapentin capsule product provides for gabapentin compositions that are substantially lactam-free and fall within the claims of the '482 patent.

16. Warner-Lambert is the holder of approved New Drug Applications ("NDAs") No. 20-235 for gabapentin capsules and No. 20-882 for gabapentin tablets. On April

25, 2000 Warner-Lambert submitted to the F.D.A. patent information regarding the '482 patent for its NDAs Nos. 20-235 and 20-882 and the F.D.A. has listed the '482 patent in its "Orange Book". Warner-Lambert, through its Parke-Davis Division, sells gabapentin under the tradename "NEURONTIN®".

17. On information and belief at some time prior to December 19, 2002, Mutual filed Abbreviated New Drug Application ("ANDA") No. 76-537 for gabapentin capsules. Mutual's ANDA No. 76-537 includes a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) of the Federal Food Drug and Cosmetic Act that the '482 patent is not infringed by Mutual's gabapentin capsule product.

18. On information and belief, Mutual sent a notice of that certification to Warner-Lambert on or about December 19, 2002. Warner-Lambert received a copy of the notice on or about December 24, 2002.

19. On information and belief, Warner-Lambert alleges that Mutual's manufacture, use and/or sale of its substantially lactam-free gabapentin product will infringe one or more claims of the '482 patent. Because Mutual seeks to market its gabapentin product before the expiration date of the '482 patent, Mutual's submission of its ANDA for gabapentin capsules with the certification directed to the '482 patent constitutes infringement of the '482 patent under 35 U.S.C. § 271(e)(2)(A).

20. Warner-Lambert is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of Mutual's ANDA for gabapentin capsules be a date which is not earlier than the April 25, 2017 expiration date of the '482 patent.

SECOND CLAIM FOR PATENT INFRINGEMENT

21. United States Patent No. 4,894,476 (the "'476 patent") discloses and claims a crystal form of the drug 1-aminomethyl-1-cyclohexaneacetic acid, having the generic name "gabapentin". The '476 patent was duly and legally issued on January 16, 1990 and expires on May 2, 2008. Warner-Lambert is the assignee of the '476 patent. A copy of the '476 patent is attached as Exhibit B.

22. In its '476 patent, Warner-Lambert discloses a method for preparing gabapentin in a highly pure state. This method takes advantage of the crystalline monohydrate form of gabapentin.

23. On information and belief, at some time prior to December 19, 2002, Mutual filed Abbreviated New Drug Application ("ANDA") No. 76-537 for gabapentin capsules. Mutual's ANDA No. 76-537 includes a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) of the Federal Food Drug and Cosmetic Act that the '476 patent is not infringed by Mutual's gabapentin capsule product.

24. On information and belief, Mutual sent a notice of that certification to Warner-Lambert on or about December 19, 2002. Warner-Lambert received a copy of the notice on or about December 24, 2002.

25. Mutual asserted in its certification that the manufacture, use or sale of its gabapentin capsule product does not infringe the '476 patent. Nevertheless, Mutual has provided Warner-Lambert with no information whatsoever regarding the chemical manufacture of its bulk gabapentin active ingredient.

26. Because of Mutual's failure to provide such information, Warner-Lambert cannot evaluate, confirm or test the correctness of the statements in the Mutual certification. On information and belief, therefore, Warner-Lambert alleges that Mutual's manufacture, use and/or sale of a gabapentin capsule product pursuant to its ANDA No. 76-537 will infringe one or more claims of the '476 patent. Because Mutual seeks to market its gabapentin capsule product before the expiration date of the '476 patent, Mutual's submission of ANDA No. 76-537 with the patent certification challenging the '476 patent constitutes infringement of the '476 patent under 35 U.S.C. § 271(e)(2)(A).

27. Warner-Lambert is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of Mutual's ANDA No. 76-537 be a date which is not earlier than the May 2, 2008 expiration date of the '476 patent.

PRAYER FOR RELIEF

28. Warner-Lambert requests that:

a. Judgment be entered that Mutual has infringed the '482 and '476 patents by submitting its ANDA for gabapentin capsules with the patent certification directed to the '482 and '476 patents;

b. A permanent injunction be issued pursuant to 35 U.S.C. § 271(e)(4)(B) restraining and enjoining Mutual, its officers, agents, attorneys and employees, and those acting in privity or concert with it, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, any gabapentin composition covered by the '482 or '476 patents;

c. An order be issued pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of Mutual's ANDA for gabapentin capsules be a date which is not earlier than the April 25, 2017 expiration date of the '482 patent;

d. Judgment be entered for costs and reasonable attorney fees to be awarded to Warner-Lambert; and

e. This Court award such other and further relief as the Court may deem proper under the circumstances.

DRINKER BIDDLE & REATH LLP
One Logan Square
18th and Cherry Streets
Philadelphia, Pennsylvania 19103-6996
(215) 988-2700

Dated: 05 Feb 2003

Gregory J. Lavorgna PA I.D. # 34874

Attorneys for Plaintiffs
Pfizer Inc.
Warner-Lambert Company
and Gödecke Aktiengesellschaft

Of Counsel:
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Hugh C. Barrett (HB 8146)
Leisa M. Smith (LS 8069)
FITZPATRICK, CELLA, HARPER
& SCINTO
30 Rockefeller Plaza
New York, New York 10112

EXHIBIT A

US006054482A

United States Patent [19]

Augart et al.

[11] **Patent Number: 6,054,482**

[45] **Date of Patent: Apr. 25, 2000**

[54] **LACTAM-FREE AMINO ACIDS**

[75] Inventors: **Helmut Augart**; **Uwe Gebhardt**, both of Waldkirch; **Wolfgang Herrmann**, Merzhausen, all of Germany

[73] Assignee: **Gödecke Aktiengesellschaft**, Berlin, Germany

[21] Appl. No.: **08/377,618**

[22] Filed: **Jan. 25, 1995**

Related U.S. Application Data

[63] Continuation of application No. 08/020,270, Feb. 18, 1993, abandoned, which is a continuation of application No. 07/865,723, Apr. 8, 1992, abandoned, which is a continuation of application No. 07/570,500, Aug. 21, 1990, abandoned.

[30] **Foreign Application Priority Data**

Aug. 25, 1989 [DE] Germany 39 28 183

[51] **Int. Cl.**[7] **A01N 37/12**

[52] **U.S. Cl.** **514/561**; 562/504; 562/507

[58] **Field of Search** 562/504, 507; 514/561

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,024,175	5/1977	Satzinger et al.	260/514
4,087,544	5/1978	Satzinger et al.	424/305
4,152,326	5/1979	Hartenstein et al.	546/16
4,228,179	10/1980	Hartenstein	424/274
4,894,476	1/1990	Butler et al.	562/504

FOREIGN PATENT DOCUMENTS

2543821 4/1977 Germany .

OTHER PUBLICATIONS

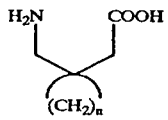
Copending U.S. application 399056, filed Aug. 25, 1989.

Primary Examiner—Michael L. Shippen
Attorney, Agent, or Firm—Francis J. Tinney

[57] **ABSTRACT**

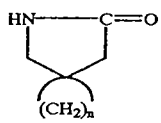
The present invention concerns cyclic amino acids of formula

VII



substantially free from the lactam

VIII



wherein n is an integer of from 4 to 6, a process for the preparation thereof, compositions containing the compounds and methods of using them.

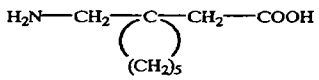
11 Claims, No Drawings

LACTAM-FREE AMINO ACIDS

This is a continuation of application Ser. No. 08/020,270, filed Feb. 18, 1993, now abandoned, which is a continuation of application Ser. No. 07/865,723, filed Apr. 8, 1992, now abandoned, is a continuation of application Ser. No. 07/570,500, filed Aug. 21, 1990, now abandoned.

BACKGROUND OF THE INVENTION

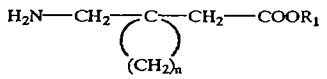
Gabapentin is a generic term used to identify the chemical compound (1-aminomethyl)-1-cyclohexaneacetic acid.



It is useful in therapy of certain cerebral disorders such as certain forms of epilepsy, faintness attacks, hypokinesis, and cranial traumas. U.S. Pat. Nos. 4,024,175 and 4,087,544 cover the compound and its uses. They also disclose an acid salt, i.e., gabapentin hydrochloride hydrate, in a ratio of 4:4:1 and a sodium salt of gabapentin hydrate in a ratio of 2:1.

U.S. Pat. No. 4,894,476 covers crystalline gabapentin monohydrate and methods for producing the same.

The patents describe various processes for the preparation of this and similar compounds of general formula



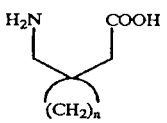
wherein R_1 is a hydrogen atom or a lower alkyl radical and n is 4, 5, or 6 and the pharmaceutically acceptable salts thereof, which depend upon known methods used for the preparation of primary amines or amino acid.

These patents are hereby incorporated by reference.

SUMMARY OF THE INVENTION

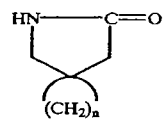
The instant invention covers a compound of formula

VII



or a pharmaceutically acceptable salt thereof substantially free from

VIII



wherein n is an integer of from 4 to 6.

The preferred compound of formula VII is that where n is 5.

The instant invention also concerns a process for the purification of a compound of the instant invention comprising

(a) treating a compound of formula VII substantially free from compound VIII with a semiconcentrated mineral acid, converting the lactam VIII into VII,

(b) removing the anions of the mineral acid by ion exchange, leaving the purified VII, and

(c) converting the product of step (b) to a pharmaceutically acceptable salt thereof, if desired.

A preferred process of the instant invention is one wherein the mineral acid hydrochloric acid is used and an ion exchanger is used for anion removal.

The instant invention further concerns pharmaceutical compositions which comprise a therapeutically effective amount of a compound according to claim 1 in combination with a pharmaceutically acceptable carrier.

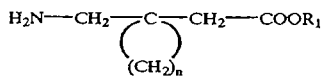
The instant invention further concerns a method for treating epilepsy in a mammal in need of such treatment which comprises administering an antiepileptically effective amount of a compound of claim 1 to a mammal in need thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is concerned with lactam-free cyclic amino acids, a process for the preparation thereof and pharmaceutical compositions containing them.

German Patent 24 60 891 concerns known cyclic amino acid derivatives of the general formula I

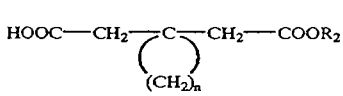
(I)



wherein R_1 is a hydrogen atom or lower alkyl and n is an integer 4, 5 or 6, as well as the pharmacologically acceptable salts thereof. These compounds possess valuable pharmacodynamic properties. The compounds of formula (I) have an extraordinarily low toxicity. In animal experiments, a remarkable protective effect was found against cramp induced by thiosemicarbazide and against cardiazole cramp. The compounds can be used for the therapy of certain cerebral diseases. They can be used in the treatment of certain forms of epilepsy, of attacks of dizziness, of hypokinesis and of cranial trauma and the improvement of the cerebral function. Therefore, they are especially effective for the treatment of geriatric conditions. The compounds of formula (I) can be prepared in known manner either by

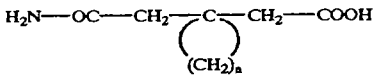
a) converting a compound of the formula II

(II)



wherein R_2 is an alkyl radical containing up to 8 carbon atoms and n has the same meaning as above, via a reactive acid derivative into an azide which is then subjected to a Curtius reaction; or

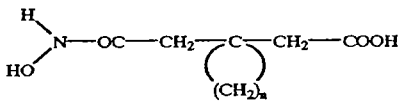
b) subjecting a compound of the formula III



(III)

wherein n has the same meaning as above, to a Hofmann reaction; or

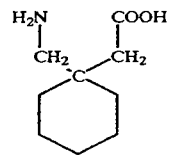
c) subjecting a compound of the general formula IV



(IV)

wherein n has the same meaning as above, to a Lossen rearrangement; whereafter, if desired, the free amino acid obtained is converted by esterification into a lower alkyl ester or by reaction with an acid or base into a pharmacologically acceptable salt.

Aminomethyl-1-cyclohexaneacetic acid (gabapentin) of the formula Va



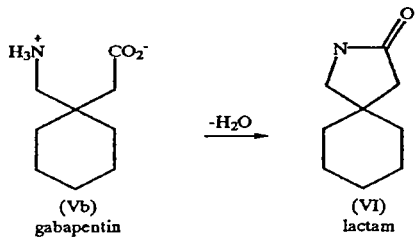
(Va)

has proved to be especially potent. Gabapentin displays a certain structural relationship to gamma-aminobutyric acid (GABA) which is not able to pass the blood-brain barrier. Gabapentin does not possess this disadvantage and thus represents a very effective anticonvulsive with an extraordinarily low toxicity (Drugs of the Future. 11/6, 518–519/1986).

The preparation and storage of compounds of formula (I) in which R_1 is hydrogen present problems. These problems have been partly overcome and they still are a problem in the development of usable forms of administration. The compounds obtained showed considerable variations in the degree of purity, without apparent reason. By means of special, additional purification steps, it first appeared that this problem could be overcome. Long-term storage stability of even very pure compounds (I) displayed greatly differing stabilities with progressively long storage times. It was difficult to determine the cause for the deficient stability since this clearly depended upon initially unknown conditions. A long series of systematic investigations led to a solution of the problem of making available stable active materials and forms of composition of the compounds (I).

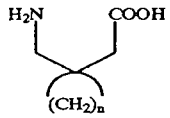
The hydrochloride of gabapentin was the most suitable form of the active material since salts and especially hydrochlorides as a rule usually provide especially good stability and good solubility. However, in some cases, pharmaceutical compositions were even more unstable than the free amino acid.

According to the reaction sequence:



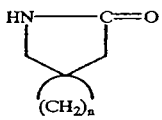
(Vb) gabapentin → (VI) lactam

gabapentin forms, in a manner analogous to the other compounds of the formula VII,



(VII)

wherein n is 4, 5, or 6 and preferably 5, the lactam (VI). However, lactams of the formula VIII



(VIII)

in which n has the same meaning as above, are formed not only in the course of the preparation but, surprisingly, also in the case of storage.

This unexpected reaction in the solid phase and under dry storage conditions led, because of the water liberated in the case of the cyclization, to additional problems for the stability of dry medicinal forms, for example, tablets and capsules, which, in the presence of moisture, tend to stick or to soften.

Attempts to keep the lactam content of the active material used as low as possible from the very beginning led, in the case of the preparation as well as in the case of storage of the active substance, not only in pure form but also in final preparations, to further initially unsolvable problems because it was found that the cyclization reaction surprisingly also took place in the alkaline region.

The lactams display a certain toxicity and must, therefore, be avoided as far as possible. For example, gabapentin has a toxicity (LD_{50}, mouse) of more than 8000 mg/kg, for the corresponding lactam (VI) a toxicity of 300 mg/kg. Consequently, these impurities and the potential formation of such decomposition products during storage of pharmaceutical compositions must be reduced to a minimum for reasons of safety.

Finally, in the case of investigations of final pharmaceutical forms, it was found, as a further problem, that the cause of the lactam formation was apparently also the catalytic effects of adjuvant materials which also did not follow any recognizable logic. In order to establish which adjuvant materials promote the lactam formation, laborious serial investigations had, therefore, to be carried out. These showed, for example, that Poloxamer NF behaved completely neutral and, in the case of the sole presence thereof, did not impair the stability of the active material gabapentin,

whereas in the case of the use of polyethylene glycol (PEG), cyclization to the lactam took place to a considerable extent. In another test series with very pure active substance, PEG was found to be indeed usable as an excipient.

The following adjuvant materials, for example, reduced the stability of the compounds (I) and should be avoided in the preparation of pharmaceutical compositions: modified maize starch, sodium croscarmelose, glycerol behenic acid ester, methacrylic acid co-polymers (types A and C), anion exchangers titanium dioxide, and silica gels such as Aerosil 200.

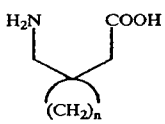
On the other hand, the following adjuvant materials had no noticeable influence on the stability of the compounds (I): hydroxypropylmethylcellulose, polyvinylpyrrolidone, crospovidon, poloxamer 407, poloxamer 188, sodium starch glycolate, copolyvidone, maize starch, cyclodextrin, lactose, talc, as well as co-polymers of dimethylamino-methacrylic acid and neutral methacrylic acid ester.

In order not to exceed the upper limit of 0.5% by weight of gabapentin lactam (referred to the gabapentin), which is regarded as being permissible, and in order to ensure the storage stability not only of the active material but also of the corresponding pharmaceutical forms of preparation, the following procedures are to be maintained:

1. The active materials of formula (I) must be prepared as highly purified, nonderivatized free amino acids, for example, from the corresponding hydrochloride by ion exchange. The proportion of remaining hydrochloride admixtures should thereby not exceed 20 ppm. The same also applies to other mineral acids.
2. In the case of pharmaceutical preparations or compositions, by the precise choice of adjuvant materials, every catalysis of the lactam formation must be suppressed.
3. By controls, it must be ensured that the above conditions are fulfilled. As a rule, this is the case when the lactam formation, under the storage conditions generally applicable for medicaments, does not increase within a period of time of 1 year after production of the pharmaceutical compositions or of the active material by more than 0.2% by weight and preferably 0.1% by weight, referred to the pure active material.

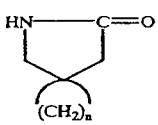
Therefore, according to the present invention, cyclic amino acids of the formula VII

(VII)



wherein n is 4, 5, or 6 and preferably 5, and pharmaceutical compositions containing them, have a content of lactam of the formula VIII

(VIII)



wherein n has the same meaning as above, of less than 0.5% by weight.

Furthermore, the present invention provides cyclic amino acids of formula (VII) and pharmaceutical compositions containing at least one compound of formula (VII) which satisfies the above-mentioned criteria, wherein the content of lactam of formula (VIII) at 25° C. and an atmospheric humidity of 50% does not increase during the course of 1 year after preparation by more than 0.2% by weight (referring to the active material).

The following examples are given for the purpose of illustrating the present invention and are not intended to limit the scope in any way.

EXAMPLE 1

1-(Aminomethyl)-cyclohexaneacetic acid hydrochloride

22.3 L of water and 22.3 L of concentrated hydrochloric acid are mixed in a T100 reactor and 6.41 kg gabapentin lactam added while stirring. The clear brown solution formed is subsequently boiled under reflux at 108° C. for 6 hours. The reaction mixture is then left until it has cooled to 28° C. The white precipitate obtained is again dissolved by the addition of a further 40 L of water. For the removal of still undissolved lactam, the reaction mixture is extracted three times with, in each case, 30 L of dichloromethane. The pale yellow aqueous phase is evaporated to dryness in a vacuum evaporator (QVF 100L). At 133 Pa, the temperature finally reached 80° C. The almost dry crystal mass is stirred up with 12.8 L of acetone and sucked off. It is then washed with 2 L of acetone and dried for 4 hours at 60° C. The yield is about 60% of theory.

EXAMPLE 2

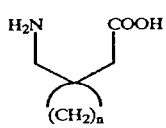
1-(Aminomethyl)-cyclohexaneacetic acid

A 3 m long and 200 mm wide chromatography column is filled with 50 L of ion exchanger resin (IRA 68). The resin is regenerated with a solution of 14 L of concentrated aqueous ammonia in 300 L of demineralized water and subsequently washed with 150 L of demineralized water. As soon as the eluate has reached a pH of 6.8 and chloride can no longer be detected, a solution of 8.67 kg (40.8 mole) 1-aminomethyl-1-cyclohexaneacetic acid hydrochloride in 43 L of demineralized water is applied to the column. The free amino acid is eluted with demineralized water at a rate of 1.5 L/min and collected in 15 fractions each of 15 L. The combined fractions are evaporated at 6.65 KPa and at most 45° C. The white solid residue is introduced into 20 L of methanol, heated to reflux, filtered, and cooled to −10° C. The product which crystallizes out is centrifuged, washed with 10 L of cold methanol, and dried for 17 hours at 30° to 40° C. 4.9 kg (71% of theory) of pure 1-(aminomethyl)-cyclohexaneacetic acid are obtained; m.p. 165° C. A further 0.8 kg can be obtained by working up the mother liquors.

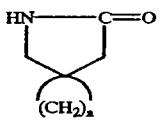
We claim:

1. A process for the preparation of a compound of Formula VII

VII



wherein n is an integer of from 5 containing less than 0.5% by weight of a compound of Formula VIII



VIII

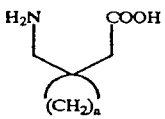
wherein n is as defined above and less than 20 ppm of an anion of a mineral acid comprising:

(a) hydrolysis of a compound of Formula VII containing a compound of Formula VIII or of a compound of Formula VIII alone with a mixture of equal volumes of a concentrated mineral acid and water to afford an acid addition salt of a compound of Formula VII and

(b) converting the acid addition salt of a compound of Formula VII by ion exchange to a compound of Formula VII containing less than 0.5% by weight of a compound of Formula VIII and less than 20 ppm of an anion of a mineral acid.

2. A process according to claim 1, wherein in step (a) the acid is hydrochloric acid.

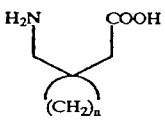
3. A process for preparing stable and pure pharmaceutical compositions containing a compound of formula (VII)



(VII)

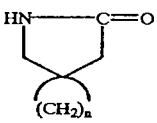
wherein n is an integer of 5 and pharmaceutically acceptable adjuvants consisting of the steps of

(a) hydrolysis of a compound of formula VII



(VII)

wherein n is as defined above containing a compound of formula VIII



(VIII)

wherein n is as defined above or a compound of Formula VIII alone with a mixture of equal volumes of a concentrated mineral acid and water to afford an acid addition salt of a compound of formula VII substantially free of a compound of formula VIII,

(b) converting the acid addition salt of a compound of formula VII by ion exchange to a compound of formula VII containing less than 0.5% by weight of a compound of formula VIII, wherein the proportion of remaining anion of a mineral acid does not exceed 20 ppm,

(c) adding pharmaceutically acceptable adjuvants to form a pharmaceutical composition wherein the adjuvants do not promote the formation of a lactam of formula VIII ensuring that the lactam formation under the storage conditions at 25° C. and an atmospheric humidity of 50% does not increase within a period of time of one year after the production of the pharmaceutical compositions or of the active material by more than 0.2% by weight, referred to the pure active material.

4. A process of claim 3, wherein the pharmaceutically acceptable adjuvants are selected from the group consisting of hydroxypropylmethylcellulose, polyvinylpyrrolidone, crospovidone, poloxamer 407, poloxamer 188, sodium starch glycolate, copolyvidone, maize starch, cyclodextrine, lactose, talc and copolymers of dimethylamino-methacrylic acid and neutral methacrylic acid ester.

5. A process of claim 3, wherein the mineral acid is hydrochloric acid.

6. A process of claim 4, wherein the mineral acid is hydrocholoric acid.

7. A stable and pure pharmaceutical composition in unit dry medicinal dosage form consisting essentially of:

(i) an active ingredient which is gabapentin in the free amino acid, crystalline anhydrous form containing less than 0.5% by weight of its corresponding lactam and less than 20 ppm of an anion of a mineral acid and

(ii) one or more pharmaceutically acceptable adjuvants that do not promote conversion of more than 0.2% by weight of the gabapentin to its corresponding lactam form when stored at 25° C. and an atmospheric humidity of 50% for one year.

8. A pharmaceutical composition according to claim 7, in which the pharmaceutically acceptable aadjuvant is selected from the group consisting of hydroxypropylmethylcellulose, polyvinylpyrrolidone, crospovidon, poloxamer 407, poloxamer 188, sodium starch glycolate, copolyvidone, maize starch, cyclodextrin, lactose, talc, co-polymers of dimethylamino-methacrylic acid and neutral methacrylic acid ester.

9. A pharmaceutical composition according to claim 7, wherein the dry medicinal dosage form is a tablet.

10. A pharmaceutical composition according to claim 7, wherein the dry medicinal dosage form is a capsule.

11. A pharmaceutical composition according to claim 7,wherein in (i) the mineral acid is hydrochloric acid.

* * * * *

EXHIBIT B

United States Patent [19]

Butler et al.

[11] **Patent Number: 4,894,476**

[45] **Date of Patent: Jan. 16, 1990**

[54] **GABAPENTIN MONOHYDRATE AND A PROCESS FOR PRODUCING THE SAME**

[75] Inventors: **Donald E. Butler**, Holland; **Barbara J. Greenman**, Door, both of Mich.

[73] Assignee: **Warner-Lambert Company**, Morris Plains, N.J.

[21] Appl. No.: **188,819**

[22] Filed: **May 2, 1988**

[51] **Int. Cl.**[4] **C07C 101/14**

[52] **U.S. Cl.** **562/504**

[58] **Field of Search** 560/122, 125; 562/504, 562/507

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,024,175	5/1977	Satzinger	260/468 J
4,087,544	5/1978	Satzinger	424/303

Primary Examiner—Michael L. Shippen

Attorney, Agent, or Firm—Elizabeth M. Anderson

[57] **ABSTRACT**

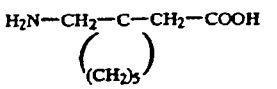
A novel crystalline form of gabapentin and a novel processes for the small and large scale preparations of the anticonvulsant compound in a highly pure state is disclosed. This novel hydrate is produced by a cost effective process which provides an additional purification stage.

2 Claims, No Drawings

GABAPENTIN MONOHYDRATE AND A PROCESS FOR PRODUCING THE SAME

BACKGROUND OF THE INVENTION

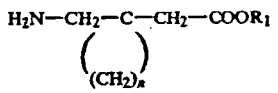
Gabapentin is a generic term used to identify the chemical compound (1-aminomethyl)-1-cyclohexaneacetic acid.



(I)

It is useful in therapy of certain cerebral disorders such as certain forms of epilepsy, faintness attacks, hypokinesia and cranial traumas. U.S. Pat. Nos. 4,024,175 and 4,087,544 cover the compound and its uses. They also disclose an acid salt, i.e. gabapentin.hydrochloride hydrate in a ratio of 4:4:1 and a sodium salt of gabapentin hydrate in a ratio of 2:1. These patents are hereby incorporated by reference.

The patents describe various processes for the preparation of this and similar compounds of general formula



wherein R_1 is a hydrogen atom or a lower alkyl radical and n is 4, 5, or 6 and the pharmaceutically acceptable salts thereof, which depend upon known methods used for the preparation of primary amines or amino acids.

All examples of the syntheses end in an isocyanate or urethane that can easily be converted into the desired (1-aminomethyl)-1-cyclohexaneacetic acid by acidic hydrolysis (preferred) to give an acid or basic hydrolysis to give a basic salt or followed by acidification to give an acid salt.

SUMMARY OF THE INVENTION

The present invention provides crystalline gabapentin monohydrate, a novel, highly pure substance of reasonable bulk density suitable for formulation in the desired forms such as capsules or tablets. Its properties are those sought in a pharmaceutical product. The present invention provides both a small scale and a large scale method for producing gabapentin monohydrate. This form, the hydrate of the free amino acid, has the advantage of being less expensive to produce than the known form of gabapentin. The process has the advantage of having barely detectable residues of solvents such as 2-propanol. No detectable methanol or ethanol residuals remain. Also, the process for producing the hydrate provides an extra purification step even if one goes on to produce the anhydrous material. The hydrate saves 12-13% of the total yield of gabapentin by eliminating the losses confronted in the final recrystallization. The hydrate also saves the cost of solvents, man hours, and utilities used in the final recrystallization. The product is a very pretty crystal which is stable at ambient temperatures (20°-25° C.).

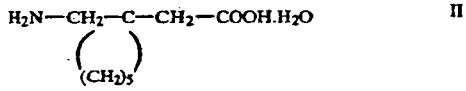
DETAILED DESCRIPTION

The instant invention is a novel form of gabapentin, crystalline gabapentin monohydrate with the following unique X-ray diffraction properties.

Spacing 'd'	Relative Intensities
14.255	99
7.196	99
5.438	4
4.848	99
4.575	7
4.291	7
3.633	99
3.376	21
3.220	9
2.903	28
2.771	23
2.356	7
2.344	12

Crystalline gabapentin monohydrate has a density within the range of 0.35 to 0.9 g/cm^3. The observed is 0.35 to 0.49 g/cm^3 + or −0.02. The crystals are obtained in a highly pure state. They are of a reasonable bulk density. The term reasonable means having a density above 0.4 g/cm^3. These characteristics readily lend themselves to pharmaceutical formulating operations.

The present invention also provides a process for producing gabapentin monohydrate on a small scale. This process is for the preparation of a compound of formula



II

which comprises:

(a) pouring a 1N solution of an acid salt of (1-aminomethyl)-cyclohexaneacetic acid onto an ion exchange column in the basic form and eluting that column with deionized water;

(b) collecting and testing fractions from step (a) for ion and product;

(c) concentrating the fractions containing product from step (b) to a slurry;

(d) mixing the slurry from step (c) with alcohol to produce a suspension and after cooling;

(e) filtering off the desired product, washing it with cold alcohol and drying it in vacuo.

Useful acid salts are hydrobromide, sulphate, methane sulfonate, hydrochloride and the like. The preferred acid salt in step (a) is the hydrochloride.

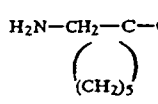
Preferably in step (b) the chloride ion is tested for by using a silver nitrate solution, but other analytical methods for chloride can be used by one skilled in the art. The product is tested by thin layer chromatography.

Preferably in step (c) the fractions are concentrated on a rotovap with about 29–31 inches vacuum at a temperature of from about 25° to about 50° C. to a volume of about three times the theoretical volume yield of 1:1 hydrate.

Preferably in step (d) the alcohol is 2-propanol and the suspension is cooled for from about 8 to about 20 hours.

The present invention further provides a process for the large scale production of gabapentin hydrate (1:1) which comprises:

A process for the preparation of a compound of formula



II

which comprises:

(a) pouring a solution of an acid salt of (1-aminomethyl)-cyclohexaneacetic acid in deionized water onto an ion exchange column in the basic form and eluting the column with deionized water;

(b) concentrating the eluate producing a slurry;

(c) cooling and adding alcohol to the slurry from step (b);

(d) cooling and centrifuging the slurry from step (c); and

(e) drying the precipitate of the desired product.

Useful acid salts include but are not limited to hydrobromide, sulphate, methanesulfonate, hydrochloride and the like. The preferred salt is the hydrochloride and in a preferred ratio is 4:4:1.

The preferred acid salt of (1-aminomethyl)-cyclohexaneacetic acid is the monohydrochloride hydrate in a ratio of 4:4:1.

Preferred process conditions in step (b) the eluate is concentrated in a glass-lined still at about 29–31 inches of vacuum at a temperature of from about 25° C. to about 50° C. to produce a slurry.

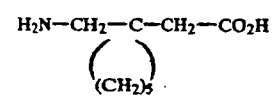
Preferred process conditions in step (c) the slurry is cooled to about 25° to about 45° C. for about 1 to 3 hours and the alcohol added is 2-propanol.

Preferred process conditions for step (d) include the slurry is cooled to about −10° C. to about 0° C. for about 12 to 16 hours.

Preferred process conditions for step (e) include the precipitate is dried in vacuo at about 25°–35° C. for about 8 to 24 hours.

The gabapentin monohydrate provides an extra purification step and can be used to produce the anhydrous material claimed in the United States Patents incorporated by reference.

The present invention further provides a process for the large scale production of essentially anhydrous gabapentin of the same crystal structure produced by the methods cited in the United States Patents incorporated by reference. This process for the preparation of the compound of formula



I

comprises:

(a) dissolving pure gabapentin monohydrate in methanol at 50° C. to 60° C.;

(b) diluting with 2-propanol and cooling to 0° C. to −10° C. the solution from step (a) resulting in a slurry;

(c) centrifuging the slurry from step (b) and drying the precipitate of gabapentin.

Preferred process conditions in step (a) the gabapentin monohydrate is dissolved in methanol in a ratio of 0.141 Kg of gabapentin monohydrate to 1.00 Kg of anhydrous methanol in a temperature range of about 50° C. to about 60° C.

Preferred process conditions in step (b) the solution is diluted with anhydrous 2-propanol in the ratio of 1 Kg of anhydrous 2-propanol to 1 Kg anhydrous methanol and the solution is chilled to 20° C. to 25° C. for two hours and then to −8° C. to −10° C. for sixteen to twenty hours.

Preferred process conditions in step (c) include the gabapentin is dried in vacuo at about 25° C. to 45° C. for about eight to forty-eight hours.

Since the compound of formula (II) has only extremely low toxicity, it can be administered enterally or parenterally within wide dosage ranges in liquid or solid form. As injection solution, water is preferably employed which contains the usual additives for injection solutions, such as stabilising agents, solubilising agents and/or buffers.

Additives of this kind include, for example, tartrate and citrate buffers, ethanol, complex-forming agents (such as ethylenediamine-tetraacetic acid and the non-toxic salts thereof), as well as high molecular weight polymers (such as liquid polyethylene oxide) for viscosity regulation. Solid carrier materials include, for example, starch, lactose, mannitol, methyl cellulose, talc, highly dispersed silicic acids, high molecular weight fatty acids (such as stearic acid), gelatine, agaragar, calcium phosphate, magnesium stearate, animal and vegetable fats and solid high molecular weight polymers (such as polyethylene glycol); compositions suitable for oral administration can, if desired, also contain flavoring and/or sweetening agents.

The individual dosage for the compounds according to the present invention can be from 100 to 3000 mg/day for an adult, preferably from 600 to 2400 mg/day, and most preferably the dosage is about 1200 mg/day or as deemed necessary by a skilled physician.

Thus, the present invention also provides pharamaceutical compositions of the compound in admixture with a solid or liquid pharmaceutical diluent or carrier.

The preparation of gabapentin monohydrate is illustrated by the following nonlimiting examples.

EXAMPLE 1

Small Scale isolation of Gabapentin hydrate (1:1) ((1-aminomethyl)-cyclohexaneaceticacid.H_2O)

An ion exchange column is prepared by filling a glass column with 380 mL of Amberlite^R IRA-68. The resin is rinsed with a dilute ammonia solution, 140 mL ammonium hydroxide in 3 L water, followed by deionized water to a neutral pH, (about 2 L). A 1 N solution of (1-aminomethyl)-cyclohexaneacetic acid hydrochloride is prepared by dissolving 64.6 g of (1-aminomethyl)-cyclohexaneacetic acid hydrochloride hydrate (4:4:1) in 310 mL of deionized water. This solution is filtered through a filter to remove any insoluble material or extracted with an organic solvent such as dichloromethane.

The solution is poured onto the column and drained to the top level of the resin. The column is eluted using deionized water at approximately 15 mL/min. Fractions of about 200–250 mL are collected. The first four fractions, about 1 L total, contain all of the product (TLC). Chloride is tested for using a silver nitrate solution. No chloride is usually detected in any of the fractions collected.

The first four fractions are concentrated on a rotovap with about 29–31 inches vacuum and the temperature

<40° C. to a slurry, about 150 mL. This is mixed with 288 mL 2-proponal and the suspension is cooled in a refrigerator overnight. The white crystalline (1-aminomethyl)-cyclohexaneacetic acid hydrate (1:1) is filtered off, washed with cold 2-propanol, and dried in vacuo to yield 42.93 g.

Analytical data: HPLC: 89.27% w/w against dry analytical standard, H_2O: 9.68%±0.5, mp 156°-156.7° C. (dec), CL^-: 8.6 ppm.

Since this is a hydrate and does melt with decomposition, the melting point range can start as low as 154° C. and can end as high as 162° C.

EXAMPLE 2

Large Scale isolation of Gabapentin hydrate (1:1) ((1-aminomethyl)-cyclohexaneacetic acid hydrate (1:1))

An ion exchange column (60 inch bed height, 15 inch radius) is charged with 250 L of filtered deionized water followed by 700 L (504 Kg wet) Amberlite® IRA-68 resin. The resin is backwashed with 2000 L of filtered deionized water. The resin is treated with 3700 L of filtered deionized water that has been mixed with 60.6 Kg of concentrated hydrochloric acid. The acid treatment is repeated with fresh acid. The resin is washed with 6400 L of filtered deionized water. The resin is treated with 1770 L of a 4% solution of sodium hydroxide. The resin is washed with 3200 L of deionized water.

The resin is treated with 3700 L of filtered deionized water that has been mixed with 60.6 Kg of concentrated hydrochloric acid. The acid treatment is repeated with fresh acid. The resin is washed with 6400 L of filtered deionized water. The resin is treated with 1770 L of a 4% solution of sodium hydroxide. The resin is washed with 3200 L of deionized water.

The resin is treated with 3700 L of filtered deionized water that has been mixed with 60.6 Kg of concentrated hydrochloric acid. The acid treatment is repeated with fresh acid. The resin is washed with 6400 L of filtered deionized water. The resin is treated with a solution of 105 Kg of 28% ammonium hydroxide in 1700 L of deionized water. The resin is washed with 6400 L of deionized water.

A solution of 122 Kg (57.5 moles) of 1-(aminomethyl)-cyclohexaneacetic acid monohydrochloride hydrate (4:4:1) in 472 Kg of deionized water is filtered to remove any insoluble material or extracted with an organic solvent such as dichloromethane and then is applied to the top of the ion exchange column and eluted with 3750 Kg of deionized water. The presence of chloride ion is tested for using silver nitrate solution and the product is tested for by using thin layer chromatography. The eluate is concentrated in a 500 gallon glass-lined still at about 29-31 inches of vacuum and wall temperature of <50° C. A total of 3500 Kg of water is removed. The resulting slurry is cooled to about 18°-20° C. and 248.5 Kg of 2-propanol is added. The slurry is cooled at −12°--8° C. for 16 hours, centrifuged and washed with 2-propanol. The precipitate is dried in vacuo about 29-31 inches at 25°-30° C. to yield 86 Kg of 1-(aminomethyl)-cyclohexaneacetic acid hydrate (1:1).

Analytical data: HPLC: 89.4 w/w against dry reference standard, H_2O (Karl Fischer): 9.69%±0.5, mp 156°-156.7° C. (dec), CL^-: 30 ppm.

Since this is a hydrate and does melt with decomposition, the melting point range can start as low as 154° C. and can end as high as 162° C.

EXAMPLE 3

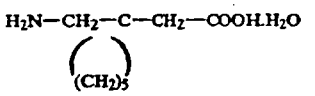
Large Scale Isolation of anhydrous 1-(aminomethyl)-cyclohexaneacetic acid from gabapentin monohydrate ((1-aminomethyl)-cyclohexaneacetic acid hydrate (1:1)

A slurry of 179 Kg of 1-(aminomethyl)-cyclohexaneacetic acid monohydrate and 1266 Kg of anhydrous methanol is heated to 60° C. to give a complete solution. The solution is diluted with 1266 Kg of anhydrous 2-propanol and the solution is cooled to 20° C. to 25° C. for two hours and then is cooled to −8° C. to −10° C. for twenty hours. The resulting slurry is centrifuged and the precipitate is dried in vacuo at 35° C. for forty-eight hours to yield 145 Kg of white, crystalline 1-(aminomethyl)-cyclohexaneacetic acid.

Analytical data: HPLC: 100.6% w/w against dry analytical standard, H_2O: 0.09%. CH_3OH: 0.01%, $(CH_3)_2CHOH$: 0.01%, CL^-: 22 ppm, Melting point: 161.7°-162.6° C. (dec.).

We claim:

1.

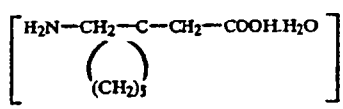


II

exhibiting essentially the following X-ray diffraction data:

Spacing 'd'	Relative Intensities
14.255	99
7.196	99
5.438	4
4.848	99
4.575	7
4.291	7
3.633	99
3.376	21
3.220	9
2.903	28
2.771	23
2.356	7
2.344	12

2.



II

according to claim 1 having a bulk density within the range of 0.35 to 0.49 g/cm³.

* * * * *