CV 01-2214 #1

UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF WASHINGTON

EDMS, LLC, a Washington State limited liability company,

Plaintiff,

v.

FRANK S. BELL and POLLY BELL, husband and wife, and the marital community composed thereof; and CABEL CORPORATION, a New Jersey corporation,

Defendants.

No. C01-2214Z

COMPLAINT FOR DAMAGES AND INJUNCTIVE RELIEF

Plaintiff EDMS, LLC alleges as follows:

INTRODUCTION

1. This is an action seeking damages and injunctive relief arising out of the defendants wrongful conduct, including without limitation, infringement of a U.S. patent, unfair competition arising under the Lanham Act, 15 U S.C. §§ 1051 *et seq*. (as amended); unfair business practices arising under RCW 19 86 *et seq*.; common law business disparagement; and interference with business relationships and expectancies.

PARTIES

2. Plaintiff EDMS, LLC ("EDMS") is a limited liability company organized under the laws of the State of Washington and having its principal place of business in Stanwood, Washington.

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EDMS is the exclusive formulation licensee of the certain proprietary compounds comprising histamine and caffeine delivered via transdermal means for treating symptoms of Multiple Sclerosis (MS) and related diseases. The rights thereto are protected by and described in U.S. Patent number 6,277,402 (hereinafter, "the '402 Patent"), issued on August 21, 2001. EDMS also has foreign patents pending throughout Europe for this method for treatment of MS and related diseases.

3. On information and belief, defendants Frank S. Bell and Polly Bell are married person residing in Palm Beach, Florida, and/or Williamstown, Massachusetts. All wrongful acts of these defendants as alleged herein were performed for the benefit of their marital community.

4. On information and belief, defendants Frank S. Bell and Polly Bell have been and are acting together in a *de facto* partnership (the "Bell Partnership"), doing business and/or representing themselves, individually and collectively, using the pseudonym "GoodShape."

5 On information and belief, defendant Cabel Corporation ("Cabel"), is a New Jersey for-profit corporation having its principal place of business in Parsippany, New Jersey. Defendant Frank S. Bell is the sole shareholder of Cabel. Cabel acts in concert with, and aids and abets the wrongful conduct of, defendants Frank S. Bell and Polly Bell, and thus Cabel is a member of the *de facto* Bell Partnership.

JURISDICTION AND VENUE

6. This action relates in part to the direct and indirect infringement of a United States patent, and thus the Court has original subject matter jurisdiction under 35 U.S.C. § 101 *et seq.* pursuant to 28 U.S.C. § 1338(a).

7. This court has original jurisdiction over claims arising under the Lanham Act, 15 U.S.C. §§ 1051 *et seq.* (as amended) and for unfair competition claims arising under RCW 19.86.020 pursuant to 28 U.S.C. § 1338(b) and 28 U.S.C. § 1367.

8. This court has subject matter jurisdiction over the remaining claims pursuant to 28 U.S.C. § 1332(a).

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9. By application of Washington State "long arm statute," RCW 4.28.185, this court has personal jurisdiction over defendants Frank S. Bell, Polly Bell; and Cabel, arising out of their purposeful direction of tortious and wrongful conduct at the residents of the State of Washington. The injuries for which recovery is sought in this action arise out of or are related to these activities, in whole or in part.

10. Venue is proper in this Court pursuant to 28 U.S.C. § 1391(b) , in that a substantial part of the events giving rise to the claim occurred in this district and the property that is the subject action, i.e., the '402 Patent, is situated in this district Additionally, venue is proper pursuant to 28 U.S.C § 1391(c) as to Cabel in that it is subject to personal jurisdiction in this district.

FACTS RELATED TO THE INVENTION AND PLAINTIFF

11. Ms Elaine DeLack is a registered nurse and the inventor of certain proprietary compounds comprising histamine and caffeine delivered via transdermal means for treating MS symptoms and related disease states. Her interest in MS treatments arises from her professional background in addition to the fact that she, too, suffers from MS.

12. EDMS is a business engaged, among other things, in the licensing of certain intellectual property used in the treatment of persons with MS and related disease states. EDMS is the exclusive formulation licensee of the certain proprietary compounds comprising histamine and caffeine delivered via transdermal means for treatment of MS and related diseases that is owned by Ms. DeLack. In particular, EDMS sublicenses various compounding pharmacies so that these pharmacies can prepare a proprietary compound comprising histamine and caffeine delivered via a topical cream and optionally a transdermal patch. The proprietary compound in one embodiment has been sold in conjunction with the trademark "PROCARIN" and is presently being sold in conjunction with the trademark "PROKARIN." For purposes of these proceedings, the branded compound will be referred to as Prokarin™.

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13. Users of Prokarin™ obtain a prescription therefor from a medical practitioner and then have the prescription fulfilled by a compounding pharmacy. Licensed pharmacies then prepare and deliver the filled prescription to the prescription holder. The licensed pharmacies are then obligated by contract to pay a royalty to EDMS. Such payments are EDMS' only source of revenue.

14. Ms. DeLack is the first and only named inventor identified in the '402 Patent, which is entitled "Method for Treatment of Multiple Sclerosis and Related Medical Disease States " She is also a principal of EDMS and of "MS Helping Hands" (formerly known as the PROCARIN Reach Foundation, and referred to hereafter as "the Foundation"). The Foundation is a not-for-profit entity established for the purpose of providing subsidized Prokarin™ prescriptions as well as MS-related seminars, workshops, research promotion and the like.

15. EDMS and the Foundation have commissioned a double blind study to evaluate the efficacy of the Prokarin™ product, the results of which are scheduled for publication in *MS Journal* in its February 2002 issue. EDMS expects that one result of the publication of the study results will be a substantial increase in the public's interest in Prokarin™.

THE INVENTION COVERED BY THE '402 PATENT

16 The '402 Patent consists of twenty-nine independent and dependent claims.

17. Claim 1 reads as follows:

> A method of treatment of multiple sclerosis, said method comprising the steps of:
> administering to a patient transdermally and on a continuing basis and substantially without the presence of an immunogen a composition comprising:
> a histamine H2 agonist, in an amount effective to stimulate and sustain production of cyclic AMP at a level which is adequate to maintain myelin against self-degeneration; and
> a phosphodiesterase inhibitor, in an amount effective for conservation of said levels of cyclic AMP which is produced in response to administration of said histamine H2 agonist.

18. Claim 8 reads as follows:

> A method for treatment of multiple sclerosis, said method comprising the steps of:

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administering to a patient transdermally and on a continuing basis substantially without the presence of an immunogen a histamine H2 agonist so as to stimulate and sustain production of cyclic AMP; and administering to said patient a phosphodiesterase inhibitor so as to conserve said cyclic AMP which is produced in response to administration of said histamine H2 agonist.

19. Claim 16 reads as follows:

A composition for treatment of multiple sclerosis, said composition being substantially free of an immunogen and comprising:
histamine phosphate
a phosphodiesterase inhibitor; and
a fluid carrier for transdermal administration in which said histamine phosphate and said phosphodiesterase are mixed for simultaneous administration to a patient.

20. Claim 20 reads as follows:

An apparatus for treatment of multiple sclerosis, said apparatus comprising;
a transdermal patch; and
a treatment composition deposited on said patch for administration to a patient, said treatment composition being substantially free of an immunogen and comprising, in predetermined amounts:
histamine phosphate;
a phosphodiesterase inhibitor; and
a fluid medium in which said histamine phosphate and said phosphodiesterase inhibitor are mixed for simultaneous transdermal administration to said patient.

21. Claim 25 reads as follows:

A combined preparation for simultaneous, separate, or sequential administration for the treatment of multiple sclerosis and related disease states, preparation consisting essentially of:
histamine phosphate
caffeine; and
at least one fluid carrier for transdermal administration of said preparation.

22. Claim 28 reads as follows:

A method for treatment of multiple sclerosis, comprising administering to a patient transdermally and on a continuing basis a preparation consisting essentially of:
histamine phosphate
caffeine, and
at least one fluid carrier for transdermal administration of said preparation.

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23. The dependent claims describe in greater detail, among other things, the preferred embodiments of the invention.

FACTS RELATED TO DEFENDANTS' CONDUCT

24. EDMS first became aware of Frank Bell on or about September 9, 1999. On that date, EDMS observed an electronic message posted by Mr. Bell to a message board. In the electronic message, Mr. Bell simultaneously extolled the benefits of Prokarin™ while attacking EDMS' motivation in selling the Prokarin™ product, and especially its practice of receiving license fees paid by the licensing compounding pharmacies.

25. Mr. Bell wrote a letter to EDMS, dated December 17, 1999, and sent by facsimile, in which he outlined one or more business plans for EDMS and the Foundation and in which he additionally made suggestions regarding the nature of research studies being contemplated by EDMS and the Foundation.

26. On or about December 19, 1999, EDMS responded courteously to Mr. Bell, but declining to follow the business suggestions that he had offered.

27. Within four days, on December 23, 1999, Mr. Bell sent an e-mail message to EDMS in which he again objected to EDMS' business operations and further questioned EDMS about its financial arrangements with the compounding pharmacies and matters related to charitable contributions by EDMS and/or the Foundation.

28. In the following months, there was further correspondence between Mr. Bell and EDMS which finally ended in April of 2000. At our about this time, Mr. Bell, the Bell Partnership, and/or Cabel, acting through the pseudonym "GoodShape," began publishing one or more detailed sets of instructions for making and using a knock-off of the Prokarin™ proprietary compound, as well as the transdermal patch means for delivering the compound. The publication took place on an Internet World Wide Web site found at URL "www.goodshape.net."

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29 The knock-off was represented as comprising histamine and caffeine, which are two of the main ingredients of the Prokarin™ proprietary compound, and the subject of the '402 Patent claims.

30. In addition to detailing how to make and use the Prokarin™ knock-off, GoodShape has also identified and provided contact information for numerous compounding pharmacies for the purpose of enabling visitors to the "goodshape.net" web-site to cause the manufacture and use of knock-off Prokarin™, thereby infringing the '402 Patent.

31. On information and belief, GoodShape has actively and knowingly induced one or more compounding pharmacies to fulfill orders for knock-off Prokarin™. On information and belief, GoodShape has actively and knowingly assisted unknown third parties in formulating their own Prokarin™ knock-off.

32. The above described activities by GoodShape are ongoing.

33. Defendant Cabel administers numerous Internet web-sites, including several domains and on information and belief at it administers at least one message board, or "chat room," entitled "Histamine, AMP, LDN, Antivirals and Alternative MS Therapies." This chat room is presently hosted at URL "disc.server.com/Indicies/148285.html".

34. Cabel is listed in Internet domain records as the administrative contact for the following domains: "givenshare.com", "givenshare.net"; "givenshare.org"; "histamineangel.com"; "histamineangel.net", "histamineangel.org"; and "medangel.org".

35. Currently, "goodshape.net", histamineangel.com", "histamineangel.org"; and "histamineangel.net" are active sites. The "goodshape.net" site provides information, instruction and encouragement to others regarding the manufacture, use and efficacy of histamine and caffeine compounds as a means for treatment of MS symptoms. The "histamineangel.com", "histamineangel.net" and "histamineangel.org" sites provide a means for requesting delivery of histamine and caffeine compounds for treatment of MS symptoms and related conditions. The

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histamine and caffeine compounds delivered through the "histamineangel" sites are prepared by, or on behalf of, Cabel, Mr. Bell, Mrs. Bell, and/or the Bell Partnership.

36. On information and belief, the compounds delivered through the "histamineangel" sites infringe the '402 Patent.

37. EDMS has neither expressly nor impliedly licensed or otherwise granted permission to any of the defendants to make, use, sell or offer for sale such compounds. On the contrary, EDMS has repeatedly requested and demanded that the defendants cease the infringing activities. The defendants have refused to comply with these requests and demands.

38. The defendants, or one or more of them, list on the "goodshape.net" web-site the identities of four pharmacies as sources for procuring the ingredients for the Prokarin™ knock-off compound, to wit, Town & Country Pharmacy, Rock Ridge Pharmacy, Liberty Drug, and Healthway Pharmacy (collectively, the "Contracting Pharmacies"). According to the defendants' web-site, three of these pharmacies are located in New Jersey and the fourth is located in Michigan. Prior to being listed on the "goodshape.net" web-site, these pharmacies had entered into confidentiality agreements with EDMS wherein they agreed to maintain in confidence the composition of the PORCARIN compound. After the execution of these agreements, but before the issuance of the '402 Patent, the Contracting Pharmacies fulfilled order requests for the Prokarin™ knock-off compound On information and belief, the Contracting Pharmacies acted in this manner in response to requests from the defendants, or one or more of them, or in response to requests from third parties acting in consort with or at the instruction and urging of one or more of the defendants By fulfilling these orders, the Contracting Pharmacies breached their contractual obligations to EDMS.

39. After the '402 Patent was issued, EDMS requested that each of the Contracting Pharmacies cease from filling orders for the knock-off Prokarin™ compound based on its belief that the knock-off compounds infringed the '402 Patent On information and belief, some Contracting Pharmacies continued infringing activities despite EDMS' request.

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40. One of the services offered by the "histamineangel" web-sites was a free "starter kit," that contains the "GoodShape" knock-off of Prokarin™. The starter kit included premixed samples of the infringing compound described in detail on the web-site pages.

41. At least one Washington State resident residing within the U.S. Western District of Washington has received "starter kit" from the defendants containing a histamine and caffeine compound for treatment of MS symptoms through one of the "histamineangel" web-sites. On information and belief, such persons include one Marlene Hanson of Federal Way, Washington.

42. On information and belief, at least one of the Contracting Pharmacies formulated the infringing compound that was delivered to a resident of western Washington State.

43. Cabel, Mr. and Mrs. Bell, and/or the Bell Partnership have instituted and maintained an electronic message board since at least May 6, 2000. The message board contains, among other things, links to the other web-sites administered by Cabel, identified above, that provide detailed instructions on the formulation and use of the infringing Prokarin™ compound Both the links and the information submitted by the defendants encourage other to "experiment" with various histamine and caffeine compounds in an attempt to duplicate the Prokarin™ formulation.

44. On one or more occasions, the defendants, or some of them, have published on the web-sites false, defamatory and/or disparaging remarks, or remarks designed to induce infringement of the '402 Patent, including statements such as.

> "My take is that Procarin is a poorly formulated mixture of 8 unknown ingredients that cause Histamine to breakdown unless kept under impossible refrigerated conditions."
>
> and
>
> "It is overpriced and controlled by extremely greedy people and has driven desperate MSers [MS sufferers] to take matters into their own hands."
>
> and
>
> "It [the GoodShape knock-off formulation] ... is more effective than Procarin. Of the 200 current users, half have switched from Procarin and all of those (so far) report improvement over the Procarin level."

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45 Mr. Bell has made other false statements in his inducement activities. He has implied that his Histamine/Caffeine Cream preparation is the same as Prokarin™ and states that his preparation is more stable, cheaper, and more effective than Prokarin™.

46. Mr Bell's statements give the false impression that his infringing preparation is better than Prokarin™ or that his infringing preparation is just like Prokarin™ He has stated on the websites that "GoodShape's recipe exactly matches the histamine caffeine in Procarin" and that the knock-off histamine/caffeine cream preparation offered by GoodShape is "Procarin without refrigeration!!! and only $70 for three month supply."

47. As indicated by various publications posted by Cabel, Mr. Bell and/or the Bell Partnership, the defendants claim to have assisted over 300 people during a four month period in making and using a histamine and caffeine compound to treat MS symptoms and related disease states. These claims, if true, describe over 300 individual acts of direct infringement.

48. The assistance to direct infringers provided by the defendants is continuing. Moreover, as each encouraged direct infringer makes and uses a histamine and caffeine compound covered by the '402 patent, they are encouraged to post results and comments on one of the defendants' Internet message boards, thus similarly encouraging others to infringe. By encouraging such actions, the defendants aid and abet further acts of infringement.

49. Cabel is an alter ego of Mr. Bell or vice versa. As noted above, Cabel administers the various Internet sites used for infringing activity. Both Cabel and Mr. Bell appear to use the "GoodShape" pseudonym within the data pages of these domains. On information and belief, Cabel has no other on-going business activities. Mr. Bell is the sole shareholder of Cabel.

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FACTS RELATED TO FUTURE HARM FROM MISREPESENTATION AND INFRINGEMENT

50. Two of the primary ingredients of Prokarin™ are histamine phosphate and caffeine citrate. These are FDA approved for indications other than MS and related disease states; accordingly Prokarin™ is an "off-label" legal prescription medication.

51. Because of this "off label" medication classification, EDMS may not employ commercial advertisements of Prokarin™ as a treatment for MS or related disease states. For this reason, news coverage is the only approved means of promoting Prokarin™.

52. EDMS has sponsored a double blind study proving the efficacy of Prokarin™ that is scheduled for publication in January of 2002. EDMS has invested $187,000.00 in the cost of the double blind study. The study results prove that Prokarin™ is scientifically significant in improving fatigue and cognition in MS patients, which according to the National MS Society are the most debilitating symptoms of MS. There currently is no effective medication for relief of these symptoms. Thus, Prokarin™ is in the forefront in the market for MS symptom relief.

53. Currently there are about 400,000 diagnosed cases of MS in the U.S. and about 4 million in the world. On average, 200 new cases of MS are diagnosed weekly in the U.S.

54. Because of the above-described advertising restrictions, EDMS desires to make full advantage of the immediate news coverage to promote Prokarin™. Accordingly, EDMS plans to saturate the news media with a video news release via satellite feed to 500 television stations, a business wire release to search engines on the internet, and a radio news release to 2500 radio stations nationally.

55. By disseminating false information, suppressing other information, and promoting infringement of the '402 Patent, the defendants have already greatly impacted the sales of Prokarin™, both in the U.S. as well as abroad, since the start up of his website in May 2000. The sales of Prokarin™ and royalties paid to EDMS will be impacted many times over if the defendants' website and activities of promoting and infringing histamine/caffeine cream preparation are allowed

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to continue during and after the time that the double-blind study is published and media attention is focussed on Prokarin™.

FIRST CAUSE OF ACTION
Patent Infringement – 28 U.S.C. § 271

56. As described more fully above, defendants have infringed the '402 Patent by making, using, and or selling the patented invention in the United States during the term of the patent, pursuant to the provisions of 28 U.S C. 271(a).

57. As described more fully above, defendants have infringed the '402 Patent by actively inducing third parties to infringe the patent, pursuant to the provisions of 28 U.S.C. 271(b).

58. As described more fully above, defendants are contributory infringers of the '402 Patent pursuant to the provisions of 28 U.S.C. § 271(c).

59. As a proximate result of the defendants' unlawful conduct, plaintiff has suffered damages in an amount to be proven at trial and is entitled to injunctive relief.

SECOND CAUSE OF ACTION
Federal Unfair Competition – 15 U.S.C. § 1125

60. As described more fully above, defendants' publications and communications over the Internet or otherwise constitute false designations of origin and/or false or misleading descriptions or representations of fact in commerce which are likely to cause confusion or mistake or to deceive as to the commercial activities by EDMS.

61. As described more fully above, defendants' publications and communications over the Internet or otherwise constitute misrepresentations in commerce as to the nature, characteristics and qualities of their own and/or EDMS' goods, services and commercial activities.

62. As a proximate result of the defendants' unlawful conduct, plaintiff has suffered damages in an amount to be proven at trial and is entitled to injunctive relief under 15 U.S.C. § 1125(c).

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THIRD CAUSE OF ACTION
State Unfair Competition – RCW 19.86.020

63. As described more fully above, defendants have willfully and knowingly engaged in unfair competition and in unfair and deceptive acts and practices in violation of RCW 19.86.020. One or more of these violations took place in the State of Washington. Defendant's acts or practices occurred in trade or commerce, and impacted the public interest.

64. As a proximate result of these acts of unfair competition and deceptive acts and practices, EDMS has suffered damages to its business and/or property in an amount to be determined at trial and is entitled to injunctive relief.

FOURTH CAUSE OF ACTION
Common Law Business Disparagement

65. As described more fully above, defendants have published false and disparaging statements regarding the plaintiff and its product(s) As a proximate result thereof, plaintiff has been damaged in an amount to be proven at trial.

FIFTH CAUSE OF ACTION
Interference with Business Relationships and Expectancies

66. As described more fully above, defendants wrongfully interfered with EDMS's business relationships with the Contracting Pharmacies and with EDMS's related business expectancies. As a proximate result thereof, plaintiff has been damaged in an amount to be proven at trial.

WHEREFORE plaintiff prays for the following relief:

1 For actual damages in an amount to be proven at trial.

2. For exemplary and/or punitive damages to the extent provided by any applicable provision of law.

3. For an award of attorneys' fees and costs as provided by any applicable provision of law.

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4. For injunctive relief in the form of a temporary restraining order, preliminary injunction and permanent injunction ordering defendants to cease and desist from engaging in wrongful conduct of the types alleged herein.

DATED this 20th day of December, 2001.

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US006277402B1

(12) **United States Patent**
DeLack

(10) **Patent No.: US 6,277,402 B1**
(45) **Date of Patent: Aug. 21, 2001**

(54) **METHOD FOR TREATMENT OF MULTIPLE SCLEROSIS AND RELATED DISEASE STATES**

(76) Inventor **Elaine Alice DeLack**, 17317 E Lake Goodwin Rd , Stanwood, WA (US) 98292

(*) 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 · **09/340,277**

(22) Filed **Jun. 25, 1999**

Related U.S. Application Data

(60) Provisional application No 60/090,832, filed on Jun 26, 1998.

(51) **Int. Cl.**[7] *A61F 13/00, A61M 29/00*

(52) **U.S. Cl.** ... **424/449**, 424/443, 514/903, 514/944, 514/946, 604/109

(58) **Field of Search** 424/449, 448, 424/447, 514/26

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(74) *Attorney, Agent, or Firm*—Todd N Hathaway

(57) **ABSTRACT**

A method for treatment of multiple sclerosis and related disease states A histamine H2 mimicking agent is administered in an amount which is effective to stimulate production of a cyclic AMP in the body A phosphodiesterase inhibitor is administered in conjunction with the histamine H2 mimicking agent to conserve the cyclic AMP which is thus produced It is believed that the increased cyclic AMP levels serve to maintain the patient's myelin against self degeneration The histamine H2 mimicking agent may be histamine phosphate and the phosphodiesterase inhibitor may be caffeine The histamine H2 mimicking agent and the phosphodiesterase inhibitor may be mixed in a gel and administered using a transdermal patch

29 Claims, No Drawings

METHOD FOR TREATMENT OF MULTIPLE SCLEROSIS AND RELATED DISEASE STATES

This application claims benefit of provisional application Ser No 60/090,832 filed Jun 26, 1998

BACKGROUND

a Field of the Invention

The present invention relates generally to methods for the treatment of multiple sclerosis and related disease states, and, more particularly, to a method for alleviating/controlling the symptoms associated with multiple sclerosis and related disease states, by administration of compositions which induce an increased presence of cyclic AMP in the body so as to reduce or reverse demyelination of the nervous system

b Related Art

Multiple sclerosis (referred to from time-to-time hereinafter as "MS") is a chronic degenerative disease of the central nervous system, characterized by demyelination of the nerve axons Symptoms include varying degrees of fatigue, numbness, tremors/muscle spasms and paralysis, coupled with a heightened susceptibility to heat and other environmental stressors. Currently, approximately 2,500,000 people worldwide have been diagnosed as having multiple sclerosis. Onset of the disease usually occurs between 20 and 40 years of age

It is recognized that MS occurs in at least two general types, i.e , "remissive-relapsive", in which acute exacerbations are separated by periods of partial recovery, and "chronic-progressive", in which the symptoms continue generally unrelieved and there is a progressive deterioration of the patient's condition that may eventually result in total debilitation.

Efforts at treatment of MS have heretofore concentrated almost entirely on the body's autoimmune response system The prevailing theory has been that some agent causes the myelin sheath to be attacked by the immune system, resulting in destruction of the myelin and creation of the lesions It is also believed that certain viruses may play a role in causing or precipitating MS In particular, the measles virus may be involved in the disease, in that studies have not only found that people suffering from MS almost invariably possess the measles antigen, but also that MS patients generally have higher than normal levels of measles antibodies in their serum and cerebrospinal fluid One theory has been that the measles or other virus triggers the T-cells to attack and destroy the myelin sheath

Proceeding on the theory that MS is the result of an autoimmune response triggered by measles or another virus, most conventional treatment techniques have involved the use of Betaseron, Avonex and/or other anti-viral substances, generally referred to collectively as "Interferon" The intended purpose of these materials is to impede the RNA-DNA transcription process in the T-cells which are believed to be triggered by the virus into attacking the myelin While interferon has demonstrated some positive results when treating remissive-relapsive type MS, it is proven almost entirely ineffective against the chronic-progressive type

Another treatment method which has yielded a limited degree of success involves the injection of adenosine monophosphate This material is not readily absorbed, in part because it is ordinarily available only in an oil-based solution, and is not "friendly" to the patient's tissues The tissues have a tendency to wall off the material and form a small abscess capsule around it, and with each injection the material becomes harder and harder to absorb In order for the material to be absorbed, most patients must walk vigorously on a tread mill for 20–30 minutes or engage in other strenuous exercise, or else the material will simply remain at the injection site with the result that the patient becomes extremely sore and the symptoms do not improve Most people suffering from MS, however, are not mobile and are simply incapable of engaging in such exercise Consequently, while many individuals experience significant benefits at the beginning of adenosine monophosphate treatments, these results eventually fade as the person's body becomes unable to absorb the material

As will be described in greater detail below, the present invention is not postulated on conventional autoimmune theories, and instead employs application of histamine phosphate or other histamine H2 analogue to prevent/repair self-degeneration of the myelin With the exception of experimental studies by Hinton D Jonez, M D (Jonez, "Management of Multiple Sclerosis", *Postgraduate Medicine*, May 1952) and certain methods described in patents to John McMichael (U S Pat Nos 4,521,405 and 4,705,685), histamine phosphate (which is most commonly employed for diagnosis of stomach conditions) has not been used in connection with multiple sclerosis and related disorders

The work of both Jonez and McMichael is founded on conventional autoimmune response theories Dr Jonez's experiments in the early 1950's attempted to manipulate the body's allergic responses using histamine phosphate, and also used the material as a vasodilator to get more blood to the brain and other parts of the nervous system In this context, it should be understood that the present invention employs histamine phosphate to mimic histamine H2, the functions of which are confined mainly to the central nervous system, whereas the primary agent in allergic reactions is in fact histamine H1 At the time of Dr Jonez's work, however, this distinction (between histamine H1 and histamine H2) was not fully appreciated.

McMichael's method involves the injection of a small amount of an "immunogen" consisting of viral fragments or other antigens (under the theory known as "provocative neutralization"), together with a small amount of histamine phosphate McMichael identifies histamine phosphate as a vasodilator, and theorizes that the histamine phosphate reacts with the immunogen to form an "active complex" which affects absorption of the material In any event, the amounts of histamine phosphate which are involved in McMichael's treatment are far too small to have any significant impact on overall levels of histamine H2 in the body

Accordingly, there exists a need for a treatment method which effectively alleviates the symptoms of multiple sclerosis and related disease conditions Furthermore, there exists a need for such a method which provides an effective treatment for both the remissive-relapsive and chronic-progressive forms of the disease Still further, there exists a need for such a method in which the treatment compositions are readily absorbed into the patient's body, without requiring resort to physical exercise for effective absorption Still further, there exists a need for such a method which is sufficiently economical to be widely available to the great number of individuals who suffer from MS and related diseases

SUMMARY OF THE INVENTION

The present invention has solved the problems cited above, and is a method for treatment of multiple sclerosis and related disease states

Broadly, the method comprises administering a composition comprising a histamine H2 mimicking agent, in an amount effective to stimulate production of cyclic AMP at a level which is adequate to maintain the patient's myelin

against self degeneration The treatment composition may further comprise a phosphodiesterase inhibitor, administered in an amount effective for conservation of the increased levels of cyclic AMP in the patient's body

The histamine H2 mimicking agent may comprise histamine phosphate, or may comprise a selected beta adrenergic agent which mimics histamine H2 The phosphodiesterase inhibitor may comprise a methylxanthine agent, the methylxanthine agent may comprise caffeine, or may comprise theophylline or a theophylline derivative

The method may comprise administering histamine phosphate transdermally at a rate in the range of about 0 06 mg/hr to about 0 50 mg/hr, and administering caffeine transdermally at a rate in the range from about 2 mg/hr to about 25 mg/hr

The present invention also provides a treatment method which comprises administering histamine phosphate and caffeine simultaneously using a transdermal patch In a preferred embodiment, the histamine phosphate is administered transdermally at a rate in the range from about 0 1 mg/hr to about 0 3 mg/hr, and the caffeine is administered transdermally at a rate of about 12.5 mg/hr

The histamine phosphate may also be administered by subcutaneous injection or intravenously, and the caffeine may also be administered by oral ingestion or subcutaneous injection

The invention further provides a composition for treatment of multiple sclerosis and related disease states The composition may comprise a histamine H2 mimicking agent, a phosphodiesterase inhibitor, and a fluid medium in which the histamine H2 mimicking agent and phosphodiesterase inhibitor are mixed for simultaneous administration to a patient. The histamine H2 mimicking agent may be histamine phosphate and the phosphodiesterase inhibitor may be caffeine, and the fluid medium may comprise a transdermal gel or injectable solution

Still further, the invention provides an apparatus for treatment of multiple sclerosis and related disease states The apparatus comprises a transdermal patch and a treatment composition which is deposited thereon for administration to a patient, the treatment composition comprising, in predetermined amounts, a histamine H2 mimicking agent, a phosphodiesterase inhibitor, and a fluid medium in which the histamine H2 mimicking agent and phosphodiesterase inhibitor are mixed for simultaneous transdermal administration to the patient Again, in a preferred embodiment the histamine H2 mimicking agent may be histamine phosphate and the phosphodiesterase inhibitor may be caffeine

For an 8 hour transdermal dose, the histamine phosphate may be present in an amount from about 1 1 mg to about 2 2 mg, and the caffeine may be present in an amount from about 100 mg to about 200 mg.

DETAILED DESCRIPTION

The present invention provides a method for treatment of MS and related disease states by application of a histamine H2 mimicking agent in combination with a phosphodiesterase inhibitor. A preferred histamine H2 mimicking agent is histamine phosphate, and a preferred phosphodiesterase inhibitor is caffeine As will be described below, the method has been observed to alleviate the symptoms of multiple sclerosis in a test application

While not intended to be binding with respect to the practice or scope of the present invention, a hypothesis has been developed which explains the success which has been achieved with the treatment described herein As was noted above, the conventional theory has been that demyelination is the result of an autoimmune response However, it is also known that integrity of the nervous system is highly dependent on cyclic AMP, in that cyclic AMP stimulates the synthesis of myelin components by oligodendrocytes and Schwann cells Studies have shown that oligodendrocytes will undergo self-induced degeneration in the absence of cyclic AMP, resulting in demyelination, but that the degenerating cells will again become viable and capable of synthesizing myelin if treated with cyclic AMP (e g , see Kim, S U , Neurobiology of human oligodendrocytes in culture, *Journal of Neuroscience Research* 27 (1990, December))

Cyclic AMP, in turn, is produced naturally in brain tissue, largely in the pineal gland In persons suffering from MS, especially in the chronic-progressive phase, the levels of histamine H2 have been observed to be very low, and the pineal gland functions tend to be atrophied. It is also known that production of cyclic AMP by the pineal gland is controlled to a large extent by the presence of histamine H2 in the blood stream Histamine H2 (as differentiated from histamine H1) is produced by cells in the central nervous system, particularly those in the hypothalamus. In other words, certain cells in the central nervous system produce the histamine H2 which stimulates the pineal gland to produce cyclic AMP, which in turn is essential to protect the myelin against self-degeneration

It is Applicant's hypothesis that in persons suffering from MS and related disease states, the histamine H2 producing cells in the central nervous system are damaged by an agent, possibly one or more strains of the measles virus, so that over time these cells cease production of histamine H2 Inadequate production of histamine H2, in turn, results in greatly reduced output of cyclic AMP from the pineal gland, leading ultimately to self-degeneration of the myelin Hence, under Applicant's hypothesis, the lesions do not result directly from an autoimmune attack on the myelin, but are instead the result of self-degeneration of the myelin precipitated by damage to the histamine H2 producing cells of the central nervous system

It is further hypothesized that the damage is progressive, in that the remissive-relapsive form of the disease represents an earlier phase in which the histamine H2 cells are subjected to ongoing attack but some capacity to produce histamine H2 remains, while the chronic-progressive form represents a subsequent phase in which virtually no viable histamine H2 producing cells are left.

Applicant's hypothesis is consistent with prior observations concerning attempted treatment of the disease For example, as was noted above, MS symptoms tend to respond favorably to treatment with interferon and other anti-viral agents when the disease in the remissive-relapsive phase, but such treatments become ineffective when the disease enters the chronic-progressive phase This pattern is consistent with the above hypothesis, since the interferon serves to inhibit virus replication in virus-infected cells and therefore slows damage to the remaining histamine H2 producing cells during the remissive-relapsive phase, but when the disease has reached the chronic-progressive phase virtually all of the histamine H2 producing cells have a been destroyed, so that further interferon treatments can have no effect on histamine H2 output

Additional corroborating evidence includes observations that the histamine H2 levels of MS patients in the remissive-relapsive phase tend to fluctuate, sometimes being abnormally high and at other times being abnormally low This observation is also consistent with the above hypothesis, in that it will be understood that as viruses replicate and spread they cause physical disruption of cellular structures, i e , the cells become filled with replicated virus and ultimately "explode", releasing their contents into the blood stream In the case of histamine H2 producing cells, these contents would include not only replicated virus bodies, but also the

histamine H2 contained in the cell, which accounts for the sometimes increased levels of histamine H2 which are observed during periods of exacerbation in the remissive-relapsive phase

Furthermore, histamine H2 is a known heat stress modulator, and inability to handle heat stress (reflecting a low level of histamine H2) is a classic symptom of MS Histamine H2 is also believed to regulate the number of T-cells in the body, and research has shown that people with MS tend to have abnormally low numbers of T-cells during periods of exacerbation

Under Applicant's hypothesis, therefore, it is believed that MS is precipitated by the body's inability to produce adequate levels of histamine H2 Consequently, the present invention employs histamine phosphate or selected beta adrenergic agents to replace or "mimic" the histamine H2, in an amount which is sufficient to induce increased production of cyclic AMP (i e , by the pineal gland), at levels which are adequate to eliminate and/or repair the self-degeneration of the myelin The purpose of the caffeine or other phosphodiesterase inhibitor, in turn, is to reduce the action of phosphodiesterase (the enzyme in the human body which breaks down cyclic AMP), thereby providing higher cyclic AMP levels over longer periods time without having to rely on excessively high dosages of histamine phosphate

Histamine phosphate is generally preferred for the histamine H2 analogue component in the present invention, because of its wide availability and comparatively low cost, and because it very effectively mimics the action of the body's natural histamine H2 (e g , see *Fact and Comparisons* (January 1988)) Moreover, in addition to stimulating production of cyclic AMP, the histamine phosphate helps to provide stress modulation, again similar to the natural histamine H2

Histamine phosphate is most commonly supplied in the form of histamine diphosphate A suitable source of histamine phosphate for use in the present invention is a solution available from Eli Lily and Company as "histamine phosphate injection, U S P", this material is currently recognized by the US Food and Drug Administration (FDA) for use as a gastric acid test Other suitable compounds which mimic the presence of histamine H2 for purposes of stimulating cyclic AMP production by the pineal gland may be used in the method of the present invention, in combination with or in place of the histamine phosphate For example, isoproterenol and/or other beta adrenergic agents which are known or determined to be histamine H2 mimicking agents may be used in this component.

Similarly, caffeine is a preferred choice for the phosphodiesterase inhibitor because of its low expense and long half life, plus its minimal side effects and wider therapeutic index. Other suitable phosphodiesterase inhibitors may also be used in accordance with the present invention to enhance the production of cyclic AMP, however, such as theophylline, theophylline derivatives, and other methylxanthine agents As was noted above, the purpose of this component is to enhance the effect of the increased levels of cyclic AMP which are produced by the histamine H2 analog, by conserving the cyclic AMP against breakdown by the phosphodiesterase enzymes In the absence of the phosphodiesterase inhibitor component, much higher levels of histamine phosphate would be required to achieve the same result, increasing the risk of adverse cardiovascular reactions and other negative side effects

Caffeine citrate is generally preferred for the caffeine component in transdermal applications, due to its solubility and ability to achieve high concentrations in transdermal gel Also, it should be noted that references to amounts and dosages of caffeine herein refer to measures of caffeine base (i.e , the caffeine molecule), and do not include other materials which are sometimes found associated with the caffeine in a commercially available product

The treatment composition may be administered by any suitable means, such as orally or by transdermal patch, subcutaneous injection, intravenous injection, or inhaler, to give just a few examples Administration by transdermal patch may be preferable by many embodiments, in that this provides significant advantages in terms of ease of use and consistent dosage levels As used in this description and appended claims, the term "transdermal patch" includes both adhesive patches and other systems and devices for transdermal administration of treatment compositions.

The following illustrative examples relate to actual practice of the invention described above in the alleviation of the symptoms of MS patients

EXAMPLE ONE

A 39 year old, 144 pound female patient clinically diagnosed as suffering from multiple sclerosis was treated in accordance with the method of the present invention The patient has suffered from Multiple Sclerosis for approximately 12 years prior to treatment, and exhibited symptoms indicating that the disease had advanced to the chronic-progressive phase Approximately 0 069 milligrams of histamine phosphate solution (Eli Lily & Co , see above) were administered subcutaneously three times daily, accompanied by simultaneous oral administration of approximately 200 milligrams of caffeine in aqueous solution Clinically significant improvements were observed within 24 hours, and full mobility was regained in about 2 days. The patient subsequently continued the treatment regimen, with no additional exacerbation episodes having occurred to date

EXAMPLE ONE

Ten patients participating in clinical trials were treated in accordance with the present invention The patients were selected from a larger group of candidates on the following basis

(a) Each was clinically diagnosed as suffering from multiple sclerosis,

(b) Each was diagnosed as being in the "chronic-progressive" phase of the disease, so as to minimize the possibility of erroneous results due to spontaneous remission, and

(c) Each was assessed as exhibiting physical deterioration in the range from about 5 0 to 7 5 on the MS Expanded Disability Status Scale (EDSS), so that the disability would be severe enough that an improvement in condition would be clinically noticeable, but not so severe that the musculatory structure would have atrophied to the point where no improvement could be observed even if neurological damage was reversed

Transdermal patches were used to administer the treatment compositions, as opposed to the subcutaneous/oral regimen described in Example One Each patch was used for an 8-hour period and contained approximately 1 1 mg of histamine diphosphate and 100 mg of caffeine citrate, dissolved in approximately 0 2 ml of transdermal gel The gel was deposited on the patch in an area approximately 6 mm in diameter, so as to minimize the area of potential skin irritation The patch was both air and light occlusive, in order to protect the treatment material from decomposition

Each patient's condition was assessed at the commencement of the trial to establish a baseline score The assessments were performed using the following standard tools (1) MS-Related Symptoms checklist (MS-RS), (2) Fatigue Severity Scale (FSS), (3) Kurtzke Functional Systems tool (FS), and (4) the EDSS scale The assessment was repeated

after forty-five (45) days of treatment, and again at the ninety (90) day point

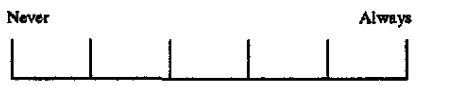
The assessment tools listed above will be familiar to those skilled in the relevant art For purposes of illustration, however, each will be summarized below, together with representative data produced during the trial

The MS-RS tool is a self-reporting system which utilizes a 6-point Likert scale (0=never, 5=always) that measures the prevalence of symptoms involving the following fine and gross motor (arm and leg weakness, spasms, tremors, balance problems), brainstem (vision problems, memory impairment, dysphagia), sensory pain (pain, burning sensations, tingling), mental (anxiety, depression), elimination (urine frequency and urgency) An example MS-RS report for one of the patients in the trial is set forth below

MS Study

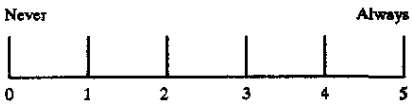
Respondent No 4337
MR-RS (Self-reporting)

Please indicate how frequently you experience each of the symptoms using the following scale.



	Base Line	45 days	90 days
Arm weakness	5	2	0
Leg weakness	5	2	3
Spasms	5	4	2
Tremors	4	3	1
Knee locking	3	1	1
Balance problems	4	1	0
Falling	3	0	0

-continued



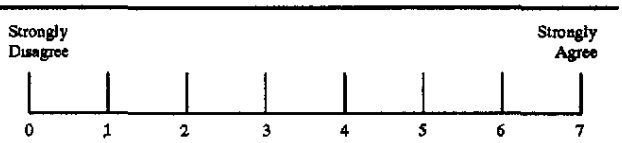
	Base Line	45 days	90 days
Urine frequency day	3	2	0
Urine frequency night	3	2	0
Trouble making bathroom· day	1	0	0
Trouble making bathroom. night	1	0	0
Loneliness	0	0	0
Depression	3	2	2
Anxiety	2	2	0
Pain	4	3	4
Burning	0	0	0
Numbness	4	2	1
Pins and needles	5	3	1
Double vision	4	4	2
Blurred Vision	4	3	2
Difficulty swallowing	1	2	0
Forgetfulness	3	4	0

The FSS tool provides a quantitative measure of fatigue, which is a prominent complaint of MS patients The FSS tool employs a 1 to 7 Likert scale (1=strongly disagree, 7=strongly agree), and is also a self reporting system An example FSS report, for the same patient as in the previous example, is set forth below·

MS Study

Respondent No 4337
FSS (Self-reporting)

Please indicate to what extent you agree or disagree with the following statements using the scale·



		Baseline	45 days	90 days
1	My motivation is lower when I am fatigued	7	5	5
2.	Exercise brings on my fatigue	5	4	5
3	I am easily fatigued	6	5	1
4	Fatigue interferes with my physical functioning	6	5	1
5	Fatigue causes frequent problems for me	6	3	1
6	My fatigue prevents sustained physical functioning	5	3	2
7	Fatigue interferes with carrying out certain duties and responsibilities	6	2	1
8	Fatigue is among my three most disabling symptoms	4	4	3
9	Fatigue interferes with my work, family, or social life	3	2	1

The FS tool provides an objective measurement of neurological impairment in the following systems pyramidal, cerebellar, brain stem, sensory, bowel/bladder, optic, mental The data is physician-reported, as opposed to the self-reporting systems used in the MS-RS and FSS tools The cumulative FS data for the trial is set forth in the following table·

CUMULATIVE TEST DATA
Functional Systems (FS)

Patient	Pyra-midal	Cere-bellar	Brain Stem	Sen-sory	Bowel Bladder	Optic	Mental	Other
1 4344								
Baseline	2	5	0	1	0	0	3	0
45 days	2	5	0	1	0	0	3	0
90 days	2	5	0	1	0	0	3	0
2. 4337								
Baseline	3	2	3	1	0	2	1	0
45 days	3	2	3	1	0	2	1	0
90 days	1	1	1	0	0	1	1	0
3. 4366								
Baseline	2	2	0	0	3	1	0	0
45 days	2	2	0	0	3	1	0	0
90 days	1	2	0	0	2–3	1	0	0
4 4339								
Baseline	3	1	2	0	2	2	2	0
45 days	3	1	2	0	2	2	2	0
90 days	3	1	2	0	2	2	2	0
5. 4336								
Baseline	4	3	1	2	6	3	0	0
45 days	2	2	1	2	6	3	0	0
90 days	2	2	1	2	6	3	0	0
6 4338								
Baseline	4	3	2	3	2	3	0	0
45 days	4	3	2	3	2	3	0	0
90 days	4	3	2	3	2	3	0	0
7 4341								
Baseline	3	0	0	2	1	0	0	0
45 days	3	0	0	2	1	0	0	0
90 days	3	0	0	2	1	0	0	0
8 4424								
Baseline	4	0	0	0	2	3	0	0
45 days	4	0	0	0	2	3	0	0
90 days	INCOMPLETE							
9 4340								
Baseline	4	3	0	2	5	3	0	0
45 days	4	2	0	2	5	3	0	0
90 days	4	2	0	2	5	3	0	0
10 4550								
Baseline	2–3	0	0	1	3	0	0	0
45 days	2–3	0	0	1	3	0	0	0
90 days	2–3	0	0	0	3	0	0	0

Finally, the EDSS scale measures progressive disability in increments of 0.5, where 0 represents normal and 10 indicates death due to MS For reference, the portion of the EDSS scale which encompasses the conditions of subjects participating in the trial is reproduced below.

Expanded Disability Status Scale (EDSS)

Scale

4 5=Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance, characterized by relatively severe disability, usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps Able to walk without aid or rest for some 300 meters

5 0=Ambulatory without aid or rest for about 200 meters, disability severe enough to impair full daily activities (eg, to work full day without special provisions) (Usual FS equivalents are one grade 5 alone, others 0 or 1, or combinations of lesser grades usually exceeding specifications for step 4 0)

5.5=Ambulatory without aid or rest for about 100 meters, disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 or 1, or combinations of lesser grades usually exceeding those for step 4 0)

6.0=Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk about 100 meters with or without resting (Usual FS equivalents are combinations with more than two FS grade 3+)

6 5=Constant bilateral assistance (canes, crutches, or braces) required to walk about 20 meters without resting (Usual FS equivalents are combinations with more than two FS grade 3+)

7 0 Unable to walk beyond about 5 meters even with aid, essentially restricted to wheelchair wheels self in standard wheelchair and transfers alone, up and about in w/c some 12 hours a day (Usual FS equivalents are combinations with more than one FS grade 4+, very rarely, pyramidal grade 5 alone)

7.5—Unable to take more than a few steps, restricted to wheelchair, may need aid in transfer, wheels self but cannot carry on in standard wheelchair a full day, may require motorized wheelchair (Usual FS equivalents are combinations with more than one FS grade 4+)

Cumulative EDSS data for the trial is set forth in the following table

Cumulative Test Data
Expanded Disability Status Scale (EDSS)

	Patient	Baseline Score	45 Days Score	90 Days Score
1	4344	5 0	5 0	5 0
2	4337	6 0	5 5	5 0
3	4366	6 0	6 0	6 0
4	4339	6.0	6 0	6 0
5	4336	6.0	5 0	5.0
6	4338	6.5	6 5	6 5
7	4341	6.0	6 0	6 0
8	4424	7 5	7 5	Inc.
9	4340	7 0	7 0	7 0
10	4550	6.0–6 5	6.0	6 0

As was noted, the full assessment was performed at the beginning of the trial and then repeated at the 45 and 90-day points The overall results, showing the data acquired using the test tools described above, are set forth in the following Table A.

TABLE A

	MS-RS TOOL			FSS TOOL			FS TOOL			EDSS			
Pt.#	B	45D	90D	B	45D	90D	B	45D	90D	B	45D	90D	Qualitative
4344	51	55 5	44	57	56	55	11	11	11	5 0	5 0	5 0	NO CHANGE
4337	67	42	19	47	31	20	12	12	5	6.0	5 5	5 0	Improved ambulation No longer using cane Increase left side strength
4366	31	7	28	45	36	33	8	8	7	6.0	6 0	6 0	Increased energy Improved ambulation Improved bladder function Reports overall improved
4339	23	33	31	46	54	48	12	12	12	6 0	6 0	6 0	NO CHANGE
4336	47	30	27	50	33	Inc	19	16	16	6 0	5 0	5 0	Increased energy Improved ambulation No longer using cane Increased sense of well being
4338	58	50	56	29	25	41	17	17	17	6 5	6 5	6 5	Reports overall improved Improved vision Improved writing function Imp bladder function Improved balance Improved sexual function
4341	34	28	31	33	38	45	6	6	6	6 0	6 0	6 0	Increased energy Imp sleeping at night
4424	63	53	Inc	56	63	Inc	9	9	Inc	7 5	7 5	Inc	Improved bladder function
4340	56	39	41	49	26	28	17	16	16	7 0	7 0	7 0	Decrease in ataxia Improved speech, first time able to sing in 18 years Increased energy Improved right arm function
4550	46	33	Inc	54	37	Inc	7	7	Inc.	6 5	6 5	Inc	Increased energy Improved speech Imp thought process Improved sensory function
	most disabled score 110	least disabled score 0		most disabled score 63	least disabled score 9		most disabled score 40	least disabled score 0		most disabled score 10 0	least disabled score 0		

Key
B = Baseline score
45D = 45 days on Tx score
90D = 90 days on Tx score

A review of the data in Table A shows that roughly 80% of the subjects reported a qualitative improvement in their condition as a result of the treatment, and roughly 30% exhibited an improvement of one or more levels on the EDSS scale (see patient numbers 4337, 4336 and 4550) The MS-RS tool, FSS tool and FS tool, in turn, appear to show measurable improvement in about 40% of the patients (see patient numbers 4337, 4366, 4336 and 4340)

It should be noted that, in contrast to the general pattern of trials and studies associated with interferon treatments, the trial set forth in Example Two recorded actual improvement in the condition of a significant number of the subjects, rather than simply a slowing in the rate of deterioration In other words, while treatment methods based on the autoimmune theory have measured "success" in terms of slowing progression of MS, the clinical trial of the present invention demonstrated an apparent reversal of the effects of the disease

Furthermore, it should be noted that the trial was conducted using essentially the smallest dose of histamine phosphate judged likely to produce observable results Based on the study results and post-trial testing, it has been determined that an average 8-hour transdermal dose of about 1 65 mg histamine phosphate generally proves more effective 8-hour transdermal dosages of about 2 2 mg have been tested on an individual basis, and in some instances dosages of 2 5 mg or higher may be suitable

Based in part on the above examples, and using the preferred constituents of histamine phosphate and caffeine, the following approximate parameters are believed to cover the majority of dosages suitable for use with physically typical patients suffering from relatively advanced MS It will be understood, however, that the actual dosages will vary with certain factors, including the individual's weight, physical condition, and environmental and mental stressors, for example

Example Dose Ranges

Caffeine·

Oral form (time release preferred) 600 mg–2500 mg qd

transdermal. 6–40 mg/hr

Histamine phosphate

Intravenous 0 01–2.75 mg qd-qid

Subcutaneous Injection. 0 001–0 04 mg/kg qd-qid

Transdermal 0 13–0 63 mg/hr

Example 8-Hour Transdermal Dose Ranges

In 0 2 ml Transdermal Gel

Histamine Phosphate 1 0–5 0 mg

Caffeine (Caffeine Citrate) 50–300 mg

It is to be recognized that various alterations, modifications, and/or additions may be introduced into the constructions and arrangements of parts described above without departing from the spirit or ambit of the present invention

What is claimed is·

1 A *method for treatment of multiple sclerosis, said* method comprising the steps of·

administering to a patient transdermally and on a continuing basis and substantially without the presence of an immunogen a composition comprising

a histamine H2 agonist, in an amount effective to stimulate and sustain production of cyclic AMP at a level which is adequate to maintain myelin against self-degeneration; and

a phosphodiesterase inhibitor, in an amount effective for conservation of said level of cyclic AMP which is produced in response to administration of said histamine H2 agonist

2 The method of claim 1 wherein said histamine H2 agonist comprises histamine phophate

3. The method of claim 1, wherein said phosphodiesterase *inhibitor comprises caffeine*

4 The method of claim 1, wherein said phosphodiesterase inhibitor comprises a methylxanthine agent.

5 The method of claim 1, wherein said phosphodiesterase inibitor comprises theophylline or a theophylline derivative

6 The method of claim 1, wherein the step of administering a composition comprising a histamine H2 agonist comprises

administering histamine phosphate transdermally at rate in the range from about 0 13 mg/hr to 0 63 mg/hr

7 The method of claim 6, wherein the step of administering a composition comprising a phosphodiesterase inhibitor comprises·

administering caffeine transdermally at a rate in the range from about 6 mg/hr to about 40 mg/hr

8 A method for treatment of multiple sclerosis, said method comprising the steps of

administering to a patient transdermally and on a continuing basis substantially without the presence of an immunogen a histamine H2 agomst so as to stimulate and sustain production of cyclic AMP, and

administering to said patient a phosphodiesterase inhibitor so as to conserve said cyclic AMP which is produced in response to adminstration of said histamine H2 agonist.

9 The method of claim 8, wherein said histamine H2 agonist comprises histamine phosphate

10 The method of claim 9, wherein said phosphodiesterase inhibitor comprises caffeine

11 The method of claim 10, further comprising the step of:

administering said histamine phosphate and caffeine simultaneously using a transdermal patch.

12 The method of claim 11, wherein the step of administering said histamine phosphate comprises.

administering said histamine phosphate transdermally at a rate in the range from about 0 13 mg/hr to about 0.63 mg/hr

13 The method of claim 12, wherein the step of administering said caffeine comprises·

administering said caffeine transdermally at a range in the range from about 6 mg/hr to about 40 mg/hr.

14 The method of claim 11, wherein the step of administering said histamine phosphate comprises.

administering said histamine phosphate transdermally at a rate in the range from about 0 13 mg/hr to about 0 63 mg/hr

15 The method of claim 14, wherein the step of administering said caffeine comprises

administering said caffeine transdermally at a rate of about 12 5 mg/hr

16 A composition for treatment of multiple sclerosis, said composition being substantially free of an immunogen and comprising.

histamine phosphate,

a phosphodiesterase inhibitor, and

a fluid carrier for transdermal administration in which said histamine phosphate and said phosphodiesterase are mixed for simultaneous administration to a patient.

17 The composition of claim 16, wherein said phosphodiesterase inhibitor comprises caffeine

18 The composition of claim 17, wherein said fluid medium comprises a transdermal gel or injectable solution

19 The composition of claim 18, wherein said caffeine comprises caffeine citrate dissolved in said transdermal gel of *injectable solution.*

20 An apparatus for treatment of multiple sclerosis, said apparatus comprising,

a transdermal patch, and

a treatment composition deposited on said patch for administration to a patient, said treatment composition being substantially free of an immunogen and comprising, in predetermined amounts

histamine phosphate,

a phosphodiesterase inhibitor, and

a fluid medium in which said histamine phosphate and said phosphodiesterase inhibitor are mixed for simultaneous transdermal administration to said patient

21 The apparatus of claim 20, wherein said phosphodiesterase inhibitor comprises caffeine

22 The apparatus of claim 20, wherein said fluid medium comprises a transdermal gel

23 The apparatus of claim 20, wherein said apparatus is configured to administer an approximately 8-hour dose

24 The apparatus of claim 23, wherein said treatment composition comprises

histamine phosphate, in an amount from about 1 0 mg to about 5 0 mg; and

caffeine in an amount from about 50 mg to about 300 mg

25 A combined preparation for simultaneous, separate, or sequential administration for the treatment of multiple sclerosis and related disease states, preparation consisting essentialy of

histamine phosphate,

caffeine, and

at least one fluid carrier for transdermal administration of said perparation

26. The preparation of claim **25**, wherein said caffeine is in the form of caffeine citrate

27 The preparation of claim **25**, wherein said at least one fluid carrier is a transdermal gel in which said histamine phosphate and caffeine are mixed for transdermal administration

28 A method for treatment of multiple sclerosis, comprising administering to a patient transdermally and on a continuing basis a preparation consisting essentially of,

histamine phosphate,

caffeine, and

At least one fluid carrier for transdermal administration of said preparation

29 The method of claim **28**, wherein said caffeine is in the form of caffeine citrate

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