(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 February 2001 (08.02.2001)

PCT

(10) International Publication Number
WO 01/08659 A1

(51) International Patent Classification[7]: A61K 9/00, 47/20, A61P 15/10

(21) International Application Number: PCT/CA00/00799

(22) International Filing Date: 5 July 2000 (05.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/365,048 30 July 1999 (30.07.1999) US

(71) Applicant: **LAKEFIELD MINERALS LTD.** [CA/CA]; 55 University Avenue, Suite 1000, Toronto, Ontario M5J 2P8 (CA).

(72) Inventors: **McGRAIL, J., Simon**; 142 Spruce Street, Toronto, Ontario M5A 2J5 (CA). **KERESTECI, Ara, G.**; 24 Almond Avenue, Thornhill, Ontario L3T 1L1 (CA). **KASMAN, Barry**; 327 Brooke Avenue, Toronto, Ontario M5M 2L4 (CA).

(74) Agent: **DONAHUE ERNST & YOUNG LLP**; Ernst & Young Tower, 222 Bay Street, Suite 1800, P.O. Box 197, T.D. Centre, Toronto, Ontario M5K 1H6 (CA).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/08659 A1

(54) Title: PHARMACEUTICAL COMPOSITIONS FOR TOPICAL APPLICATION TO TREAT ERECTILE DYSFUNCTION

(57) Abstract: A pharmaceutical composition for topical application to treat erectile dysfunction is provided. The composition includes at least one of the following compounds: paparevine, phentolamine and prostaglandin E1. The compounds are mixed with dimethyl sulfoxide (DMSO) which acts as a suitable penetrant carrier to enhance absorption of the compounds. The pharmaceutical composition is effective for creating erections of normal duration through topical application.

Pharmaceutical Compositions for Topical Application to Treat Erectile Dysfunction

Field of the Invention

The invention relates to pharmaceutical preparations for treating erectile dysfunction.

Background

Male impotency or erectile dysfunction is a problem affecting millions of men across North America and the rest of the world. Up to thirty million men are affected by male impotency in the United States alone. The problem is especially common in aging men. There are several treatments available for this condition.

External vacuum therapies are available for treating all types of impotence. This is often used as a first step treatment for erectile dysfunction. Generally, this therapy involves the creation of negative pressure in a plastic cylinder through the use of a pump. The user inserts his penis into the cylinder. The vacuum causes blood to enter the penis in a way similar to a natural erection. Despite the fact that this therapy has a ninety percent success rate, it is an awkward and uncomfortable treatment. Because of these drawbacks, men are often reluctant to use this treatment.

Erectile dysfunction can also be treated through oral prescription medication. The best known is Sildenafil Citrate (Viagra™). Viagra™ received FDA approval on

March 27, 1998 and has received much publicity since being introduced into the marketplace. Viagra™ can be taken orally in a pill form. This treatment has had a good success rate in treating impotent men.

However, many men are reluctant to try this treatment. The consistent use of a pill is considered to be undesirable by many men since the drug enters the user's entire system. The drug is therefore circulated through the user's entire body and is not concentrated in the affected region. This is a concern because it is still unknown what the long-term effects of Viagra ™ may be on other organs and organ systems of the body.

Hormone therapy is used to treat impotence caused by a testosterone deficiency. Raising the level of testosterone in men having a deficiency has proved to be effective for treating impotency in many cases. This treatment has the drawback of having serious side effects.

Another method for treating erectile dysfunction is the use of a urethral suppository. This procedure involves the insertion of an applicator tip into the urethra for delivery of a suppository. Absorption occurs through the urethral wall. This treatment is quite awkward, uncomfortable, and often painful.

More radical treatments for erectile dysfunction include penile implant surgery and vascular surgery. This is a last resort because of the inherent risks of undertaking any surgical procedure.

It has been known since the early nineteen eighties that penile injection therapy is effective for creating erections. Three drugs, papaverine, phentolamine and prostaglandin E1 have been used successfully to create erections through this technique.

The patient must inject a solution containing one or more of these drugs directly into the penis. Hand pressure must be applied afterwards for a few minutes to prevent bleeding.

Despite the fact that impotent men have enjoyed a high success rate through this treatment, the method has several obvious drawbacks. The prospect of injecting a needle into the penis is quite daunting to many men. The puncture of the needle can also cause a great deal of pain. As a result, few choose this method when presented with other alternatives.

Another drawback of penile injection therapy is priapism. This is an unwanted prolonged erection that results from injecting more of the drug than is required for an erection of normal duration. Penile injection therapy also has a drawback of being extremely costly. Injections normally cost about twenty to twenty-five dollars.

A pharmaceutical preparation that can be applied topically to the penis would avoid the drawbacks of the current treatments for erectile dysfunction. A topical treatment has not been previously developed because there has previously not been a known carrier for drugs such as papaverine, phentolamine and prostaglandin E1 that can both be absorbed through the skin into the bloodstream while effectively carrying the drugs into the bloodstream.

There is therefore a need for a pharmaceutical preparation that is effective for creating an erection in impotent men through topical application to the penis.

Summary of the Invention

The invention comprises a pharmaceutical composition that is effective for treating erectile dysfunction through topical application to the penis. The pharmaceutical composition includes at least one compound that is effective for creating an erection when entering the bloodstream of the penis and a suitable penetrant carrier to enhance absorption of the compound.

According to one aspect of the invention a pharmaceutical composition for topical application to treat erectile dysfunction is provided. The composition includes at least one of the following compounds:

- Papaverine
- Phentolamine
- Prostaglandin E1.

A suitable penetrant carrier to enhance absorption of at least one of these compounds is also provided.

According to another aspect of the invention a pharmaceutical composition for topical application to treat erectile dysfunction is provided. The composition includes at least one compound that is effective in creating erections in impotent men upon

entering the bloodstream of the penis. The compound is dissolved in dimethyl sulfoxide (DMSO).

According to another aspect of the invention a method of making a pharmaceutical composition for topical application to treat erectile dysfunction is provided. The method comprises the steps of providing a quantity of at least one compound that creates an erection upon entering the bloodstream of the penis, mixing at least one compound in a volume of water, providing a volume of DMSO and mixing the compound /water mixture in the DMSO.

According to yet another aspect of the present invention, a method for making a pharmaceutical composition for topical application to treat erectile dysfunction is provided. The method comprises the steps of providing a quantity of papaverine, providing a quantity of phentolamine, providing a quantity of prostaglandin E1, mixing the papaverine, phentolamine and prostaglandin E1 in a quantity of water to create a solution, providing a quantity of a suitable penetrant carrier to enhance absorption of the papaverine, phentolamine and prostaglandin E1 and mixing the solution in the suitable penetrant carrier.

According to another aspect of the present invention, a method of making a pharmaceutical composition for topical application to treat erectile dysfunction is provided. The method comprises the steps of providing a quantity of papaverine, providing a quantity of phentolamine, providing a quantity of prostaglandin E1, mixing the papaverine, phentolamine and prostaglandin E1 in a quantity of water to create a solution, providing a quantity of DMSO and mixing the solution in the DMSO.

According to another aspect of the present invention, a method of making a pharmaceutical composition for topical application to treat erectile dysfunction is provided. The method comprises the steps of providing a quantity of papaverine, providing a quantity of phentolamine, providing a quantity of prostaglandin E1, providing a quantity of DMSO and mixing the papaverine, phentolamine and prostaglandin E1 in the DMSO.

According to another aspect of the present invention, use is made of the pharmaceutical composition for topical application to treat erectile dysfunction. The composition includes at least one of the following compounds:

- Papaverine
- Phentolamine
- Prostaglandin E1,

and a suitable penetrant carrier to enhance absorption of said at least one compound.

According to yet another aspect of the present invention, use is made of a pharmaceutical preparation to topically treat male impotency. A pharmaceutical composition has at least one pharmaceutical that enlarges blood vessels. The pharmaceutical is dissolved in DMSO.

Description

The pharmaceutical composition of the present invention is prepared by mixing an effective amount of papaverine, phentolamine and prostaglandin E1 into a quantity of water sufficient to dissolve these compounds. The solution is then mixed with preferably an equal volume of dimethyl sulfoxide (DMSO). It is not strictly necessary that the volume should be equal but this is preferred for ease of preparation. The resulting mixture is then applied directly onto the penis. The DMSO acts as a carrier for the papaverine, phentolomine and prostaglandin E1 as the DMSO is absorbed through the skin of the penis into the blood vessels of the penis. Once these compounds reach the blood vessels of the penis, an erection is achieved rapidly by the user.

It is also possible two prepare a pharmaceutical composition that is effective for creating an erection in this manner, that includes only one or two of the three drugs mentioned above.

An effective topical preparation may also be prepared by dissolving papaverine, phentolomine and prostaglandin E1 directly into DMSO. The solution is then applied directly to the penis resulting in rapid erection.

It is preferred to mix all three drugs together with DMSO. However, it is also possible to prepare a composition containing either one or two of the three drugs mixed with DMSO. Positive results are achieved with these formulations but the best results are achieved when all three drugs are mixed together.

Compositions containing one or more of papaverine, phentolamine or prostaglandin E1 mixed with an effective penetrant carrier other than DMSO such as a cream are within the scope of the present invention.

The following examples illustrate the invention:

Example 1: Preparation of water/DMSO formulation.

Papaverine: 300 milligrams
Phentolamine: 15 milligrams
Prostaglandin E1: 100 micrograms

The compounds above are mixed into approximately 4 milliliters of water to produce solution A. Solution A is then mixed into approximately four milliliters of DMSO to produce solution B. The resulting solution B is appropriate and effective for a single topical application to create an erection.

Example 2: Preparation of pure DMSO mixture.

Papaverine: 300 milligrams
Phentolamine: 15 milligrams
Prostaglandin E1: 100 micrograms,

The compounds above are mixed into 4 milliliters of DMSO. The resulting mixture is appropriate and effective for a single topical application to create erection.

The mixtures of example 1 and example 2 are effective for rapidly producing high quality erections of normal duration.

Although the invention has been described with preferred embodiments, it is to be understood that modifications may be resorted to as will be apparent to those skilled in the art. Such modifications and variations are to be considered within the purview and scope of the present invention.

Claims

We claim:

1. A pharmaceutical composition for topical application to treat erectile dysfunction, the composition including at least one of the following compounds:

   - Papaverine
   - Phentolamine
   - Prostaglandin E1,

and a suitable penetrant carrier to enhance absorption of said at least one compound.

2. A pharmaceutical composition according to claim 1 wherein the penetrant carrier is dimethyl sulfoxide (DMS0).

3. A pharmaceutical composition according to claim 2 wherein the composition includes papaverine and prostaglandin E1.

4. A pharmaceutical composition according to claim 2 wherein the composition includes papaverine and phentolamine.

5. A pharmaceutical composition according to claim 2 wherein the composition includes prostaglandin E1 and phentolamine.

6. A pharmaceutical composition according to claim 2 wherein the composition includes papaverine, phentolamine and prostaglandin E1.

7. A pharmaceutical composition for topical application to treat erectile dysfunction, the composition including at least one compound that is effective for producing an erection upon entry into the bloodstream of the penis, dissolved in dimethyl sulfoxide (DMSO).

8. A pharmaceutical composition according to claim 7 wherein the at least one compound is selected from the group comprising papaverine, phentolamine and prostaglandin E1.

9. A pharmaceutical composition according to claim 7 wherein the at least one compound includes papaverine and prostaglandin E1.

10. A pharmaceutical composition according to claim 7 wherein the at least one pharmaceutical includes papaverine and phentolamine.

11. A pharmaceutical according to claim 7 wherein the at least one pharmaceutical includes phentolamine and prostaglandin E1

12. A pharmaceutical composition according to claim 7 wherein the at least one compound includes papaverine, phentolamine and prostaglandin E1.

13. A method of making a pharmaceutical composition for topical application to treat erectile dysfunction comprising the steps of:

- providing a quantity of at least one compound that is effective for producing an erection upon entry into the bloodstream of the penis;
- mixing said at least one compound in a volume of water;
- providing a volume of DMSO; and
- mixing the compound/water mixture in said DMSO.

14. A method according to claim 13 wherein the at least the compound includes papaverine, phentolamine and prostaglandin E1.

15. A method of making a pharmaceutical composition for topical application to treat erectile dysfunction comprising the steps of:

- Providing a quantity of papaverine;
- Providing a quantity of phentolamine;
- Providing a quantity of prostaglandin E1;
- Mixing the papaverine, phentolamine and prostaglandin E1 in a quantity of water;
- Providing a quantity of a suitable penetrant carrier to enhance absorption of said papaverine, phentolamine and prostaglandin E1; and
- Mixing the solution in said suitable penetrant carrier.

16. A method according to claim 16 wherein the suitable penetrant carrier is DMSO.

17. A method of making a pharmaceutical composition for topical application to treat erectile dysfunction comprising the steps of:

- Providing a quantity of papaverine;
- Providing a quantity of phentolamine;
- Providing a quantity of prostaglandin E1;
- Mixing the papaverine, phentolamine and prostaglandin E1 in a quantity of water to create a solution;
- Providing a quantity of DMSO; and
- Mixing the solution in said DMSO.

18. A method of making a pharmaceutical composition for topical application to treat erectile dysfunction comprising the steps of:

- Providing a quantity of papaverine;
- Providing a quantity of phentolamine;
- Providing a quantity of prostaglandin E1;
- Providing a quantity of DMSO; and
- Mixing the papaverine, phentolamine and prostaglandin E1 in said DMSO.

19. Use of the pharmaceutical composition of claim 1 to topically treat erectile dysfunction.

20. Use of the pharmaceutical composition of claim 7 to topically treat erectile dysfunction.

INTERNATIONAL SEARCH REPORT

Intern. ial Application No
PCT/CA 00/00799

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K47/20 A61P15/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 4 801 587 A (GENE VOSS, ET AL.) 31 January 1989 (1989-01-31) claim 1 ---	1,2,7,8, 13-20 3-6,9-12
P,X	US 6 031 002 A (MICHAEL S. WYSOR) 29 February 2000 (2000-02-29) claims 1,6-8,13,14 ---	1,2,7,8, 13-20
X Y	WO 98 43614 A (LAM PHARMACEUTICALS) 8 October 1998 (1998-10-08) claims 15,24 ---	1,19 3-6,9-12
X	EP 0 346 297 A (CENTRO MEDICO HARVEY) 13 December 1989 (1989-12-13) claim 1 --- -/--	1,19

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 November 2000	28/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Ventura Amat, A

3

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interr. nal Application No
PCT/CA 00/00799

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 52569 A (ZONAGEN) 26 November 1998 (1998-11-26) claims 1,2 page 7, line 5 - line 15	1,19
X	US 5 741 511 A (HUN HAN LEE, ET AL.) 21 April 1998 (1998-04-21) claims 7-9	1,19
P,X	US 5 942 545 A (CARLOS M. SAMOUR, ET AL.) 24 August 1999 (1999-08-24) claim 9	1,19
A	DE 197 28 103 A (HEINICKE, WINFRIED) 7 January 1999 (1999-01-07) the whole document	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/CA 00/00799

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4801587 A	31-01-1989	CA 1320442 A	20-07-1993
US 6031002 A	29-02-2000	US 5891915 A	06-04-1999
WO 9843614 A	08-10-1998	US 5952006 A	14-09-1999
		AU 6588198 A	22-10-1998
		EP 0971694 A	19-01-2000
		US 6036977 A	14-03-2000
EP 346297 A	13-12-1989	IT 1221826 B	12-07-1990
WO 9852569 A	26-11-1998	AU 7498098 A	11-12-1998
		BR 9809848 A	27-06-2000
		CN 1262622 T	09-08-2000
		EP 0996447 A	03-05-2000
		NO 995657 A	18-01-2000
US 5741511 A	21-04-1998	KR 161638 B	15-01-1999
		CN 1181022 A	06-05-1998
		EP 0831942 A	01-04-1998
		JP 10512173 T	24-11-1998
		WO 9632141 A	17-10-1996
US 5942545 A	24-08-1999	WO 9965303 A	23-12-1999
		AU 7838798 A	05-01-2000
		BR 9811797 A	26-09-2000
		EP 1026947 A	16-08-2000
		NO 20000157 A	09-02-2000
DE 19728103 A	07-01-1999	NONE	