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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 February 2006 (16.02.2006)

PCT

(10) International Publication Number
WO 2006/015485 A1

(51) International Patent Classification[7]: A61K 31/137, 9/52, 9/56, A61P 25/24

(21) International Application Number: PCT/CA2005/001233

(22) International Filing Date: 11 August 2005 (11.08.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2,476,101 12 August 2004 (12.08.2004) CA

(71) Applicant and
(72) Inventor: **SHERMAN, Bernard, Charles** [CA/CA]; 50 Old Colony Road, Toronto, Ontario M2L 2K1 (CA).

(74) Common Representative: **SHERMAN, Bernard, Charles**; Apotex Inc., 150 Signet Drive, Toronto, Ontario M9L 1T9 (CA).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*

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 2006/015485 A1

(54) Title: EXTENDED-RELEASE CAPSULES COMPRISING VENLAFAXINE HYDROCHLORIDE

(57) Abstract: A capsule comprising venlafaxine hydrochloride wherein part of the drug content is in the form of delayed-release coated spheroids and a second part of the drug content is in a prompt-release form.

Extended-Release Capsules Comprising Venlafaxine Hydrochloride

Background

Venlafaxine is a drug used for treatment of depression. Venlafaxine and its acid addition salts are disclosed in U.S. patent 4,535,186. Venlafaxine hydrochloride is sold in the United States and elsewhere under the tradename Effexor™ as tablets, in strengths of 25, 37.5, 50, 75 and 100 mg. The tablets are administered to adults in doses ranging from 75 to 350 mg/day, in divided doses two or three times a day. Upon ingestion of venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound, followed by a decrease over several hours, as the active compound is eliminated or metabolized, until subtherapeutic levels are approached about eight to twelve hours following administration, thus requiring further dosing. With the plural daily dosing regimen, the most common side effect is nausea. Vomiting also occurs in some patients.

Venlafaxine hydrochloride is now also sold in the United States and elsewhere, under the tradename Effexor XR™, as extended-release capsules in strengths of 37.5, 75 and 150 mg. These capsules provide gradual release of venlafaxine hydrochloride over a 24-hour period after ingestion, thus enabling a dosing schedule of once daily, while at the same time providing a lower incidence of nausea and vomiting.

™ – Trademark.

Effexor XR™ capsules are made in accordance with the disclosure of U.S. patent 6,274,171. Each capsule contains a multitude of small granules or beads, referred to as "spheroids". Each spheroid is comprised of a core, and a coating applied to the core. The core is comprised of venlafaxine hydrochloride, microcrystalline cellulose, and hydroxypropylmethylcellulose. The cores are coated with a mixture of ethylcellulose and hydroxypropylmethylcellulose. The ethylcellulose makes the film water-insoluble, while the hydroxypropylmethylcellulose makes the film water-permeable. The result is slow release by permeation through the film, with the release rate dependent on the ratio of hydroxypropylmethylcellulose to ethylcellulose and the thickness of the coat.

The cores are made by a process of mixing the venlafaxine hydrochloride, microcrystalline cellulose, and hydroxypropylmethylcellulose with water to produce a wet plastic mass, which is then extruded, spheronized and dried.

The film coating is then applied by dissolving the ethylcellulose and hydroxypropylmethylcellulose in solvent, and spraying the solution onto the cores in a fluid bed drying system.

According to the disclosure of U.S. patent 6,274,171, the acceptability of the coating level is determined by the dissolution rate of the coated spheroids using USP Apparatus 1 at 100 rpm in water at 37°C.

Appropriate dissolution specifications are said to be as follows:

Time (hours)	Average % Venlafaxine HCl Released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

It is further disclosed that capsules made in accordance with the disclosure and meeting these dissolution specifications will result in a peak blood level of venlafaxine at from about four to about eight hours after ingestion.

While capsules according to U.S. patent 6,274,171 provide a satisfactory extended release product, coating all of the spheroids to reduce the dissolution to below 30% at two hours is costly.

In light of the foregoing, an objective of the present invention is to provide a formulation of extended-release capsules comprising venlafaxine hydrochloride, which does not require coating all of the spheroids to the extent necessary to reduce dissolution of all of the spheroids to below 30% in two hours.

Description of the Invention

The present invention is an extended-release formulation of venlafaxine hydrochloride in the form a capsule characterized as follows:

1. From 40% to 70% of the venlafaxine hydrochloride is in the form of coated spheroids, referred to as delayed-release spheroids, which exhibit average dissolution of less than 30% at 2 hours;

2. From 30% to 60% of the venlafaxine hydrochloride is in another form, referred to as a prompt-release form, which exhibits average dissolution of more than 60% at 2 hours. This prompt-release form may be in any of a number of physical forms including, for example, uncoated spheroids, coated spheroids, tablets, or powder; and

3. As a result of containing venlafaxine hydrochloride in both forms, the average dissolution of the capsules exceeds 30% but is less than 60% at 2 hours.

For purposes of this specification, the dissolution testing is done in USP Apparatus 1 at 100 rpm in 900 mL of phosphate buffer of pH6.8 at 37°C.

The reason for maintaining dissolution of the capsule below 60% at two hours is to reduce the side effects of nausea and vomiting, just as is achieved by compositions of U.S. patent 6,274,171. The average dissolution of the mixture at two hours will preferably be between 35 and 55%, and will most preferably be about 45%.

As aforesaid, the delayed-release spheroids will be coated spheroids, which will be comprised of core spheroids, to which a coating is applied to delay release. The core spheroids will comprise venlafaxine hydrochloride along with one or more excipients (inactive ingredients). For example, the core spheroids may be made as in U.S. patent 6,274,171 by mixing venlafaxine hydrochloride with microcrystalline cellulose, hydroxypropylmethylcellulose and water to form a wet plastic mass, extruding, spheronizing, and drying.

A preferred method of making the core spheroids is to use, as an excipient, a water insoluble polymer, such as, for example, ethylcellulose. This enables the core spheroids themselves to exhibit somewhat extended dissolution, so as to reduce the amount of coating required on the core spheroids.

Such core spheroids can be made, for example, by preparing a solution of ethylcellulose in an organic solvent, such as methanol or methylene chloride, mixing the solution into the venlafaxine hydrochloride, drying the wet mass, milling the dried material into granules (i.e. spheroids), and selecting granules of the desired size by sieving.

The coating that is applied to the core spheroids will be a film-coating comprising a water-insoluble polymer, such as, for example, ethylcellulose.

As aforesaid, in addition to containing delayed-release spheroids, the capsules will contain additional venlafaxine hydrochloride in a prompt-release form, which may be in any of a number of physical forms, including, for example, uncoated spheroids, coated spheroids, tablets, or powder.

For example, the core spheroids that are used to make delayed-release coated spheroids may be used, uncoated, as the prompt-release form.

Alternatively, the prompt-release form may consist of the same core spheroids, which, instead of being uncoated, may be coated, but with a lesser amount of coating than the delayed-release spheroids, so as to only slightly delay release.

The capsules of the present invention not only have a lower cost of production than capsules according to U.S. patent 6,274,171, but also enable greater flexibility of absorption profile, as a result of having the drug present in two forms instead of only one form. The capsules of U.S. patent 6,274,171 provide a peak venlafaxine blood level at from about 4 to about 8 hours after ingestion. The present invention enables capsules for which the peak venlafaxine blood level is reached in less than 4hours, but for which the peak

level is still no higher than, or not significantly higher than, that obtained with capsules according to U.S. patent 6,274,171.

The invention will be better understood from the following illustrative examples.

Example 1 – Core Spheroids

Core spheroids were made as follows:

A quantity of venlafaxine hydrochloride was granulated by adding an equal quantity of ethylcellulose dissolved in methylene chloride, mixing and evaporating the methylene chloride. The resultant dried mass comprised 50% venlafaxine hydrochloride and 50% ethylcellulose. This dried mass was then milled through a #10 screen (10 wires per inch). The milled material was then sifted on a #20 screen. The granules that remained on the #20 screen, having a size from about 850 to about 2000 microns, were then retained for use as core spheroids. As aforesaid, such core spheroids may be used directly, in uncoated form, as the prompt-release form; or they may be coated with a film coat comprising a water insoluble polymer to form delayed-release spheroids.

The average dissolution of these core spheroids was found to exceed 90% at 2 hours when tested in USP Apparatus 1 at 100 rpm in 900 mL of phosphate buffer of pH6.8 at 37°C.

Example 2 – Delayed-Release Spheroids

600 grams of core spheroids of example 1 were spray-coated with the following coating solution in a fluid bed coating system:

Ethylcellulose	200.0 g
Dibulyl Sebeate	30.0 g
Methanol	1800.0 g
	2030.0 g
Total Dry	230.0 g

The content of venlafaxine hydrochloride in these delayed-release coated spheroids was 50% x 600/830 = 36.1%. The average dissolution of these delayed-release spheroids was found to be about 15% at 2 hours, when tested in USP Apparatus 1 at 100 rpm in 900 mL of phosphate buffer of pH6.8 at 37°C.

Example 3

Size 0 two-piece hard gelatin capsules were filled with spheroids as follows:

Capsule	Quantity Per Capsule	Venlafaxine Hydrochloride Content Per Capsule
Core spheroids of example 1	120.0 mg	60.0 mg
Delayed-release spheroids of example 2	249.0 mg	90.0 mg
	369.0 mg	150.0 mg

The average dissolution of these capsules is about 40% to 45% at 2 hours when tested in USP Apparatus 1 at 100 rpm in 900 mL of phosphate buffer of pH6.8 at 37°C.

Claims:

1. A capsule comprising venlafaxine hydrochloride wherein:

   i) from 40% to 70% of the venlafaxine hydrochloride is in coated spheroids, which exhibit average dissolution of less than 30% at 2 hours;

   ii) from 30% to 60% of the venlafaxine hydrochloride is in a second form which exhibits average dissolution of more than 60% at 2 hours; and

   iii) the average dissolution of the capsule exceeds 30% but is less than 60% at 2 hours.

2. A capsule of claim 1, for which the average dissolution is between 35 and 55% at 2 hours.

3. A capsule of claim 1 or 2 wherein the coated spheroids comprise core spheroids, which are coated with a film coating comprising a water-insoluble polymer.

4. A capsule of claim 3 wherein the second form is the uncoated core spheroids.

5. A capsule of any of claims 1 to 4, which exhibits an average time to peak venlafaxine blood level of less than 4 hours after ingestion.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/001233

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7): A61K 31/137, A61K 9/52, A61K 9/56, A61P 25/24

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; A61P

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
DWPI/Delphion; PlusPat database; Esp@cenet; Canadian Patent database- full text plus bibliography; PubMed, Google
venlafaxine, venlafaxine hydrochloride, venlafaxine AND release, (extended or sustained or delayed or prolonged) AND (immediate or prompt) AND release AND (capsule or drug)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	US 2005/0106248 A1 (ANDRX PHARMACEUTICALS, LLC) 19 May 2005 (19-05-2005) see the whole document	1-5
P, Y	WO 2004/100929 A1 (SYNERGIA PHARMA, INC) 25 November 2004 (25-11-2004) see page 6, lines 3-21, lines 27-30; page 7, lines 30-31; Examples 4, 8; and claims 7-8	1-5
P, Y	US 2004/0185100 A1 (SPRL FRANPHARMA) 23 September 2004 (23-09-2004) see abstract, Examples 10, 12, 13; and claims 1, 10	1-5
Y	US 6274171 B1 (AMERICAN HOME PRODUCTS CORPORATION) 14 August 2001 (14-08-2001) cited in the application, see the whole document	1-5

[X] Further documents are listed in the continuation of Box C. [X] See patent family 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 application or patent 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
3 October 2005 (03-10-2005)	28 October 2005 (28-10-2005)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	Authorized officer Connie Kuang (819) 934-3597

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/001233

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2004/0126427 A1 (GOPI M. VENKATESH, ET AL.) 01 July 2004 (01-07-2004) see the whole document	1-5
Y	US 6126969A (L. PERRIGO COMPANY) 03 October 2000 (03-10-2000) see abstract; column 4, lines 29-33, lines 59-62; column 5, lines 30-40; and examples	1-5
Y	WO 02/34234 A2 (EURAND AMERICA, INC) 2 May 2002 (02-05-2002) see abstract; page 3, second paragraph; examples; Tables 1-2; and claims 1, 10	1-5
Y	JP10120571A2 (SATO YAKUHIN KOGYO KK) 12 May 1998 (12-05-1998) see abstract	1-5
Y	US 2003/0031707 A1 (ALAN A. RUBIN) 13 Febuary 2003 (13-02-2003) See Example 3 and claim 5	1-5
Y	WO 03/088952 A1 (ADAMS LABORATORIES, INC) 30 October 2003 (30-10-2003) see page 5, [016]; page 14, [074]; page 32, [0119]; page 33, [0120]; and Example 1	1-5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/001233

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
US2005106248	19-05-2005	WO2005048923 A2	02-06-2005
WO2004100929	25-11-2004	NONE	
US2004185100	23-09-2004	AU2004200716 A1	23-09-2004
		CA2456410 A1	03-09-2004
		EP1462098 A1	29-09-2004
US6274171	14-08-2001	AT237320T T	15-05-2003
		AT257011T T	15-01-2004
		AU727653 B2	21-12-2000
		AU747978 B2	30-05-2002
		AU1300399 A	24-05-1999
		AU1640097 A	02-10-1997
		BG104397 A	28-02-2001
		BR9701304 A	29-09-1998
		BR9813179 A	22-08-2000
		CA2199778 A1	25-09-1997
		CA2305242 A1	14-05-1999
		CN1090018C C	04-09-2002
		CN1278165 A	27-12-2000
		CN1403077 A	19-03-2003
		CY2442 A	12-11-2004
		CZ291637 B6	16-04-2003
		CZ20001659 A3	17-10-2001
		DE69727000D D1	05-02-2004
		DE69727000T T2	09-06-2004
		DE69813602D D1	22-05-2003
		DE69813602T T2	06-11-2003
		DK797991T T3	05-04-2004
		DK1028718T T3	28-07-2003
		EE200000212 A	16-04-2001
		EP0797991 A1	01-10-1997
		EP1028718 A2	23-08-2000
		EP1331003 A1	30-07-2003
		ES2196620T T3	16-12-2003
		ES2210454T T3	01-07-2004
		HK1029056 A1	21-11-2003
		HR20000213 A1	31-12-2000
		HU0004287 A2	29-04-2002
		HU9700589 A2	29-09-1997
		ID26317 A	14-12-2000
		IL120382 A	24-06-2003
		IL135457D D0	20-05-2001
		IL151450D D0	10-04-2003
		IN187337 A1	30-03-2002
		JP10007552 A	13-01-1998
		JP2001521892T T	13-11-2001
		MA24691 A1	01-07-1999
		NO971206 A	26-09-1997
		NO20002126 A	04-05-2000
		NZ314442 A	29-06-1999
		NZ504460 A	31-01-2003
		PL188444B B1	28-02-2005
		PL341141 A1	26-03-2001
		PT797991T T	31-05-2004
		PT1028718T T	31-07-2003
		RU2176912 C2	20-12-2001
		SI797991T T1	30-04-2004
		SI1028718T T1	31-08-2003
		SK30197 A3	08-10-1997
		SK6472000 A3	07-11-2000
		TR9700190 A2	21-10-1997
		TR200001232T T2	21-12-2000
		TW493993 B	11-07-2002
		TW555568 B	01-10-2003
		US6403120 B1	11-06-2002

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/001233

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
		US6419958 B2	16-07-2002
		US2002197307 A1	26-12-2002
		US2003215507 A1	20-11-2003
		WO9922724 A2	14-05-1999
		ZA9702403 A	21-09-1998
		ZA9810081 A	04-05-2000
US2004126427	01-07-2004	NONE	
US6126969	03-10-2000	CA2198630 A1	27-08-1997
		GB2310601 A	03-09-1997
		JP10029936 A	03-02-1998
		US5773031 A	30-06-1998
WO0234234	02-05-2002	AU9701101 A	06-05-2002
		CA2426883 A1	02-05-2002
		EP1328251 A2	23-07-2003
		HU0303695 A2	01-03-2004
		JP2004512296T T	22-04-2004
		NO20031843 A	24-04-2003
		PL361673 A1	04-10-2004
		US6344215 B1	05-02-2002
JP10120571	12-05-1998	NONE	
US2003031707	13-02-2003	US6238699 B1	29-05-2001
		US6756056 B2	29-06-2004
WO03088952	30-10-2003	AU5568001 A	12-11-2001
		AU2003237807 A1	03-11-2003
		CA2405031 A1	08-11-2001
		CA2481739 A1	30-10-2003
		CN1655766 A	17-08-2005
		EP1276467 A2	22-01-2003
		EP1503739 A1	09-02-2005
		IL152012D D0	10-04-2003
		JP2003531849T T	28-10-2003
		MXPA02010556 A	14-10-2003
		NZ521959 A	29-10-2004
		US6372252 B1	16-04-2002
		US2003049318 A1	13-03-2003
		US2003215508 A1	20-11-2003
		US2004018233 A1	29-01-2004
		US2004022851 A1	05-02-2004
		WO0182895 A2	08-11-2001