PRESCRIPTION AND OTC DRUG PRODUCT
PATENT AND EXCLUSIVITY DATA
See report footnote for information regarding report content

	APPL/PROD NUMBER	INGREDIENT NAME; TRADE NAME	PATENT NUMBER	PATENT/PED EXCL EXPIRES	PATENT CODE(S)	EXCLUS CODE	EXCLUS EXPIRES
	021278 003	DEXMETHYLPHENIDATE HYDROCHLORIDE;FOCALIN	6528530	DEC 04, 2015	DS DP		
	021392 001	DILTIAZEM HYDROCHLORIDE;CARDIZEM LA				I-133	APR 09, 2007
	021392 002	DILTIAZEM HYDROCHLORIDE;CARDIZEM LA				I-133	APR 09, 2007
	021392 003	DILTIAZEM HYDROCHLORIDE;CARDIZEM LA				I-133	APR 09, 2007
	021392 004	DILTIAZEM HYDROCHLORIDE;CARDIZEM LA				I-133	APR 09, 2007
	021392 005	DILTIAZEM HYDROCHLORIDE;CARDIZEM LA				I-133	APR 09, 2007
	021392 006	DILTIAZEM HYDROCHLORIDE;CARDIZEM LA				I-133	APR 09, 2007
	021168 001	DIVALPROEX SODIUM;DEPAKOTE ER	6528090	DEC 18, 2018	DP		
			6713086	DEC 18, 2018	DP U579		
			5212326	JAN 29, 2008	DS DP		
			6528091	DEC 18, 2018	U106		
	021168 002	DIVALPROEX SODIUM;DEPAKOTE ER	6528090	DEC 18, 2018	DP		
			6713086	DEC 18, 2018	DP U579		
			5212326	JAN 29, 2008	DS DP		
	020449 001	DOCETAXEL;TAXOTERE				I-429	MAY 19, 2007
						I-436	AUG 18, 2007
	020931 001	DOFETILIDE;TIKOSYN	4959366	SEP 25, 2007			
	020931 002	DOFETILIDE;TIKOSYN	4959366	SEP 25, 2007			
	020931 003	DOFETILIDE;TIKOSYN	4959366	SEP 25, 2007			
	020869 001	DORZOLAMIDE HYDROCHLORIDE;COSOPT	6316443	APR 17, 2011	DP U561		
	020408 001	DORZOLAMIDE HYDROCHLORIDE;TRUSOPT	4797413	APR 28, 2008	DS DP U103		
			4619939	OCT 28, 2003	DP U104		
	020862 001	DOXERCALCIFEROL;HECTOROL				I-424	APR 23, 2007
	020862 002	DOXERCALCIFEROL;HECTOROL	5869473	AUG 02, 2008	U278	I-424	APR 23, 2007
	018651 001	DRONABINOL;MARINOL	6703418	FEB 26, 2011	U563		
	018651 002	DRONABINOL;MARINOL	6703418	FEB 26, 2011	U563		
	018651 003	DRONABINOL;MARINOL	6703418	FEB 26, 2011	U563		
	021098 001	DROSPIRENONE;YASMIN	6787531	AUG 31, 2020	DP		
>ADD>	021427 001	DULOXETINE HYDROCHLORIDE;CYMBALTA	5023269	JUN 11, 2008	DS DP U605	NCE	AUG 03, 2009
>ADD>			5508276	JUL 18, 2014	DP		
>ADD>	021427 002	DULOXETINE HYDROCHLORIDE;CYMBALTA	5023269	JUN 11, 2008	DS DP U605	NCE	AUG 03, 2009
>ADD>			5508276	JUL 18, 2014	DP		
>ADD>	021427 004	DULOXETINE HYDROCHLORIDE;CYMBALTA	5023269	JUN 11, 2008	DS DP U605	NCE	AUG 03, 2009
>ADD>			5508276	JUL 18, 2014	DP		
>ADD>	021733 001	DULOXETINE HYDROCHLORIDE;CYMBALTA				NCE	AUG 03, 2009
>ADD>						NDF	SEP 03, 2007
>ADD>	021733 002	DULOXETINE HYDROCHLORIDE;CYMBALTA				NCE	AUG 03, 2009
>ADD>						NDF	SEP 03, 2007
>ADD>	021733 004	DULOXETINE HYDROCHLORIDE;CYMBALTA				NCE	AUG 03, 2009
>ADD>						NDF	SEP 03, 2007
	021500 001	EMTRICITABINE;EMTRIVA	6703396	MAR 09, 2021	DS DP		
	021504 001	EPINEPHRINE;LIDOSITE TOPICAL SYS	5246418	SEP 30, 2013	DS DP	NP	MAY 04, 2007
			5873850	SEP 30, 2013	DS DP		
			6377847	SEP 30, 2013	DS DP		
			6385488	SEP 30, 2013	DS DP		
			6629968	JUN 30, 2020	DS DP		
			6635045	JUN 29, 2021	DS DP		
	021437 001	EPLERENONE;INSPRA	6747020	NOV 05, 2019	U587		
	021437 002	EPLERENONE;INSPRA	6747020	NOV 05, 2019	U587		
	021437 003	EPLERENONE;INSPRA	6747020	NOV 05, 2019	U587		
	021633 001	ESTRADIOL ACETATE;FEMTRACE				NDF	AUG 20, 2007
	021633 002	ESTRADIOL ACETATE;FEMTRACE				NDF	AUG 20, 2007

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PATENT IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 5,023,269

Attn: Mail Stop Patent Ext.

Patentees : David W. Robertson, David T. Wong and Joseph H. Krushinski, Jr.

Assignee : Eli Lilly and Company

Issue Date : June 11, 1991

REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156

Commissioner for Patents
P.O. Box 1450
Arlington, VA 22313-1450

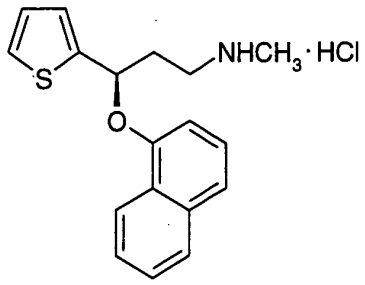
Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. 156, Eli Lilly and Company, owner of the above-identified patent by an Assignment recorded on February 19, 1997, in Reel 8360, Frame 804, hereby requests an extension of the patent term of U.S. Patent No. 5,023,269 (hereinafter variously referred to either as "U.S. Patent No. 5,023,269" or "the '269 patent"). The following information is submitted in accordance with 35 U.S.C. 156(d) and 37 C.F.R. 1.710 et seq. and follows the numerical format set forth in 37 C.F.R. 1.740(a):

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:

The approved product is duloxetine hydrochloride which has the chemical name (+)-(S)-*N*-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride. Duloxetine hydrochloride has the molecular formula $C_{18}H_{19}NOS \cdot HCl$, the molecular weight is 333.88 and is identified by CAS Registry Number 136434-34-9.

Duloxetine hydrochloride has the following structure:



Duloxetine hydrochloride is the active ingredient in the product CYMBALTA™ as can be seen from attached Exhibit I, which is the Product Information sheet for this product.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred:

The regulatory review occurred under Section 505 of the Federal Food, Drug and Cosmetic Act (FFDCA), 21 U.S.C. 301 et seq. Section 505 provides for the submission and approval of new drug applications (NDAs) for human drug products meeting the definition of "new drug" under Section 201(p) of the Act.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

Duloxetine hydrochloride was approved by the Food and Drug Administration (FDA) for commercial marketing pursuant to Section 505 of the FFDCA on August 3, 2004.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination

with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

As stated in Sections 1, 2, and 3 above, the active ingredient in the product CYMBALTA™ is Duloxetine hydrochloride. Duloxetine hydrochloride had not previously been approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act. Approval under the Federal Food, Drug and Cosmetic Act was received on August 3, 2004 for the use of duloxetine hydrochloride in the treatment of major depressive disorder under Section 505 of the FFDCA.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. §1.720(f) and an identification of the date of the last day on which the application could be submitted:

The product was approved on August 3, 2004. The last day within the sixty day period permitted for submission of this application for extension of a patent is October 2, 2004, which is a Sunday. As this application is being hand-carried to Karin Ferriter, Senior Legal Advisor, on Friday, September 17, 2004 this application is timely filed within the permitted sixty day period.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

The patent for which extension is being sought is:

U.S. Patent No.: 5,023,269
Inventors: David W. Robertson, David T. Wong and Joseph H. Krushinski, Jr.
Issued: June 11, 1991
Expires: June 11, 2008

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings:

A complete copy of U.S. Patent No. 5,023,269 is attached hereto as Exhibit II.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent:

A copy of the receipt of maintenance fee payment is attached hereto as Exhibit III. No disclaimer or reexamination certificate has issued in connection with the '269 patent. A certificate of correction has issued in connection with the '269 patent. It is attached as Exhibit IV.

(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on the approved product or a method of using or manufacturing the approved product:

The '269 patent contains 51 claims. Claims 1, 20, 24, 28, 32, 36, 40, 44 and 48 are independent. Claims 1, 2 and 8-12 recite claims for the approved product, duloxetine hydrochloride. Claim 28 recites a method of using the approved product, duloxetine hydrochloride. Claims 48-51 recite claims for a pharmaceutical formulation containing the approved product, duloxetine hydrochloride.

Claim 28 of the '269 patent, which recites a method of using duloxetine hydrochloride, reads as follows:

Claim 28. A method of treating depression in humans comprising administering to a human suffering from depression an effective antidepressant dose of a compound of Claim 1.

The nonproprietary name duloxetine hydrochloride was adopted by the United States Adopted Name (USAN) Council in 1992 as evidenced by the Statement of Nonproprietary Name Adopted by the USAN Council attached hereto as Exhibit V.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services

or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted, and the NDA or PLA number and the date on which the NDA was approved or the Product License issued;

On June 3, 1991, Eli Lilly and Company, the assignee of U.S. Patent No. 5,023,269, submitted to the FDA a "Notice of Claimed Investigational Exemption for a New Drug" (IND) under Section 505(i) of the FFDCA to permit the interstate shipment of LY248686 (now known as duloxetine hydrochloride) for the purpose of conducting clinical studies to support the approval of a subsequent NDA for duloxetine hydrochloride. A copy of the letter transmitting the IND to the FDA is attached hereto as Exhibit VI. The FDA acknowledged receipt of the IND, assigned the IND number 37,071, and indicated that the IND would become effective thirty days after the date of its receipt on June 4, 1991. A copy of this letter is attached hereto as Exhibit VII. This establishes the beginning of the "regulatory review period" under 35 U.S.C. 156(g)(1) as July 4, 1991, the effective date of an exemption under Section 505(i).

Eli Lilly and Company submitted an NDA for duloxetine hydrochloride, NDA 21-411, on November 12, 2001. A copy of the letter transmitting the NDA is attached hereto as Exhibit VIII. The NDA submission was received by the FDA on November 13, 2001 as indicated by the electronic mail set forth in Exhibit IX. Thus, for the purpose of the "regulatory review period" under 35 U.S.C. 156(g)(1), November 13, 2001 is the date of initial submission of a new drug application under Section 505 for duloxetine hydrochloride.

The NDA described above was approved on August 3, 2004. Attached as Exhibit X is a letter electronically mailed on August 3, 2004 from the FDA to Eli Lilly and Company approving the NDA for duloxetine hydrochloride. Thus, for the purpose of the "regulatory review period" under 35 U.S.C. 156(g)(1), August 3, 2004 is the date of approval of the NDA application for duloxetine hydrochloride submitted on November 13, 2001.

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

During the applicable regulatory review period, Eli Lilly and Company was actively involved in obtaining NDA approval for duloxetine hydrochloride. As discussed in Section (10) above, the IND for duloxetine hydrochloride was submitted on July 4, 1991, the NDA was submitted on November 13, 2001, and the NDA was approved on August 3, 2004. Eli Lilly and Company was in close consultation with the FDA during the clinical studies conducted under the IND. Similarly, subsequent to the submission of the NDA, Eli Lilly and Company had numerous contacts and meetings with the FDA with respect to the NDA approval. The description of significant activities undertaken by Eli Lilly and Company with respect to duloxetine hydrochloride during the applicable regulatory review period as set forth in Exhibit XI attached hereto is illustrative of the activities undertaken.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined:

(a) Statement regarding eligibility of the '269 patent for extension under 35 U.S.C. 156(a):

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended from the original expiration date of the patent if (1) the term of the patent has not expired before an application for extension is submitted, (2) the term of the patent has never been extended, (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. 156(d), (4) the product has been subject to a regulatory review period before its commercial marketing or use, and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied in the present case:

(1) The term of U.S. Patent No. 5,023,269 expires on June 11, 2008. This application for patent term extension has, therefore, been submitted before the expiration of the patent term.

(2) The term of the '269 patent has never been extended.

(3) This application is submitted by the owner of record of the '269 patent, Eli Lilly and Company (Assignment recorded on February 19, 1997, in Reel 8360, Frame 804). This application is submitted in accordance with 35 U.S.C. 156(d) in that it is submitted within the sixty day period beginning on the date, August 3, 2004, the product received permission for marketing under the FFDCA and contains the information required under 35 U.S.C. 156(d).

(4) As evidenced by the August 3, 2004 letter from the FDA (Exhibit X), the product was subject to a regulatory review period under Section 505 of the FFDCA before its

commercial marketing or use.

(5) Finally, the permission for the commercial marketing of duloxetine hydrochloride after regulatory review under Section 505 is the first permitted commercial marketing of duloxetine hydrochloride. This is confirmed by the absence of any approved new drug application for duloxetine hydrochloride prior to August 3, 2004.

(b) Statement as to length of extension claimed, including how the length of extension was determined:

The term of U.S. Patent No. 5,023,269 should be extended by 1826 days to June 11, 2013. This extension was determined as follows.

As set forth in 35 U.S.C. 156(g)(1) and 37 C.F.R. 1.775(c), the regulatory review period equals the length of time between the effective date of the initial IND (July 4, 1991) and the initial submission of the NDA (November 13, 2001), a period of 3785 days, plus the length of time between the initial submission of the NDA (November 13, 2001) to NDA approval (August 3, 2004), a period of 994 days. These two periods added together equal 4779 days.

Pursuant to 35 U.S.C. 156(c) and 37 C.F.R. 1.775 (d)(1)(i), the term of the patent eligible for extension shall be extended by the time equal to the regulatory review period which occurs after the date the patent was issued. In this case, this is a period running from the effective IND filing date of July 4, 1991, to the date of NDA approval, August 3, 2004, a period of 4779 days.

As discussed in paragraph (11) above and as illustrated in Exhibit XI, Eli Lilly and Company was continuously and diligently working toward securing NDA approval for duloxetine hydrochloride. As Eli Lilly and Company acted with due diligence during the entire period of regulatory review, the 4779 day period calculated above as the term of the patent eligible for extension should not be reduced for lack of diligence under 35 U.S.C. 156(c)(1) or 37 C.F.R. 1.775 (d)(1)(ii).

Pursuant to 35 U.S.C. 156(c)(2) and 37 C.F.R. 1.775 (d)(1)(iii), this 4779 day period is to be reduced by one-half of the time from the effective date of the initial IND, July 4, 1991, or the date of patent issue, June 11, 1991, whichever is later, to the date of initial submission of the NDA, November 13, 2001, a period of 3785 days. One half of this period is 1892 days. Ignoring the half day for purposes of subtraction in accordance with 37 C.F.R. 1.775(d)(1)(iii), the 4779-day period is reduced by 1892 days, leaving a revised regulatory period of 2887 days.

Pursuant to 35 U.S.C. 156(c)(3) and 37 C.F.R. 1.775(d)(2-4), the period remaining in the term of the patent after the date of approval August 3, 2004 to June 11, 2008, a period of 1408 days, when added to the revised regulatory review period (2887 days) does not exceed 14 years (5113 days), such that period of extension would need to be reduced so that the total of both such periods does not exceed fourteen years

The period of patent term extension as calculated above is also subject to the provisions of 35 U.S.C. 156(g)(4) and 37 C.F.R. 1.775(d)(5-6). The patent to be extended issued after, and clinical evaluation of the approved product began, before the enactment of the statute, September 24, 1984. Since commercial marketing of the drug was approved after enactment of the statute, the five year maximum on extension as provided in 35 U.S.C. 156(g)(6)(B) and 37 C.F.R. 1.775(d)(6) is applicable. Thus, the term of the '269 patent is eligible for a 1826-day extension until June 11, 2013. As 2012 is a leap year, the period of extension of the '269 patent inherently includes one additional day, resulting in a total extension of 1826 days.

(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (See §1.765):

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information that is material to the determination of entitlement to the extension sought herein.

Further to the information already presented in this application and attached exhibits, Applicant respectfully points out that via letter submitted August 26, 1992 (Exhibit XII), Applicant designated IND 38,838 enteric coated tablet formulation as the primary IND for the study of duloxetine hydrochloride.

(14) The prescribed fee for receiving and acting upon the application for extension (See §1.20(j)):

As indicated on the letter of transmittal submitted with this application, the Commissioner of Patents and Trademarks has been authorized to charge the filing fee of $1,120.00, and any additional fees which may be required by this or any other related paper, or credit any overpayment, to Deposit Account No. 05-0840 in the name of Eli Lilly and Company.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

Please address all correspondence to Arvie J. Anderson, Eli Lilly and Company, Patent Division/CEC, Lilly Corporate Center, Indianapolis, Indiana 46285. Please direct telephone calls to Arvie J. Anderson, 317-277-7217. Please direct facsimiles to 317-276-3861.

(16) In accordance with 37 C.F.R. 1.740(b), submission of two additional copies of the present application. In accordance with M.P.E.P. § 2753, submission of two additional copies of the present application, for a total of five copies:

In addition to the present application for extension of the patent term of U.S. Patent No. 5,023,269, Applicant also submits herewith four additional complete copies, for a total of five copies of the present application.

(17) Signature Requirements: In accordance with 37 C.F.R. 1.730, submission of proof that the present application for extension of the term of U.S. Patent No. 5,023,269 is submitted on behalf of the patent owner by a registered practitioner who is authorized to act on behalf of the patent owner:

By an assignment recorded on February 19, 1997, in Reel 8360, Frame 804, Eli Lilly and Company is the owner of U.S. Patent No. 5,023,269, for which an extension of the term is sought in the present application.

This application is submitted on behalf of Eli Lilly and Company by Arvie J. Anderson, Registration No. 45,263, authorized as an agent thereof with full power to transact all business in the United States Patent and Trademark Office in connection therewith. This is evidenced by the Power of Attorney submitted concurrently with this application.

Respectfully submitted,

Arvie J. Anderson
Attorney for Applicants
Registration No. 45,263
Phone: 317-277-7217

Eli Lilly and Company
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288

9/15/04

Exhibits

I. Product Information Sheet

II. U.S. Patent No. 5,023,269

III. Maintenance Fee Statement

IV. Certificate Of Correction Issued In Connection With U.S. Patent No. 5,023,269

V. Statement On A Nonproprietary Name Adopted By The USAN Council

VI. Letter Transmitting The IND To The FDA

VII. FDA Receipt Letter For Notice Of Claim Investigational Exemption For A New Drug

VIII. Letter Transmitting The NDA

IX. FDA Receipt Letter For NDA

X. FDA Approval Letter For Duloxetine Hydrochloride

XI. Description Of Significant Activities Undertaken By Eli Lilly And Company With Respect To Duloxetine Hydrochloride Review Period

XII. IND Information Amendment For Duloxetine Hydrochloride Enteric Coated Formulation

United States Patent [19]

Robertson et al.

[11] **Patent Number: 5,023,269**

[45] **Date of Patent: Jun. 11, 1991**

[54] **3-ARYLOXY-3-SUBSTITUTED PROPANAMINES**

[75] Inventors: **David W. Robertson**, Greenwood; **David T. Wong**; **Joseph H. Krushinski, Jr.**, both of Indianapolis, all of Ind.

[73] Assignee: **Eli Lilly and Company**, Indianapolis, Ind.

[21] Appl. No.: **499,940**

[22] Filed: **Mar. 27, 1990**

Related U.S. Application Data

[60] Division of Ser. No. 462,925, Jan. 12, 1990, Pat. No. 4,956,388, which is a continuation of Ser. No. 945,122, Dec. 22, 1986, abandoned.

[51] Int. Cl.[5] **A61K 31/38**; A61K 31/44; C07D 333/16

[52] U.S. Cl. **514/438**; 514/357; 514/365; 514/471; 546/334; 548/205; 549/75; 549/491

[58] Field of Search 549/75, 491; 546/334; 548/205; 514/438, 471, 357, 365

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,842,555	7/1958	Harfenist et al.	548/574
3,423,510	1/1969	Sigg	514/357
3,433,804	3/1969	Hollinger et al.	549/59
3,814,750	6/1974	Cross et al.	540/596
4,018,895	4/1977	Molloy et al.	514/649
4,194,009	3/1980	Molloy et al.	514/651
4,314,081	2/1982	Molloy et al.	564/347
4,329,356	5/1986	Holland	514/419
4,857,543	8/1989	Hayashi et al.	549/75
4,902,710	2/1990	Foster et al.	514/438

FOREIGN PATENT DOCUMENTS

2482956	5/1980	France .
1343527	1/1974	United Kingdom .
2060618	5/1981	United Kingdom .

Primary Examiner—Mary C. Lee
Assistant Examiner—Lenora Miltenberger
Attorney, Agent, or Firm—Robert A. Conrad; Leroy Whitaker

[57] **ABSTRACT**

The present invention provides 3-aryloxy-3-substituted propanamines capable of inhibiting the uptake of serotonin and norepinephrine.

51 Claims, No Drawings

3-ARYLOXY-3-SUBSTITUTED PROPANAMINES

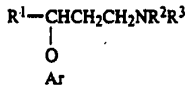
This application is a division of application Ser. No. 07/462,925, filed Jan. 12, 1990, now U.S. Pat. No. 4,956,388, continuation of application Ser. No. 06/945,122, filed on Dec. 22, 1986, now abandoned.

BACKGROUND OF THE INVENTION

During the past decade, the relationship between monoamine uptake and a variety of diseases and conditions has been appreciated and investigated. For example, the hydrochloride salt of fluoxetine (dl-N-methyl-γ-[4-(trifluoromethyl)phenoxy]benzenepropanamine) is a selective serotonin (5-hydroxytryptamine) uptake inhibitor presently undergoing clinical evaluation for the treatment of depression, anxiety, appetite suppression, and other disorders. Similarly, tomoxetine hydrochloride ((−)-N-methyl-δ-(2-methylphenoxy)benzenepropanamine hydrochloride) is a selective inhibitor of norepinephrine uptake being investigated clinically for its antidepressant activity. These compounds are among many taught in U.S. Pat. Nos. 4,018,895, 4,194,009, and 4,314,081 as being potent but selective blockers of the uptake of a particular monoamine.

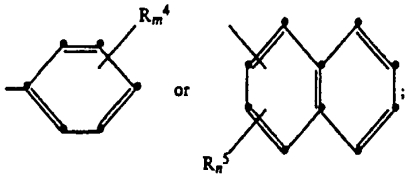
SUMMARY OF THE INVENTION

The present invention provides novel 3-aryloxy-3-substituted propanamines which are potent inhibitors of both serotonin and norepinephrine uptake. More specifically, the present invention relates to a compound of the formula



wherein:

R^1 is C_5–C_7 cycloalkyl, thienyl, halothienyl, (C_1–C_4 alkyl)thienyl, furanyl, pyridyl or thiazolyl;



each of R^2 and R^3 independently is hydrogen or methyl;

each R^4 independently is halo, C_1–C_4 alkyl, C_1–C_3 alkoxy or trifluoromethyl;

each R^5 independently is halo, C_1–C_4 alkyl or trifluoromethyl;

m is 0, 1 or 2;

n is 0 or 1; and

the pharmaceutically acceptable acid addition salts thereof.

The invention also provides pharmaceutical formulations comprising a compound of the above formula and a pharmaceutically acceptable carrier, diluent or excipient therefor.

A further embodiment of the invention are methods for selectively inhibiting the uptake of serotonin and norepinephrine, as well as for treating a variety of disorders which have been linked to decreased neurotransmission of serotonin and norepinephrine in mammals including obesity, depression, alcoholism, pain, loss of memory, anxiety, smoking, and the like, employing a compound of the invention.

DETAILED DESCRIPTION OF THE INVENTION

In the above formula, the term C_1–C_4 alkyl represents a straight or branched alkyl chain bearing from one to four carbon atoms. Typical C_1–C_4 alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.-butyl and t-butyl.

C_1–C_3 Alkoxy represents methoxy, ethoxy, n-propoxy or isopropoxy.

Halo represents fluoro, chloro, bromo or iodo.

When Ar is naphthalenyl, it can be either 1-naphthalenyl or 2-naphthalenyl.

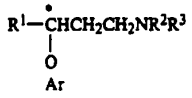
When R^1 is thienyl, it can be either 2-thienyl or 3-thienyl; when R^1 is furanyl, it can be either 2-furanyl or 3-furanyl; when R' is pyridyl, it can be either 2-pyridyl, 3-pyridyl or 4-pyridyl; when R^1 is thiazolyl, it can be either 2-thiazolyl, 4-thiazolyl or 5-thiazolyl.

(C_1–C_4 Alkyl)thienyl represents a thienyl ring monosubstituted with a C_1–C_4 alkyl substituent. Typical C_1–C_4 alkyl)thienyl groups include 4-methyl-2-thienyl, 3-ethyl-2-thienyl, 2-methyl-3-thienyl, 4-propyl-3-thienyl, 5-n-butyl-2-thienyl, 4-methyl-3-thienyl, 3-methyl-2thienyl, and the like.

Halothienyl represents a thienyl ring monosubstituted with a halo substituent. Typical halo-thienyl groups include 3-chloro-2-thienyl, 4-bromo-3-thienyl, 2-iodo-3-thienyl, 5-iodo-3-thienyl, 4-fluoro-2-thienyl, 2-bromo-3-thienyl, 4-chloro-2-thienyl and the like.

While all of the compounds of the present invention are believed to inhibit the uptake of serotonin and norepinephrine in mammals, there are certain of these compounds which are preferred for such uses. Preferably, R^1 is halothienyl, (C_1–C_4 alkyl)thienyl and especially thienyl. Further, one of R^2 and R^3 is hydrogen and the other is methyl. It is also preferred that those compounds wherein both R^2 and R^3 are other than methyl are preferred for inhibiting the uptake of norepinephrine in mammals. Other preferred aspects of the present invention will be noted hereinafter.

The compounds of the present invention possess an asymmetric carbon represented by the carbon atom labeled "C" in the following formula:



As such, the compounds can exist as the individual stereoisomers as well as the racemic mixture. Accordingly, the compounds of the present invention will include not only the dl-racemates, but also their respective optically active d- and l-isomers.

As pointed out above, the invention includes the pharmaceutically acceptable acid addition salts of the compounds defined by the above formula. Since the compounds of this invention are amines, they are basic in nature and accordingly react with any number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Since the free amines of the invention are typically oils at room temperature, it is preferable to convert the free amines to their corresponding pharmaceutically acceptable acid addition salts, which are routinely solid at room temperature, for

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ease of handling. Acids commonly employed to form such salts include inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, as well as organic acids such as para-toluenesulfonic, methanesulfonic, oxalic, para-bromophenylsulfonic, carbonic, succinic, citric, benzoic and acetic acid, and related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephathalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate, glycollate, maleate, tartrate, methanesulfonate, propanesulfonates, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like salts. Preferred pharmaceutically aoceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and especially those formed with organic acids such oxalic acid and maleic acid.

The following compounds further illustrate compounds contemplated within the scope of the present invention:

N-Methyl-3-(1-naphthalenyloxy)-3-(3-thienyl)-propanamine phosphate

N-Methyl-3-(2-naphthalenyloxy)-3-(cyclohexyl)-propanamine citrate

N,N-Dimethyl-3-(4-chloro-1-naphthalenyloxy)-3-(3-furanyl)propanamine hydrochloride

N-Methyl-3-(5-methyl-2-naphthalenyloxy)-3-(2-thiazolyl)propanamine hydrobromide

N-Methyl-3-[3-(trifluoromethyl)-1-naphthalemyloxy]-3-(3-methyl-2-thienyl)propanamine oxalate

N-Methyl-3-(6-iodo-1-naphthalenyloxy)-3-(4-pyridyl)-propanamine maleate

N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(cycloheptyl)-propanamine formate

N,N-Dimethyl-3-(2-naphthalenyloxy)-3-(2-pyridyl)-propanamine

N-Methyl-3-(1-naphthalenyloxy)-3-(2-furanyl)propanamine sulfate

N-Methyl-3-(4-met naphthalenyloxy)-3-(4-thiazolyl)-propanamine oxalate

N-Methyl-3-(2-naphthalenyloxy)-3-(2-thienyl)propanamine hydrochloride

N,N-Dimethyl-3-6-iodo-2-naphthalenyloxy)-3-(4-bromo-3-thienyl)propanamine malonate

N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(3-pyridyl)-propanamine hydroiodide

N,N-Dimethyl-3-(4-methyl-2-naphthalenyloxy)-3-(3-furanyl)propanamine maleate

N-Methyl-3-(2-naphthalenyloxy)-3-(cyclohexyl)-propanamine caprate

N-Methyl-3-(6-n-propyl-1-naphthalenyloxy)-3-(3-isopropyl-2-thienyl)propanamine citrate

N,N-Dimethyl-3-(2-methyl-1-naphthalenyloxy)-3-(4-thiazolyl)propanamine monohydrogen phosphate

3-(1-Naphthalenyloxy)-3-(5-ethyl-3-thienyl)propanamine succinate

3-3-(Trifluoromethyl)-1-naphthalenyloxy]-3-(pyridyl)-propanamine acetate

N-Methyl-3-(6-methyl-1-naphthalenyl-3-(4-chloro-2-thienyl)propanamine tartrate

3-(2-Naphthalenyloxy)-3-(cyclopentyl)propanamine

N-Methyl-3-(4-n-butyl-1-naphthalenyloxy)-3-(3-furanyl)propanamine methanesulfonate

3-(2-Chloro-1-naphthalenyloxy)-3-(5-thiazolyl)-propanamine oxalate

N-Methyl-3-(1-naphthalenyloxy)-3-(3-furanyl)propanamine tartrate

N,N-Dimethyl-3-(phenoxy)-3-(2-furanyl)propanamine oxalate

N,N-Dimethyl-3-[4-(trifluoromethyl)phenoxy]-3-(cyclohexyl)propanamine hydrochloride

N-Methyl-3-(4-methylphenoxy)-3-(4-chloro-2-thienyl)-propanamine propionate

N-Methyl-3-(phenoxy)-3-(3-pyridyl)propanamine oxalate

3-[2-Chloro-4-(trifluoromethyl)phenoxy]-3-(2-thienyl)-propanamine

N,N-Dimethyl-3-(3-methoxyphenoxy)-3-(3-bromo-2-thienyl)propanamine citrate

N-Methyl-3-(4-bromophenoxy)-3-(4-thiazolyl)propanamine maleate

N,N-Dimethyl-3-(2-ethylphenoxy)-3-(5-methyl-3thienyl)propanamine

N-Methyl-3-(2-bromophenoxy)-3-(3-thienyl)propanamine succinate

N-Methyl-3-(2,6-dimethylphenoxy)-3-(3-methyl-2-thienyl)propanamine acetate

3-[3-(Trifluoromethyl)phenoxy]-3-(3-furanyl)propanamine oxalate

N-Methyl-3-(2,5-dichlorophenoxy)-3-(cyclopentyl)-propanamine

3-4-(Trifluoromethyl)phenoxy]-3-(2-thiazolyl)propanamine

N-Methyl-3-(phenoxy)-3-(5-methyl-2-thienyl)propanamine citrate

3-(4-Methylphenoxy)-3-(4-pyridyl)propanamine hydrochloride

N,N-Dimethyl-3-(3-methyl-5-bromophenoxy)-3-(3-thienyl)propanamine

N-Methyl-3-(3-n-propylphenoxy)-3-(2-thienyl)propanamine hydrochloride

N-Methyl-3-(phenoxy)-3-(3-thienyl)propanamine phosphate

N-Methyl-3-(4-methoxyphenoxy)-3-(cycloheptyl) propanamine citrate

3-(2-Chlorophenoxy)-3-(5-thiazolyl)propanamine propionate

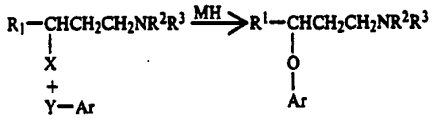
3-2-Chloro-4-(trifluoromethyl)phenoxy]-3-(3-thienyl)-propanamine oxalate

3-(Phenoxy)-3-(4-methyl-2-thienyl)propanamine

N,N-Dimethyl-3-(4-ethylphenoxy)-3-(3-pyridyl)-propanamine maleate

N,N-Dimethyl-3-[4-(trifluoromethyl)phenoxy]-3-(2-pyridyl)propanamine

The compounds of the present invention may be prepared by procedures well known to those of ordinary skill in the art. The compounds are preferably synthesized by treating an hydroxy intermediate with an alkali metal hydride to form the corresponding alkali metal salt, which is then reacted with an appropriate compound containing a good leaving group to provide the corresponding 3-aryloxy-3-substituted propanamine of the invention. This reaction may be represented by the following scheme:



wherein M is an alkali metal, R^1, R^2, R^3 and Ar are as defined above, and one of X and Y is hydroxy and the other is a good leaving group such as p-toluenesulfonyl, methanesulfonyl, triphenylphosphine oxide, halo and the like. Preferably X is hydroxy and Y is halo.

This reaction is carried out by combining approximately equimolar quantities to a slight excess of the alkali metal hydride with the alcohol to provide the corresponding alkali metal salt. Typical alkali metal hydrides include sodium hydride and potassium hydride. The compound is then reacted with an equimolar quantity to slight excess of the compound having the good leaving group. The reaction is conducted in a suitable aprotic solvent such as N,N-dimethylacetamide and related solvents. The reaction is substantially complete after about 10 minutes to about 24 hours when conducted at a temperature in the range of about 25° C. to about 150° C. More preferably, the reaction mixture will be complete within about 30 minutes to about 6 hours when conducted at a temperature in the range of about 75° C. to about 125° C. The product may be isolated by standard conditions as well. Typically, the mixture is diluted with water and extracted with a water immiscible organic solvent such as diethyl ether, ethyl acetate, chloroform and the like. The organic extracts are typically combined and dried. Following evaporation of the organic solvent the isolated residue may be further purified, if desired, by standard techniques such as crystallization from common solvents, or chromatography over solid supports such as silica gel or alumina.

The compounds of the present invention wherein one of R^2 and R^3 is hydrogen and the other is methyl are preferably prepared by demethylating the corresponding N,N-dimethylpropanamine. Preferably, a reagent such a phenyl chloroformate or trichloroethyl chloroformate is reacted with the N,N-dimethylpropanamine to provide the corresponding intermediate, which is then hydrolyzed in base to provide the corresponding N-methylpropanamine.

As noted above, the optically active isomers of the racemates of the invention are also considered part of this invention. Such optically active isomers may be prepared from their respective optically active precursors by the procedures described above, or by resolving the racemic mixtures. This resolution can be carried out in the presence of a resolving agent, by chromatography or by repeated crystallization. Particularly useful resolving agents include dibenzoyl-d- and -l-tartaric acids and the like.

The compounds employed as starting materials in the synthesis of the compounds of the invention are also prepared by standard procedures. Preferably, standard Mannich reaction conditions are employed to synthesize the corresponding Mannich Base from the appropriate ketone, formaldehyde and dimethylamine, which is then reduced with a hydride reducing agent, such as sodium brohydride, employing standard reduction conditions. The analogs containing the leaving group are also prepared by known procedures or are commercially available from various organic laboratories.

The pharmaceutically acceptable acid addition salts of the invention are typically formed by reacting a 3-aryloxy-3-substituted propanamine of the invention with an equimolar or excess amount of acid. The reactants are generally combined in a mutual solvent such as diethyl ether or benzene, and the salt normally precipitates out of solution within about one hour to 10 days, and can be isolated by filtration.

The following Examples further illustrate the compounds of the present invention and methods for their synthesis. The Examples are not intended to be limiting to the scope of the invention in any respect and should not be so construed.

EXAMPLE 1

N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)-propanamine oxalate

A. 3-Dimethylamino-1-(2-thienyl)-1-propanone hydrochloride

A mixture of 2-acetylthiophene (63.1 g, 0.5 mol), dimethylamine hydrochloride (53.0 g, 0.65 mol), paraformaldehyde (19.8 g, 0.22 mol), and 12N hydrochloric acid (1 ml) in ethanol (80 ml) was refluxed for one and one-half hours. The solution was diluted with ethanol (100 ml) and acetone (500 ml). The solution was chilled overnight and the resulting solid was collected by filtration to yield 75.0 g (73%) of 3-dimethylamino-1-(2-thienyl)-1-propanone hydrochloride as a colorless crystalline solid. mp = 182° C.–184° C.

Analysis calculated for $C_9H_{14}ClNOS$ Theory: C, 49.20; H, 6.42; N, 6.37; Found: C, 49.40; H, 6.21; N, 6.09.

B. α-[2-(Dimethylamino)ethyl]-2-thiophene methanol

To a solution of 3-dimethylamino-1-(2-thenyl)-1-propanone hydrochloride (70.0 g, 0.34 mol) in 840 ml of methanol and 420 ml of water at about 0° C. was added 5N sodium hydroxide until the solution was slightly basic. To the resulting solution was added sodium borohydride (12.9 g., 0.34 mol) in portions. The mixture was allowed to warm to room temperature overnight. The methanol was removed in vacuo and the remaining solution was diluted with water. The solution was extracted with diethyl ether, and the solution was washed with a saturated sodium chloride solution , dried over anhydrous sodium sulfate and concentrated in vacuo to provide 56.7 g of colorless crystals. Recrystallization of the crystals from hexanes gave 49.24 g (78%) of the title compound as colorless crystals. mp = 72° C.–74° C.

Analysis calculated for $C_9H_{19}NOS$ Theory: C, 58.34; H, 8.16; N, 7.56; Found: C, 58.62; H, 8.29; N, 7.68.

C. α-2-(Dimethylamino)ethyl]-2-thiophene methanol (2.0 g, 0.011 mol) was added in portions to a solution of 60% sodium hydride (463 mg, 0.012 mol) in 100 ml of dimethylacetamide. The resulting mixture was heated at 70° C. for 20 minutes. 1-Fluoronaphthalene (1.27 ml, 0.012 m) was added dropwise to the mixture and the resulting solution was heated at 110° C. for 60 minutes. The reaction mixture was diluted with water and extracted twice with diethyl ether. The extracts were combined, washed with water followed by a saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield 3.2 g of an oil. Crystallization of the oil as the oxalate salt from ethyl acetate/methanol yielded 3.28 g (75.6%) of N,N-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate as a white solid. mp = 148° C.–148.5° C.

Analysis calculated for $C_{21}H_{23}NO_5S$ Theory: C, 62.83; H, 5.77; N, 3.49; Found : C, 62.70; H, 5.88; N, 3.26.

EXAMPLE 2

N-Methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate

Phenyl chloroformate (794 μl, 0.0063 mol) was added dropwise to a refluxing solution of N,N-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine (1.79 g, 0.0058 mol) in 100 ml of toluene. The resulting solution was refluxed one and one half hours and cooled to room temperature. The solution was washed (2.5N sodium hydroxide, water, 1N hydrochloric acid, brine), dried over anhydrous sodium sulfate and concentrated in vacuo to give 2.4 g of the crude carbamate. 5N Sodium hydroxide (11.5 ml, 0.058 mol) was added to a solution of the carbamate (2.4 g, 0.0058 mole) in propylene glycol (100 ml). The mixture was heated at 110° C. for 75 minutes. The reaction mixture was diluted with water and extracted with diethyl ether. The organic phase was washed with water and then a saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under vacuum to yield 1.5 g of an oil. Crystallization of the oil as the oxalate salt from ethyl acetate/methanol gave 920 mg (41.3%) of the title compound as a white powder. mp =136° C.–138.5° C.

Analysis calculated for $C_{20}H_{21}NO_5S$ Theory: C, 62.00; H, 5.46; N, 3.62; Found: C, 62.21; H, 5.72; N, 3.57.

EXAMPLE 3

N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(5-methyl-2-thienyl)propanamine oxalate

A.

3-Dimethylamino-1-(5-methyl-2-thienyl)-1-propanone hydrochloride

The title compound was prepared according to the general procedure outlined in Example 1 employing 2-acetyl-5-methylthiophene as the starting material to provide 31.3 g (37.4%) of a yellow powder following crystallization from acetone. mp =145° C.–147° C.

Analysis calculated for $C_{10}H_{16}ClNOS$ Theory: C, 51.38; H, 6.90; N, 5.99; Found : C, 51.53; H, 6.82; N, 5.66.

B. α-[2-(Dimethylamino)ethyl]-5-methyl-2thiophene methanol

According to the general procedure set forth in Example 1 using 3-dimethylamino-1-(5-methyl-2-thienyl)-1-propanone hydrochloride as the starting material. The title compound was obtained (50.9%) as an opaque crystalline solid was synthesized. mp =66.5° C.–68° C.

Analysis calculated for $C_{10}H_{17}NOS$ Theory: C, 60.26; H, 8.60; N, 7.03; Found: C, 60.49; H, 8.58; N, 6.91.

C. According to the procedure set forth in Example 1, using α-2-(dimethylamino)ethyl]-5-methyl-2-thiophene methanol as the starting material N,N-dimethyl-3-(1-naphthalenyloxy)-3-(5-methyl-2-thienyl)propanamine was prepared. The crude material was chromatographed over silica gel (eluent-methylene chloride/methanol) to yield 1.4 g (25.5%) of an oil. Crystallization from ethyl acetate/methanol of a small portion of the oil as the oxalate salt gave the title compound as yellow crystals mp =151° C.

Analysis calculated for $C_{22}H_{25}NO_5S$ Theory: C, 63.59; H, 6.06; N, 3.37; Found: C, 63.36; H, 5 84; N, 3.33.

EXAMPLE 4

N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(3-methyl-2-thienyl)propanamine oxalate

A.

3-Dimethylamino-1-(3-methyl-2-thienyl)-1-propanone hydrochloride

The title compound was prepared according to the general procedure set forth in Example 1 using 2-acetyl-3-methylthiophene as the starting material. The crude material was crystallized from acetone to provide 43.4 g (60.7%) of the title compound as a white powder. mp =157° C.–158° C.

Analysis calculated for $C_{10}H_{16}ClNOS$ Theory: C, 51.38; H, 6.90; N, 5.99; Found: C, 51.63; H, 7.14; N, 5.82.

B. α-[2-(Dimethylamino)ethyl]-3-methyl-2-thiophene methanol

The title compound was prepared from 3-dimethylamino-1-(3-methyl-2-thienyl)-1-propanone hydrochloride according to the general procedure of Example 1. Crystallization from hexanes yielded 11.38 g (53.7%) of an opaque crystalline solid. mp =41.5° C.–42.5° C.

Analysis calculated for $C_{10}H_{17}NOS$ Theory: C, 60.26; H, 8.60; N, 7.03; Found: C, 60.80; H, 8.33; N, 6.56.

C. Crude N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(3-methyl-2-thienyl)propanamine, prepared according to the general procedure outlined in Example 1, was chromatographed over silica gel (eluent-methylene chloride/methanol) to yield 10.4 g (74.3%) of an oil. The oil was converted to the oxalate salt and crystallized from ethyl acetate/methanol to give a white powder. mp =140° C.–141° C.

Analysis calculated for $C_{22}H_{25}NO_5S$ Theory: C, 63.59; H, 6.06; N, 3.37; Found: C, 63.85; H, 6.07; N, 3.49.

EXAMPLE 5

N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(5-chloro-2-thienyl)propanamine oxalate

A.

3-Dimethylamino-1-(5-chloro-2-thienyl)-1-propanone hydrochloride

The title compound was prepared according to the general procedure of Example 1 using 2-acetyl-5-chlorothiophene as the starting material. Crystallization from acetone gave 14.55 g (36.9%). mp =170° C.–171° C.

Analysis calculated for $C_9H_{13}Cl_2NOS$ Theory: C, 42.S3; H, 5.16; N, 5.51; Found: C, 42.00; H, 5.23; N, 6.50

B. α-[2-(Dimethylamino)ethyl]-5-chloro-2-thiophene methanol

Three grams of the title compound were prepared from 3-dimethylamino-1-(5-chloro-2-thienyl)-1-propanone hydrochloride according to the general procedure of Example 1 following crystallization from hexanes (38.6%). mp =76° C.–77° C.

Analysis calculated for $C_9H_{14}ClNOS$ Theory: C, 49.20; H, 6.42; N, 6.37; Found: C, 47.37; H, 6.65; N, 6.40.

C. N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(5-chloro-2-thienyl)propanamine was prepared from α2-(dimethylamino)ethyl]-5-chloro-2-thiophene methanol according to the general procedure of Example 1. The crude product was chromatographed over silica gel employing methylene chloride/methanol/ammonium

hydroxide as the eluent to yield 320 mg (5.5%) of an oil. Crystallization of the oil as the oxalate salt from ethyl acetate/methanol gave a brown solid. mp =134° C.-135° C.

Analysis calculated for $C_{21}H_{22}ClNO_5S$ Theory: C, 57.86; H, 5.09; N, 3.21; Found: C, 57.73; H, 5.35; N, 3.30.

EXAMPLE 6

N,N-Dimethyl-3-[4-(trifluoromethyl)-1naphthalenyloxy]-3-(2-thienyl)propanamine oxalate

According to the procedure set forth in Example 1 using 4-trifluoromethyl-1-fluoronaphthalene as a starting material, 1.7 g (66.9%) of the title compound as a tan solid was prepared following crystallization from ethyl acetate/methanol. mp =146° C.-147° C.

Analysis calculated for $C_{22}H_{22}F_3NO_5S$ Theory: C, 56.28; H, 4.72; N, 2.98; Found : C, S6.04; H, 4.65; N, 3.23.

EXAMPLE 7

N-Methyl-3-[4-(trifluoromethyl)-1-naphthalenyloxy]-3-(2-thienyl)propanamine oxalate

According to the procedure set forth in Example 2 N,N-dimethyl-3-[4-(trifluoromethyl)-1-naphthalenyloxy]-3-(2-thienyl)propanamine oxalate was converted to the title compound. Crystallization from ethyl acetate/-methanol gave 430 mg (33.8%) of a tan powder. mp =154° C.-156° C.

Analysis calculated for $C_{20}H_{20}F_3NO_5S$ Theory: C, 55.38; H, 4.43; N, 3.08; Found: C, 55.63; H, 4.55; N, 3.27.

EXAMPLE 8

N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(3-thienyl)-propanamine oxalate

A. 3-Dimethylamino-1-(3-thienyl)-1-propanone hydrochloride

The title compound was prepared according to the procedure of Example 1 using 3-acetylthiophene as a starting material. Crystallization from acetone gave 73.9 g (84.9%) of a tan powder. mp =143° C.-145° C.

Analysis calculated for $C_9H_{14}ClNOS$ Theory: C, 49.20; H, 6.42; N, 6.37; Found: C, 46.27; H, 6.11; N, 7.00.

B. α-[2-(Dimethylamino)ethyl]-3-thiophene methanol

The title compound was prepared according to the procedure in Example 1 using 3-dimethylamino-1-(3-thienyl)-1-propanone hydrochloride as a starting material. Crystallization from diethyl ether/hexane gave 29.0 g (47.7%) of the title compound as a solid. mp =63° C.-65° C.

Analysis calculated for $C_9H_{15}NOS$ Theory: C, 58.34; H, 8.16; N, 7.56; Found: C, S8.34; H, 8.17; N, 7.72.

C. N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(3-thienyl)propanamine oxalate was prepared according to the procedure of Example 1 using α-[2-(dimethylamino)ethyl]-3-thiophene methanol as a starting material. Crystallization from ethyl acetate/methanol gave 5.88 g (69.8%) of a white powder. mp =164° C.-165° C.

Analysis calculated for $C_{21}H_{23}NO_5S$ Theory: C, 62.83; H, 5.77; N, 3.49; Found: C, 63.12; H, 6.01; N, 3.51.

EXAMPLE 9

N-Methyl-3-(1-naphthalenyloxy)-3-(3-thienyl)propanamine oxalate

The title compound was prepared according to procedure of Example 2 from N,N-dimethyl-3-(1-naphthalenyloxy)-3-(3-thienyl)propanamine. Crystallization from ethyl acetate/methanol gave 2.97 g (63.6%) of a white powder. mp =148° C.-150° C.

Analysis calculated for $C_{20}H_{21}NO_5S$ Theory: C, 62.00; H, 5.46; N, 3.62; Found: C, 62.23; H, 5.59; N, 3.85.

EXAMPLE 10

N,N-Dimethyl-3-(4-chloro-1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate

To a stirred mixture of 4-chloro-1-naphthol (5.36 g, 0.03 mol), α-2-(dimetlylamino)ethyl]-2-thiophene methanol (5.56 g, 0.03 mol), triphenylphosphine (7.87 g, 0.03 mol) and 75 ml of tetrahydrofuran under a nitrogen atmosphere was added 4.8 ml (0.03 mol) of diethylazodicarboxylate dropwise. Occasional cooling was needed to keep the temperature of the reaction mixture below about 30° C. The resulting solution was stirred at room temperature overnight. The volatile constituents were evaporated under vacuum. The residue was diluted with water and the mixture was basified with 5N sodium hydroxide. The mixture was extracted with diethyl ether, and the organic extracts were washed with water and dried over anhydrous sodium sulfate. Evaporation of the diethyl ether and preparative HPLC of the residue using a silica column with a methylene chloride/methanol mixture as eluant yielded 3.7 g (36% yield) of the pure free base as an oil. The oxalate salt was prepared from the above free base by treating an ethyl acetate solution of the free base with oxalic acid. The resulting precipitate was recrystallized from ethanol to afford colorless crystals. mp =155° C. dec.

Analysis calculated for $C_{21}H_{22}ClNO_5S$ Theory: C, 57.86; H, 5.09; N, 3.21; Found: C, 57.66; H, 4.94; N, 3.12.

EXAMPLE 11

N-Methyl-3-(4-chloro-1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate

To a stirred solution of N,N-dimethyl-3-(4-chloro-1-naphthalenyloxy)-3-(2-thienyl)propanamine (2.81 g, 8.12 mmol) and 20 ml of toluene heated at 85° C. was added dropwise trichloroethyl chloroformate (1.89 g, 8.93 mmol). The stirring was continued at 85° C. for three hours, and the resulting solution was cooled in an ice bath. To the mixture was added 0.13 ml of 98% formic acid followed by 0.28 ml of triethylamine. The mixture was stirred at room temperature for 30 minutes. The mixture was poured into water and the resulting mixture was extracted with diethyl ether. The organic extracts were washed successively with a saturated sodium chloride solution, a 2N hydrochloric acid solution and a saturated sodium chloride solution. The organic phase was dried over anhydrous sodium sulfate. The volatile constituents were evaporated under vacuum to yield 3.83 g (92% yield) of the crude carbamate as an oil. To a solution of the crude carbamate in 10.0 ml of DMF was added 98% formic acid (0.69 g., 14.9 mmol). The reaction solution was cooled to about 15° C. under a nitrogen atmosphere. Zinc dust (1.22 g, 18.7 mmol) was next added in portions over a 30 minute period. The mixture was stirred at about 15° C. for one hour and then overnight at room temperature. The reaction mixture was filtered through a sintered glass funnel and the filtrate was diluted with water. The acidic solution was made basic with excess cold ammonium hydroxide and then extracted with diethyl ether. The organic extracts were washed with water followed by a saturated sodium chloride solution. The organic phase was dried over anhydrous sodium sulfate and

evaporated under vacuum. The residue was purified by preparative HPLC using a silica gel column with a methylene chloride/methanol/ammonium hydroxide (100:5:1, v:v:v) mixture as eluant to give 1.26 g (51% yield) of the free base as an oil.

The oxalate salt was prepared from the free base by treating an ethyl acetate solution of the free base with oxalic acid. The resulting precipitate was crystallized from methanol to afford colorless crystals. mp =182° C. dec.

Analysis calculated for $C_{20}H_{20}ClNO_5S$ Theory: C, 56.94; H, 4.78; N, 3.32; Found: C, 57.22; H, 4.54; N, 3.48.

EXAMPLE 12

N,N-Dimethyl-3-(4-methyl-1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate

N,N-Dimethyl-3-(4-methyl-1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate was prepared in 21% yield by the general procedure described in Example 10. The oxalate salt was made and crystallized from ethanol to afford the title compound as colorless crystals. mp =151° C. dec.

Analysis calculated for $C_{22}H_{25}NO_5S$ Theory: C, 63.59: H, 6.06: N, 3.37: Found: C, 63.29: H, 6.02; N, 3.23.

EXAMPLE 13

N-Methyl-3-(4-methyl-1-naphthalenyloxy)-3-(2-thienyl)propanamine maleate

The free base of the title compound was prepared in 44% yield by the procedure described above in Example 11. The maleate salt was prepared from the free base by treating an ethyl acetate solution of the free base with maleic acid. The resulting precipitate was recrystallized from ethanol to afford colorless crystals. mp =174° C. dec.

Analysis calculated for $C_{32}H_{25}NO_5S$ Theory: C, 64.62; H, 5.89; H, 3.28; Found: C, b4.49; H, 5.71; N, 3.48.

The following compounds were prepared according to the general procedures outlined in Examples 1 and 2 above.

EXAMPLE 14

(+)-N-Methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)-propanamine maleate, mp =118° C.–122° C.

$[\alpha]_{589} = +82°$ $[\alpha]_{365} = +391°$ at C=1 in methanol,

Analysis calculated for $C_{22}H_{23}NO_5S$ Theory: C, 63.90; H, 5.61; N, 3.39; S, 7.75; Found: C, 63.78; H, 5.44; N, 3.35; S, 7.64.

EXAMPLE 15

N-Methyl-3-(1-naphthalenyloxy)-3-cyclohexyl-propanamine oxalate, mp =184° C.–185° C.

Analysis calculated for $C_{22}H_{29}NO_5$Theory: C, 68.20; H, 7.54; N, 3.61; Found: C, 68.36; H, 7.30; N, 3.45.

EXAMPLE 16

N-Methyl-3-(1-naphthalenyloxy)-3-(2-thiazolyl)-propanamine oxalate, mp =183° C.–185° C.

Analysis calculated for $C_{19}H_{20}N_2O_5S$ Theory: C, 58.75; H, 5.19; N, 7.21; Found: C, 59.02; H, 4.94; N, 7.47.

EXAMPLE 17

N,N-Dimethyl-3-[4-(trifluoromethyl)phenoxy]-3-(2-furanyl)propanamine oxalate, mp =144.5° C.–145.5° C.

Analysis calculated for $C_{18}H_{20}F_3NO_6$ Theory C, 53.60; H, 5.00; N, 3.47; Found: C, 53.83; H, 5.22; N, 3.23.

EXAMPLE 18

N,N-Dimethyl-3-[4-(trifluoromethyl)phenoxy]-3-(-22-thienyl)propanamine oxalate, mp =130° C.–131.5° C.

Analysis calculated for $C_{18}H_{20}F_3NO_5S$ Theory: C, 51.55; H, 4.81; N, 3.34; Found: C, 51.25; H, 4.91; N, 3.55.

EXAMPLE 19

N,N-Dimethyl-3-[4-(trifluoromethyl)phenoxy]-3-(3-thienyl)propanamine oxalate, mp =124° C.–125° C.

Analysis calculated $C_{18}H_{20}F_3NO_5S$ Theory: C, 51.55; H, 4.81; N, 3.34; Found: C, 51.35; H, 4.68; N, 3.39.

EXAMPLE 20

N-Methyl-3-[4-(trifluoromethyl)phenoxy-3-(2-thienyl)propanamine oxalate, mp =167° C.–168° C. dec.

Analysis calculated for $C_{17}H_{18}F_3NO_5S$ Theory: C, 50.37; H, 4.48; N, 3.46; Found: C, 50.40; H, 4.66; N, 3.72.

EXAMPLE 21

N,N-Dimethyl-3-[4-(trifluoromethyl)phenoxy]-3-(2-furanyl)propanamine, oil

Analysis calculated for $C_{16}H_{18}F_3NO_2$Theory: C, 61.34; H, 5.79; N, 4.47; Found: C, 61.07; H, 5.82; N, 4.68.

EXAMPLE 22

N-Methyl-3-[4-(trifluoromethyl)phenoxy]-3-(3-thienyl)propanamine oxalate, mp =181° C.–182° C.

Analysis calculated for $C_{17}H_{18}F_3NO_5S$ Theory: C, 50.37; H, 4.48; N, 3.46; Found: C, 50.49; H, 4.42; N, 3.67.

EXAMPLE 23

N-Methyl-3-[4-(trifluoromethyl)phenoxy]-3-(2-furanyl)propanamine oxalate, mp =98° C.–102° C. dec.

15 Analysis calculated for $C_{17}H_{18}F_3NO_6$Theory: C, 52.45; H, 4.66; N, 3.60; Found: C, 52.52; H, 4.45; N, 3.80.

EXAMPLE 24

N,N-Dimethyl-3-(4-methylphenoxy)-3-(2-thienyl)-propanamine oxalate, mp =132.5° C.–133.5° C.

Analysis calculated for $C_{18}H_{23}NO_5S$ Theory: C, 59.16; H, 6.34; N, 3.83; Found: C, 59.06; H, 6.12; N, 4.11.

EXAMPLE 25

N,N-Dimethyl-3-(4-chlorophenoxy)-3-(2-thienyl)-propanamine oxalate, mp =118° C.–119° C.

Analysis calculated for $C_{17}H_{20}ClNO_5S$ Theory: C, 52.95; H, 5.22; N, 3.63; Found: C, 52.85; H, 5.22; N, 3.48.

EXAMPLE 26

N-Methyl-3-(4-methylphenoxy)-3-(2-thienyl)-propanamine oxalate, mp =152° C.–153° C.

Analysis calculated for $C_{17}H_{21}NO_5S$ Theory: C, 58.10; H, 6.02; N, 3.99; Found C, 58.05; H, 6.04; N, 3.72.

EXAMPLE 27

N-Methyl-3-(4-chlorophenoxy)-3-(2-thienyl)-propanamine oxalate, mp =126° C.–129° C.

Analysis calculated for $C_{16}H_{18}ClNO_5S$ Theory: C, 51.68; H, 4.88; N, 3.77; Found: C, 51.60; H, 5.01; N, 3.52.

EXAMPLE 28

N-Methyl-3-(4-methoxyphenoxy)-3-(2-thienyl)-propanamine oxalate, mp =140° C.–143° C.

Analysis calculated for $C_{17}H_{21}NO_6S$ Theory: C, 55.57; H, 5.76; N, 3.81; Found: C, 55.31; H, 5.55; N, 4.06.

EXAMPLE 29

N,N-Dimethyl-3-(4-methoxyphenoxy)-3-(2thienyl)-propanamine oxalate, mp =110° C.-111.5° C.

Analysis calculated for $C_{18}H_{23}NO_6S$ Theory: C, 56.68; H, 6.08; N, 3.67; Found: C, 56.43; H, 5.85; N, 3.81.

EXAMPLE 30

N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(2furanyl)-propanamine oxalate, mp =153° C.-155.5° C.

Analysis calculated for $C_{21}H_{23}NO_6$ Theory: C, 65.44; H, 6.02; N, 3.63; Found: C, 65.21; H, 5.75; N, 3.78.

EXAMPLE 31

N-Methyl-3-(1-naphthalenyloxy)-3-(2-furanyl)-propanamine oxalate, mp =145° C.-146° C.

Analysis calculated for $C_{20}H_{21}NO_6$ Theory: C, 64.68; H, 5.70; N, 3.77; Found: C, 64.79; H, 5.51; N, 3.95.

EXAMPLE 32

N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(2thiazolyl)-propanamine oxalate, mp =190° C.-191° C. dec.

Analysis calculated for $C_{20}H_{22}N_2O_5S$ Theory: C, 59.69; H, 5.51; N, 6.96; Found: C, 59.99; H, 5.80; N, 7.01.

EXAMPLE 33

N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(cyclohexyl)propanamine oxalate, mp =167° C.-169° C.

Analysis calculated for $C_{23}H_{31}NO_5$Theory: C, 68.80; H, 7.78; N, 3.49; Found: C, 68.53; H, 7.53; N, 3.54.

EXAMPLE 34

N-Methyl-3-[4-(trifluoromethyl)phenoxy]-3(cyclohexyl)propanamine oxalate, mp =212° C.-213° C.

Analysis calculated for $C_{19}H_{26}F_3NO_5$ Theory: C, 56.29; H, 6.46; N, 3.45; Found: C, 56.19; H, 6.37; N, 3.32.

EXAMPLE 35

N,N-Dimethyl-3-[4-(trifluoromethyl)phenoxy]-3-(cyclohexyl)propanamine oxalate, mp =159° C.-160° C.

Analysis calculated for $C_{20}H_{28}F_3NO_5$ Theory: C, 57.27; H, 6.73; N, 3.34; Found: C, 57.49; H, 6.61; N, 3.20.

EXAMPLE 36

N-Methyl-3-(-naphthalenyloxy)-3-(3-pyridyl)-propanamine oxalate, mp =98° C. dec.

Analysis calculated for $C_{21}H_{22}N_2O_5$ Theory: C, 65.96; H, 5.80; N, 7.33; Found: C, 64.27; H, 5.67; N, 7.01.

EXAMPLE 37

N,N-Dimethyl-3-(1-naphthalenyloxy)-3-(3-pyridyl)-propanamine oxalate, mp =176° C.-178° C.

Analysis calculated for $C_{22}H_{24}N_2O_5$ Theory: C, 66.65; H, 6.10; N, 7.07; Found: C, 66.53; H, 6.36; N, 6.41.

EXAMPLE 38

(+)-N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)-propanamine oxalate, mp =133° C.-134° C.

Analysis calculated for $C_{20}H_{21}NO_5S$ Theory: C, 62.00; H, 5.46; N, 3.62; Found: C, 62.03; H, 5.51; N, 3.87.

EXAMPLE 39

(−)-N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)-propanamine oxalate, mp =138° C.-138.5° C.

Analysis calculated for $C_{20}H_{21}NO_5S$ Theory: C, 62.00; H, 5.46; N, 3.62; Found: C, 61.72; H, 5.32; N, 3.82.

As noted above, the compounds of this invention are useful for inhibiting the uptake of serotonin. Therefore, another embodiment of the present invention is a method for inhibiting serotonin uptake in mammals which comprises administering to a mammal requiring increased neurotransmission of serotonin a pharmaceutically effective amount of a compound of the invention.

Compounds of the invention also have the ability to inhibit the uptake of norepinephrine. As such, yet another embodiment of this invention is a method for inhibiting norepinephrine uptake in mammals which comprises administering to a mammal requiring increased neurotransmission of norepinephrine a pharmaceutically effective amount of a compound of the invention.

The term "pharmaceutically effective amount", as used herein, represents an amount of a compound of the invention which is capable of inhibiting serotonin or norepinephrine uptake. The particular dose of compound administered according to this invention will of course be determined by the particular circumstances surrounding the case, including the compound administered, the route of administration, the particular condition being treated, and similar considerations. The compounds can be administered by a variety of routes including the oral, rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal routes. The compounds of the invention unexpectedly inhibit the uptake of not only serotonin but also norepinephrine in mammals. It is a special feature of the compounds that they have good oral bioavailability without losing their substantial potent inhibiting effect of serotonin and norepinephrine uptake inhibiting effect. It is also a special feature of the compounds of the present invention in that they have been found to demonstrate a low degree of toxicity to mammals. A typical daily dose will contain from about 0.01 mg/kg to about 20 mg/kg of the active compound of this invention. Preferred daily doses will be about 0.05 to about 10 mg/kg, ideally about 0.1 to about 5 mg/kg.

A variety of physiologic functions have been shown to be subject to influence by brain serotoninengic and norepinephrinergic neural systems. As such, the compounds of the present invention are believed to have the ability to treat a variety of disorders in mammals associated with these neural systems such as obesity, depression, alcoholism, pain, loss of memory, anxiety and smoking. Therefore, the present invention also provides methods of treating the above disorders at rates set forth above for inhibiting serotonin and norepinephrine uptake in mammals.

The following experiment was conducted to demonstrate the ability of the compounds of the present invention to inhibit the uptake of serotonin and norepinephrine. This general procedure is set forth by Wong et al., in *Drug Development Research* 6:397–403 (1985).

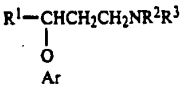
Male Sprague-Dawley rats (110–150 g) from Harlan Industries (Cumberland, IN) were fed a Purina Chow ad libitum for at least 3 days before being used in the studies. Rats were killed by decapitation. Whole brains were removed and dissected. Cerebral cortex was homogenized in 9 volumes of a medium containing 0.32 M sucrose and 10 mM glucose. Crude synaptosomal preparations were isolated after differential centrifugation at 1,000 g for 10 min. and 17,000 g for 28 min. The final pellets were suspended in the same medium and kept in ice until use within the same day.

Synaptosomal uptake of ^{3}H-serotonin(^{3}H-5hydroxytryptamine, ^{3}H-5HT) and ^{14}C-l-norepinephrine (^{14}C-NE) was determined as follows. Cortical synaptosomes (equivalent to 1 mg of protein) were incubated at 37° C. for 5 min in 1 ml of Krebs-bicarbonate medium containing also 10 mM glucose, 0.1 mM iproniazid, 1 mM ascorbic acid, 0.17 mM EDTA, 50 nM ^{3}H-5HT and 100 nM ^{14}C-NE The reaction mixture was immediately diluted with 2 ml of ice-chilled Krebs-bicarbonate buffer and filtered under vacuum with a cell harvester (Brandel, Gaithersburg, MD). Filters were rinsed twice with approximately 5 ml of ice-chilled 0.9% saline and were transferred to a counting vial containing 10 ml of scintillation fluid (PCS, Amersham, Arlington Heights, IL). Radioactivity was measured by a liquid scintillation spectrophotometer. Accumulation of ^{3}H-5HT and ^{14}C-NE at 4° C. represented the background and was subtracted from all samples.

The results of the evaluation of various compounds of the present invention are set forth below in Table I. In the Table, columns 1–4 identify the structure of the compounds evaluated when taken with the formula set forth in the heading; column 5 identifies the salt form, if any, of the compound evaluated; and columns 6 and 7 provide the concentration of the test compound at 10^{-9}M (nM) needed to inhibit 50% of serotonin (5HT) or norepinephrine, respectively, and is indicated in the Table as IC_{50}. The numbers in parentheses represent percent inhibition at 1000 nM.

TABLE I

INHIBITION OF 5HT AND NOREPINEPHRINE UPTAKE IN VITRO



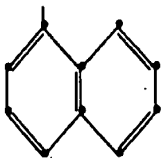
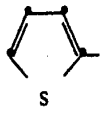
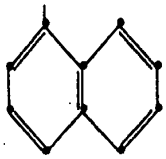
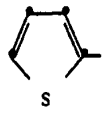
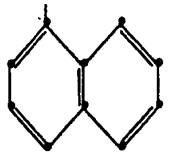
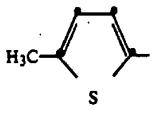
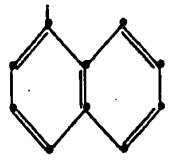
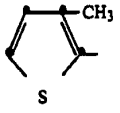
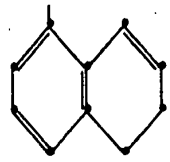
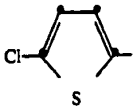
Compound of Example No.	Ar	R^1	R^2	R^3	Salt Form	IC_{50}(nM) 5HT	NE
1			CH_3	CH_3	oxalate	13	600
2			CH_3	H	oxalate	17.5	38.5
3			CH_3	CH_3	oxalate	55	720
4			CH_3	CH_3	oxalate	76	(41)
5			CH_3	CH_3	oxalate	62	725

TABLE I-continued

INHIBITION OF 5HT AND NOREPINEPHRINE UPTAKE IN VITRO

$R^1-CHCH_2CH_2NR^2R^3$
|
O
Ar

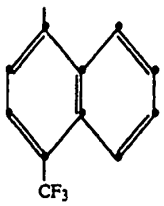
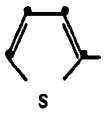
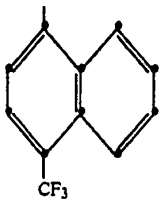
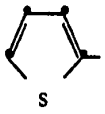
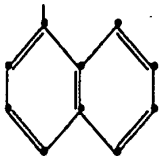
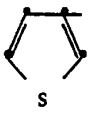
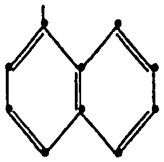
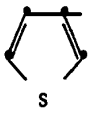
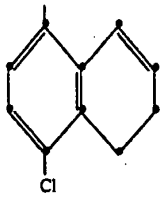
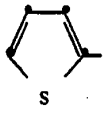
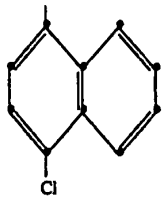
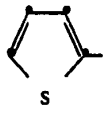
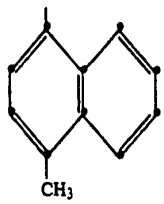
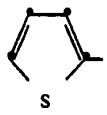
Compound of Example No.	Ar	R^1	R^2	R^3	Salt Form	IC_{50}(nM) 5HT	NE
6			CH_3	CH_3	oxalate	114	(9)
7			CH_3	H	oxalate	95	(46)
8			CH_3	CH_3	oxalate	25	630
9			CH_3	H	oxalate	18	69
10			CH_3	CH_3	oxalate	36	(31)
11			CH_3	H	oxalate	49	77
12			CH_3	CH_3	oxalate	58	(40)

TABLE I-continued

INHIBITION OF 5HT AND NOREPINEPHRINE UPTAKE IN VITRO

$R^1-CHCH_2CH_2NR^2R^3$
O
Ar

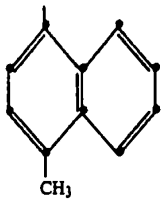
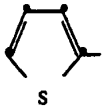
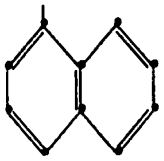
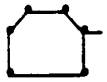
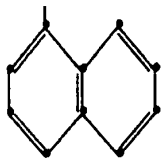
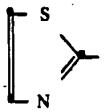
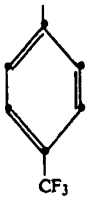
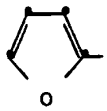
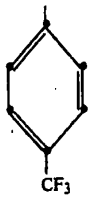
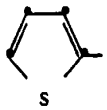
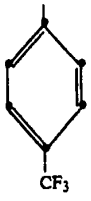
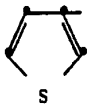
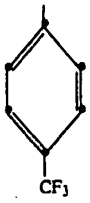
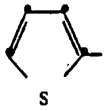
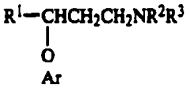
Compound of Example No.	Ar	R^1	R^2	R^3	Salt Form	IC_{50}(nM) 5HT	NE
13			CH_3	H	maleate	33	47
15			CH_3	H	oxalate	125	90
16			CH_3	H	oxalate	70	205
17			CH_3	CH_3	oxalate	210	(5)
18			CH_3	CH_3	oxalate	190	(15)
19			CH_3	CH_3	oxalate	125	(17)
20			CH_3	H	oxalate	46	(52)

TABLE I-continued

INHIBITION OF 5HT AND NOREPINEPHRINE UPTAKE IN VITRO



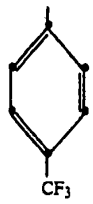
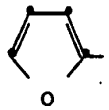
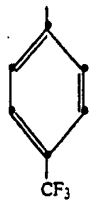
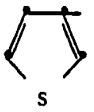
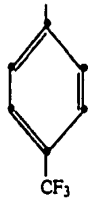
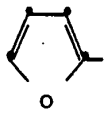
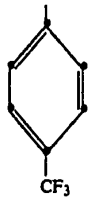
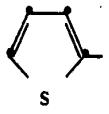
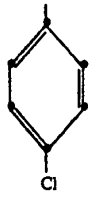
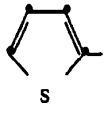
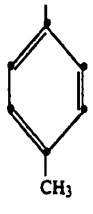
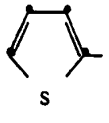
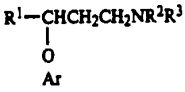
Compound of Example No.	Ar	R^1	R^2	R^3	Salt Form	IC_{50}(nM) 5HT	NE
21			CH_3	CH_3		140	(14)
22			CH_3	H	oxalate	100	(36)
23			CH_3	H	oxalate	54	1100
24			CH_3	CH_3	oxalate	125	430
25			CH_3	CH_3	oxalate	170	820
26			CH_3	H	oxalate	112	22

TABLE I-continued

INHIBITION OF 5HT AND NOREPINEPHRINE UPTAKE IN VITRO



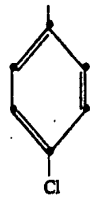
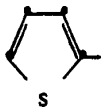
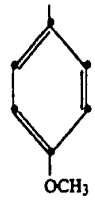
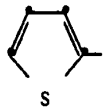
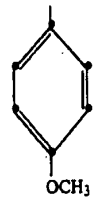
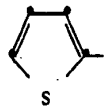
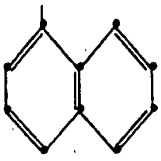
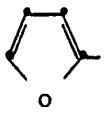
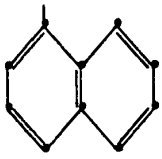
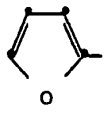
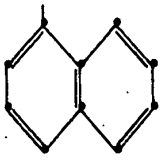
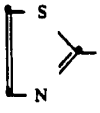
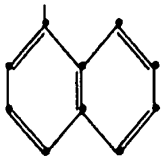
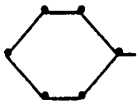
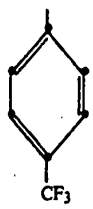
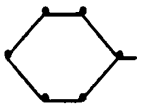
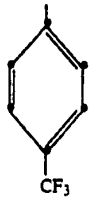
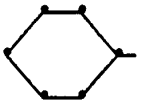
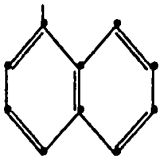
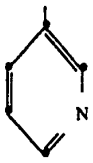
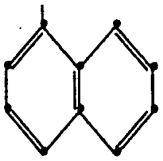
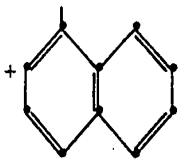
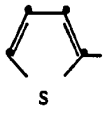
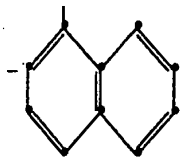
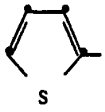
Compound of Example No.	Ar	R^1	R^2	R^3	Salt Form	IC_{50}(nM) 5HT	NE
27			CH_3	H	oxalate	91	59
28			CH_3	H	oxalate	50	260
29			CH_3	CH_3	oxalate	410	(18)
30			CH_3	CH_3	oxalate	11	30
31			CH_3	H	oxalate	20	22.7
32			CH_3	CH_3	oxalate	50	510
33			CH_3	CH_3	oxalate	210	(47)

TABLE I-continued

INHIBITION OF 5HT AND NOREPINEPHRINE UPTAKE IN VITRO

$R^1—CHCH_2CH_2NR^2R^3$
O
Ar

Compound of Example No.	Ar	R^1	R^2	R^3	Salt Form	IC_{50}(nM) 5HT	NE
34			CH_3	H	oxalate	79	285
35			CH_3	CH_3	oxalate	260	(21)
36			CH_3	H	oxalate	30	30
37			CH_3	CH_3	oxalate	315	315
38			CH_3	H	oxalate	12.3	38
39			CH_3	H	oxalate	21.5	34

The compounds of the present invention are preferably formulated prior to administration. Therefore, yet another embodiment of the present invention is a pharmaceutical formulation comprising a compound of the invention and a pharmaceutically acceptable carrier, diluent or excipient therefor.

The present pharmaceutical formulations are prepared by known procedures using well known and readily available ingredients. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semisolid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosol (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 500 mg, more usually about 25 to about 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way.

FORMULATION 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
(+)-N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine maleate	250
starch, dried	200
magnesium stearate	10
Total	460 mg

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
N,N-dimethyl-3-(1-naphthalenyloxy)-3-(5-chloro-2-thienyl)propanamine oxalate	250
cellulose, microcrystalline	400
silicon dioxide, fumed	10
stearic acid	5
Total	665 mg

The components are blended and compressed to form tablets each weighing 665 mg.

FORMULATION 3

An aerosol solution is prepared containing the following components:

	Weight %
3-(1-naphthalenyloxy)-3-(2-thiazoyl)-propanamine hydrochloride	0.25
ethanol	29.75
Propellant 22 (chlorodifluoromethane)	70.00
Total	100.00

The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to −30° C. and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are than fitted to the container.

FORMULATION 4

Tablets each containing 60 mg of active ingredient are made as follows:

N,N-dimethyl-3-[4-(trifluoromethyl)phenoxy]-3-(3-thienyl)propanamine oxalate	60 mg
starch	45 mg
microcrystalline cellulose	35 mg
polyvinylpyrrolidone (as 10% solution in water)	4 mg
sodium carboxymethyl starch	4.5 mg
magnesium stearate	0.5 mg
talc	1 mg
Total	150 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50° C. and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

FORMULATION 5

Capsules each containing 80 mg of medicament are made as follows:

N,N-dimethyl-3-[4-(trifluoromethyl)phenoxy]-3-(2-furanyl)propanamine hydrobromide	80
starch	59 mg
microcrystalline cellulose	59 mg
magnesium stearate	2 mg
Total	200 mg

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

FORMULATION 6

Suppositories each containing 225 mg of active ingredient ma be made as follows:

N-methyl-3-(2-naphthalenyloxy)-3-(2-thienyl)propanamine maleate	225 mg
saturated fatty acid glycerides	2,000 mg
Total	2,225 mg

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The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

FORMULATION 7

Suspensions each containing 50 mg of medicament per 5 ml dose are made as follows:

N,N-dimethyl-3-(4-chlorophenoxy)-3-(2-thienyl)propanamine succinate	50 mg
sodium carboxymethyl cellulose	50 mg
syrup	1.25 ml
benzoic acid solution	0.10 ml
flavor	q.v.
color	q.v.
purified water to total	5 ml

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

FORMULATION 8

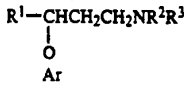
An intravenous formulation may be prepared as follows:

N-methyl-3-(1-naphthalenyloxy)-3-(3-methyl-2-thienyl)propanamine acetate	100 mg
isotonic saline	1000 ml

The solution of the above ingredients is administered intravenously at a rate of 1 ml per minute to a subject suffering from depression.

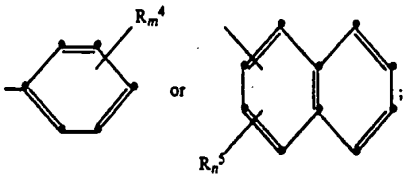
We claim:

1. A compound of the formula



wherein:

R^1 is thienyl, halothienyl, (C_1–C_4 alkyl)thienyl, furanyl, pyridyl or thiazolyl;



each of R^2 and R^3 independently is hydrogen or methyl;

each R^4 independently is halo, C_1–C_4 alkyl, C_1–C_3 alkoxy or trifluoromethyl;

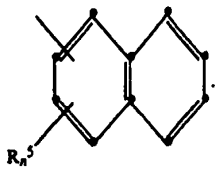
each R^5 independently is halo, C_1C_4 alkyl or trifluoromethyl;

m is 0, 1 or 2;

n is 0 or 1; and

the pharmaceutically acceptable acid addition salts thereof.

2. A compound of claim 1 wherein Ar is



3. A compound of claim 2 wherein R^1 is halothienyl.

4. A compound of claim 2 wherein R^1 is (C_1–C_4 alkyl)thienyl.

5. A compound of claim 2 wherein R^1 is furanyl.

6. A compound of claim 2 wherein R^1 is pyridyl.

7. A compound of claim 2 wherein R^1 is thiazolyl.

8. A compound of claim 2 wherein R^1 is thienyl.

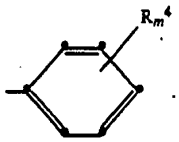
9. A compound of claim 8 wherein one of R^2 and R^3 is hydrogen and the other is methyl.

10. The compound of claim 10 which is N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine, and its pharmaceutically acceptable acid addition salts.

11. The compound of claim 11 which is the (+) stereoisomer.

12. The compound of claim 12 which is (+)-N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine maleate.

13. A compound of claim 1 wherein Ar is



14. A compound of claim 13 wherein R^1 is thienyl.

15. A compound of claim 13 wherein R^1 is halothienyl.

16. A compound of claim 13 wherein R^1 is (C_1–C_4 alkyl)thienyl.

17. A compound of claim 13 wherein R^1 is furanyl.

18. A compound of claim 13 wherein R^1 is pyridyl.

19. A compound of claim 13 wherein R^1 is thiazolyl.

20. A method for inhibiting serotonin uptake in mammals which comprises administering to a mammal requiring increased neurotransmission of serotonin a pharmaceutically effective amount of a compound of claim 1.

21. A method of claim 20 wherein R^1 is thienyl.

22. A method of claim 21 wherein the compound is N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine, and its pharmaceutically acceptable acid addition salts.

23. A method of claim 22 wherein the compound is (+)-N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)-propanamine, and its pharmaceutically acceptable acid addition salts.

24. A method for inhibiting norepinephrine uptake in mammals which comprises administering to a mammal requiring increased neurotransmission of norepinephrine a pharmaceutically effective amount of a compound of claim 1.

25. A method of claim 24 wherein one of R^2 and R^3 is hydrogen and the other is methyl.

26. A method of claim 25 wherein the compound is N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propana-

mine, and its pharmaceutically acceptable acid addition salts.

27. A method of claim 25 wherein the compound is (+)-N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)-propanamine, and its pharmaceutically acceptable acid addition salts.

28. A method of treating depression in humans comprising administering to a human suffering from depression an effective antidepressant dose of a compound of claim 1.

29. A method claim 28 wherein R^1 is thienyl.

30. A method of claim 29 wherein the compound is N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine, and its pharmaceutically acceptable acid addition salts.

31. A method of claim 30 wherein the compound is (+)-N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)-propanamine, and its pharmaceutically acceptable acid addition salts.

32. A method of treating anxiety in human comprising administering to a human suffering from anxiety an effective antianxiety dose of a compound of claim 1.

33. A method of claim 32 wherein R^1 is thienyl.

34. A method of claim 33 wherein the compound is N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine, and its pharmaceutically acceptable acid addition salts.

35. A method of claim 34 wherein the compound is (+)-N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)-propanamine, and its pharmaceutically acceptable acid addition salts.

36. A method of treating obesity in humans comprising administering to a human suffering from obesity an effective antiobesity dose of a compound of claim 1.

37. A method of claim 38 wherein R^1 is thienyl.

38. A method of claim 37 wherein the compound is N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine, and its pharmaceutically acceptable acid addition salts.

39. A method of claim 38 wherein the compound is (+)-N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)-propanamine, and its pharmaceutically acceptable acid addition salts.

40. A method of suppressing the desire of humans to smoke comprising administering to a human in need of such suppression an effective dose to relieve the desire to smoke of a compound of claim 1.

41. A method of claim 40 wherein R^1 is thienyl.

42. A method of claim 41 wherein the compound is N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine, and its pharmaceutically acceptable acid addition salts.

43. A method of claim 42 wherein the compound is (+)-N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)-propanamine, and its pharmaceutically acceptable acid addition salts.

44. A method of suppressing the desire of humans to consume alcohol comprising administering to a human in need of such suppression an effective dose to relieve the desire to consume alcohol of a compound of claim 1.

45. A method of claim 44 wherein R^1 is thienyl.

46. A method of claim 45 wherein the compound is N-methyl-3-(1-naphthalenyloxy)-3-2-thienyl)propanamine, and its pharmaceutically acceptable acid addition salts.

47. A method of claim 46 wherein the compound is (+)-N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)-propanamine, and its pharmaceutically acceptable acid addition salts.

48. A pharmaceutical formulation comprising a compound of claim 1 and a pharmaceutically acceptable carrier, diluent or excipient therefor.

49. A formulation of claim 48 wherein R^1 is thienyl.

50. A formulation of claim 49 wherein the compound is N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)-propanamine, and its pharmaceutically acceptable acid addition salts.

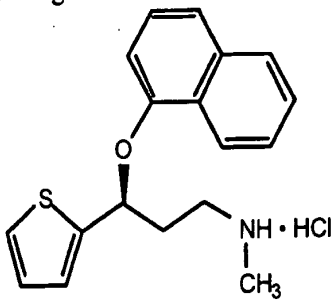
51. A formulation of claim 50 wherein the compound is (+)-N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)-propanamine, and its pharmaceutically acceptable acid.

* * * * *

CYMBALTA®
(duloxetine hydrochloride)

DESCRIPTION

Cymbalta® (duloxetine hydrochloride) is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. Its chemical designation is (+)-(*S*)-*N*-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride. The empirical formula is $C_{18}H_{19}NOS \cdot HCl$, which corresponds to a molecular weight of 333.88. The structural formula is:



Duloxetine hydrochloride is a white to slightly brownish white solid, which is slightly soluble in water.

Each capsule contains enteric-coated pellets of 22.4, 33.7, or 67.3 mg of duloxetine hydrochloride equivalent to 20, 30, or 60 mg of duloxetine, respectively. These enteric-coated pellets are designed to prevent degradation of the drug in the acidic environment of the stomach. Inactive ingredients include FD&C Blue No. 2, gelatin, hypromellose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, and triethyl citrate. The 20 and 60 mg capsules also contain iron oxide yellow.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Although the mechanism of the antidepressant action of duloxetine in humans is unknown, it is believed to be related to its potentiation of serotonergic and noradrenergic activity in the CNS. Preclinical studies have shown that duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine has no significant affinity for dopaminergic, adrenergic, cholinergic or histaminergic receptors *in vitro*. Duloxetine does not inhibit monoamine oxidase (MAO). Duloxetine undergoes extensive metabolism, but the major circulating metabolites have not been shown to contribute significantly to the pharmacologic activity of duloxetine.

Pharmacokinetics

Duloxetine has an elimination half-life of about 12 hours (range 8 to 17 hours) and its pharmacokinetics are dose proportional over the therapeutic range. Steady-state plasma concentrations are typically achieved after 3 days of dosing. Elimination of duloxetine is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP1A2.

Absorption and Distribution — Orally administered duloxetine hydrochloride is well absorbed. There is a median 2-hour lag until absorption begins (T_{lag}), with maximal plasma concentrations (C_{max}) of duloxetine occurring 6 hours post dose. Food does not affect the C_{max} of duloxetine, but delays the time to reach peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (AUC) by about 10%. There is a 3-hour delay in absorption and a one-third increase in apparent clearance of duloxetine after an evening dose as compared to a morning dose.

The apparent volume of distribution averages about 1640 L. Duloxetine is highly bound (>90%) to proteins in human plasma, binding primarily to albumin and α_1-acid glycoprotein. Plasma protein binding of duloxetine is not affected by renal or hepatic impairment.

Metabolism and Elimination — Biotransformation and disposition of duloxetine in humans have been determined following oral administration of ^{14}C-labeled duloxetine. Duloxetine comprises about 3% of the total radiolabeled material in the plasma, indicating that it undergoes extensive metabolism to numerous metabolites. The major biotransformation pathways for duloxetine involve oxidation of the naphthyl ring followed by conjugation and further oxidation. Both CYP2D6 and CYP1A2 catalyze the oxidation of the naphthyl ring *in vitro*. Metabolites found in plasma include 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate. Many additional metabolites have been identified in urine, some representing only minor pathways of elimination. Only trace (<1% of the dose) amounts of unchanged duloxetine are present in the urine. Most (about 70%) of the duloxetine dose appears in the urine as metabolites of duloxetine; about 20% is excreted in the feces.

Special Populations

Gender — Duloxetine's half-life is similar in men and women. Dosage adjustment based on gender is not necessary.

Age — The pharmacokinetics of duloxetine after a single dose of 40 mg were compared in healthy elderly females (65 to 77 years) and healthy middle-age females (32 to 50 years). There was no difference in the C_{max}, but the AUC of duloxetine was somewhat (about 25%) higher and the half-life about 4 hours longer in the elderly females. Population pharmacokinetic analyses suggest that the typical values for clearance decrease by approximately 1% for each year of age between 25 to 75 years of age; but age as a predictive factor only accounts for a small percentage of between-patient variability. Dosage adjustment based on the age of the patient is not necessary (*see* DOSAGE AND ADMINISTRATION).

Smoking Status — Duloxetine bioavailability (AUC) appears to be reduced by about one-third in smokers. Dosage modifications are not recommended for smokers.

Race — No specific pharmacokinetic study was conducted to investigate the effects of race.

Renal Insufficiency — Limited data are available on the effects of duloxetine in patients with end stage renal disease (ESRD). After a single 60 mg dose of duloxetine, C_{max} and AUC values were approximately 100% greater in patients with end stage renal disease receiving chronic intermittent hemodialysis than in subjects with normal renal function. The elimination half-life, however, was similar in both groups. The AUCs of the major circulating metabolites, 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate, largely excreted in urine, were approximately 7- to 9-fold higher and would be expected to increase further with multiple dosing. For this reason, duloxetine is not recommended for patients with ESRD (*see* DOSAGE AND ADMINISTRATION). Studies have not been conducted in patients with a moderate degree of renal dysfunction, but population PK analyses suggest that mild renal dysfunction has no significant effect on duloxetine apparent clearance.

Hepatic Insufficiency — Patients with clinically evident hepatic insufficiency have decreased duloxetine metabolism and elimination. After a single 20 mg dose of duloxetine, 6 cirrhotic patients with moderate liver impairment (Child-Pugh Class B) had a mean plasma duloxetine clearance about 15% that of age- and gender-matched healthy subjects, with a 5-fold increase in mean exposure (AUC). Although C_{max} was similar to normals in the cirrhotic patients, the half-life was about 3 times longer (*see* PRECAUTIONS). It is recommended that duloxetine not be administered to patients with any hepatic insufficiency (*see* DOSAGE AND ADMINISTRATION).

Drug-Drug Interactions (also see PRECAUTIONS, Drug Interactions)

Potential for Other Drugs to Affect Duloxetine

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Inhibitors of CYP1A2 — When duloxetine was co-administered with fluvoxamine, a potent CYP1A2 inhibitor, to male subjects (n = 14) the AUC was increased over 5-fold, the Cmax was increased about 2.5-fold, and duloxetine $t_{1/2}$ was increased approximately 3-fold. Other drugs that inhibit CYP1A2 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin.

Inhibitors of CYP2D6 — Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 would be expected to, and does, result in higher concentrations of duloxetine (*see* PRECAUTIONS, Drug Interactions).

Studies with Benzodiazepines —

Lorazepam — Under steady-state conditions, for duloxetine (60 mg Q 12 hours) and lorazepam (2 mg Q 12 hours) the pharmacokinetics of duloxetine were not affected by co-administration.

Temazepam — Under steady-state conditions, for duloxetine (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of duloxetine were not affected by co-administration.

Potential for Duloxetine to Affect Other Drugs

Drugs Metabolized by CYP1A2 — *In vitro* drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity. Therefore, an increase in the metabolism of CYP1A2 substrates (e.g., theophylline, caffeine) resulting from induction is not anticipated, although clinical studies of induction have not been performed. Although duloxetine is an inhibitor of the CYP1A2 isoform in *in vitro* studies, the pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine (60 mg BID). Duloxetine is thus unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates.

Drugs Metabolized by CYP2D6 — Duloxetine is a moderate inhibitor of CYP2D6 and increases the AUC and C_{max} of drugs metabolized by CYP2D6 (*see* PRECAUTIONS). Therefore, co-administration of duloxetine with other drugs that are extensively metabolized by this isozyme and that have a narrow therapeutic index should be approached with caution (*see* PRECAUTIONS, Drug Interactions).

Drugs Metabolized by CYP2C9 — Duloxetine does not inhibit the *in vitro* enzyme activity of CYP2C9. Inhibition of the metabolism of CYP2C9 substrates is therefore not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP3A — Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. Therefore, an increase or decrease in the metabolism of CYP3A substrates (e.g., oral contraceptives and other steroidal agents) resulting from induction or inhibition is not anticipated, although clinical studies have not been performed.

Studies with Benzodiazepines —

Lorazepam — Under steady-state conditions, for duloxetine (60 mg Q 12 hours) and lorazepam (2 mg Q 12 hours) the pharmacokinetics of lorazepam were not affected by co-administration.

Temazepam — Under steady-state conditions, for duloxetine (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of temazepam were not affected by co-administration.

Drugs Highly Bound to Plasma Protein — Because duloxetine is highly bound to plasma protein, administration of duloxetine to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events.

CLINICAL STUDIES

The efficacy of Cymbalta as a treatment for depression was established in 4 randomized, double-blind, placebo-controlled, fixed-dose studies in adult outpatients (18 to 83 years) meeting DSM-IV criteria for major depression. In 2 studies, patients were randomized to Cymbalta 60 mg once daily (N=123 and N=128, respectively) or placebo (N=122 and N=139, respectively) for 9 weeks; in the third study, patients were randomized to Cymbalta 20 or 40 mg twice daily (N=86 and N=91, respectively) or placebo (N=89) for 8 weeks; in the fourth study, patients were randomized to Cymbalta 40 or 60 mg twice daily (N=95 and N=93, respectively) or placebo (N=93) for 8 weeks. There is no evidence that doses greater than 60 mg/day confer any additional benefit.

In all 4 studies, Cymbalta demonstrated superiority over placebo as measured by improvement in the 17-item Hamilton Depression Rating Scale (HAMD-17) total score.

Analyses of the relationship between treatment outcome and age, gender, and race did not suggest any differential responsiveness on the basis of these patient characteristics.

INDICATIONS AND USAGE

Cymbalta is indicated for the treatment of major depressive disorder (MDD).

The efficacy of Cymbalta has been established in 8- and 9-week placebo-controlled trials of outpatients who met DSM-IV diagnostic criteria for major depressive disorder (*see* CLINICAL STUDIES).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or a suicide attempt or suicidal ideation.

The effectiveness of Cymbalta in hospitalized patients with major depressive disorder has not been studied.

The effectiveness of Cymbalta in long-term use for major depressive disorder, that is, for more than 9 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use Cymbalta for extended periods should periodically evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Hypersensitivity

Duloxetine is contraindicated in patients with a known hypersensitivity to the product.

Monoamine Oxidase Inhibitors

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (*see* WARNINGS).

Uncontrolled Narrow-Angle Glaucoma

In clinical trials, duloxetine use was associated with an increased risk of mydriasis; therefore, its use should be avoided in patients with uncontrolled narrow-angle glaucoma.

WARNINGS

Clinical Worsening and Suicide Risk — Patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Although there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients, a causal role for antidepressants in inducing such

behaviors has not been established. **Nevertheless, patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases.** Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and nonpsychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and nonpsychiatric disorders.

The following symptoms – anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania – have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Prescriptions for Cymbalta should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (*see* PRECAUTIONS *and* DOSAGE AND ADMINISTRATION, Discontinuing Cymbalta (duloxetine hydrochloride), for a description of the risks of discontinuation of Cymbalta).

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Cymbalta is not approved for use in treating bipolar depression.

Monoamine Oxidase Inhibitors (MAOI) — In patients receiving a serotonin reuptake inhibitor in combination with a monoamine oxidase inhibitor, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued serotonin reuptake inhibitors and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. The effects of combined use of duloxetine and MAOIs have not been evaluated in humans or animals. Therefore, because duloxetine is an inhibitor of both

serotonin and norepinephrine reuptake, it is recommended that duloxetine not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping duloxetine before starting an MAOI.

PRECAUTIONS

General

Hepatotoxicity

Duloxetine increases the risk of elevation of serum transaminase levels. Liver transaminase elevations resulted in the discontinuation of 0.3% (27/8454) of duloxetine-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In controlled trials in MDD, elevations of alanine transaminase (ALT) to > 3 times the upper limit of normal occurred in 0.9% (8/930) of duloxetine-treated patients and in 0.3% (2/652) placebo-treated patients. In the full cohort of placebo controlled trials in any indication, 1% (39/3732) of duloxetine-treated patients had a > 3 times the upper limit of normal elevation of ALT compared to 0.2% (6/2568) of placebo-treated patients. In placebo-controlled studies using a fixed dose design, there was evidence of a dose-response relationship for ALT and AST elevation of > 3 times the upper limit of normal and > 5 times the upper limit of normal, respectively.

The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally recognized as an important predictor of severe liver injury. Three duloxetine patients had elevations of transaminases and bilirubin, but also had elevation of alkaline phosphatase, suggesting an obstructive process; in these patients, there was evidence of heavy alcohol use and this may have contributed to the abnormalities seen. Two placebo-treated patients also had transaminase elevations with elevated bilirubin. Because it is possible that duloxetine and alcohol may interact to cause liver injury, duloxetine should ordinarily not be prescribed to patients with substantial alcohol use.

Effect on Blood Pressure —In clinical trials, duloxetine treatment was associated with mean increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic and an increase in the incidence of at least one measurement of systolic blood pressure over 140 mm Hg compared to placebo. Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment (*see* ADVERSE REACTIONS, Vital Sign Changes).

Activation of Mania/Hypomania — In placebo-controlled trials in patients with major depressive disorder, activation of mania or hypomania was reported in 0.1% (1/1139) of duloxetine-treated patients and 0.1% (1/777) of placebo-treated patients. Activation of mania/hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of major depressive disorder. As with these other agents, duloxetine should be used cautiously in patients with a history of mania.

Seizures — Duloxetine has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials in patients with major depressive disorder, seizures occurred in 0.1% (1/1139) of patients treated with duloxetine and 0% (0/777) of patients treated with placebo. Like other drugs effective in the treatment of major depressive disorder, duloxetine should be prescribed with care in patients with a history of a seizure disorder.

Controlled Narrow-Angle Glaucoma — In clinical trials, duloxetine was associated with an increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma. (see CONTRAINDICATIONS, Uncontrolled Narrow-Angle Glaucoma).

Discontinuation of Treatment with Cymbalta- Discontinuation symptoms have been systematically evaluated in patients taking Cymbalta. Following abrupt discontinuation in placebo-controlled clinical trials of up to 9-weeks duration, the following symptoms occurred at a rate greater than or equal to 2% and at a significantly higher rate in duloxetine-treated patients

compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; and nightmare.

During marketing of other SSRIs and SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g. paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

Use in Patients with Concomitant Illness — Clinical experience with duloxetine in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of duloxetine's enteric coating. As duloxetine is rapidly hydrolyzed in acidic media to naphthol, caution is advised in using duloxetine in patients with conditions that may slow gastric emptying.

Duloxetine has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. However, the electrocardiograms of 321 patients who received duloxetine in placebo-controlled clinical trials and had qualitatively normal ECGs at baseline were evaluated; duloxetine was not associated with the development of clinically significant ECG abnormalities (*see* ADVERSE REACTIONS, Electrocardiogram Changes).

Increased plasma concentrations of duloxetine, and especially of its metabolites, occur in patients with ESRD and severe renal impairment (creatinine clearance <30 mL/min). For this reason, duloxetine is not recommended for patients with ESRD (*see* CLINICAL PHARMACOLOGY *and* DOSAGE AND ADMINISTRATION).

Markedly increased exposure to duloxetine occurs in patients with hepatic insufficiency and duloxetine should not be administered to these patients (*see* CLINICAL PHARMACOLOGY *and* DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Cymbalta.

Patients and their families should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's physician, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Duloxetine should be swallowed whole and should not be chewed or crushed, nor should the contents be sprinkled on food or mixed with liquids. All of these might affect the enteric coating.

Any psychoactive drug may impair judgment, thinking, or motor skills. Although in controlled studies duloxetine has not been shown to impair psychomotor performance, cognitive function, or memory, it may be associated with sedation. Therefore, patients should be cautioned about operating hazardous machinery including automobiles, until they are reasonably certain that duloxetine therapy does not affect their ability to engage in such activities.

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter medications, since there is a potential for interactions.

Although duloxetine does not increase the impairment of mental and motor skills caused by alcohol, use of duloxetine concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, duloxetine should ordinarily not be prescribed for patients with substantial alcohol use.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast-feeding.

While patients may notice improvement with duloxetine therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions (also see CLINICAL PHARMACOLOGY, Drug-Drug Interactions)

Potential for Other Drugs to Affect Duloxetine

Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Inhibitors of CYP1A2 — Concomitant use of duloxetine with fluvoxamine, an inhibitor of CYP1A2, results in approximately a 6-fold increase in AUC and about a 2.5-fold increase in C_{max} of duloxetine. Some quinolone antibiotics would be expected to have similar effects and these combinations should be avoided.

Inhibitors of CYP2D6 — Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 may result in higher concentrations of duloxetine. Paroxetine (20 mg QD) increased the concentration of duloxetine (40 mg QD) by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (e.g., fluoxetine, quinidine).

Potential for Duloxetine to Affect Other Drugs

Drugs Metabolized by CYP1A2 — *In vitro* drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity, and it is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates. (*see* CLINICAL PHARMACOLOGY, Drug Interactions).

Drugs Metabolized by CYP2D6 — Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg BID) in conjunction with a single 50 mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. Therefore, co-administration of duloxetine with other drugs that are extensively metabolized by this isozyme and which have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with duloxetine. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, duloxetine and thioridazine should not be co-administered.

Drugs Metabolized by CYP3A — Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. (*see* CLINICAL PHARMACOLOGY, Drug Interactions).

Duloxetine May Have a Clinically Important Interaction with the Following Other Drugs:

Alcohol — When duloxetine and ethanol were administered several hours apart so that peak concentrations of each would coincide, duloxetine did not increase the impairment of mental and motor skills caused by alcohol.

In the duloxetine clinical trials database, three duloxetine treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen. (*see* PRECAUTIONS, Hepatotoxicity).

CNS Acting Drugs — Given the primary CNS effects of duloxetine, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action.

Potential for Interaction with Drugs that Affect Gastric Acidity — Duloxetine has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, duloxetine, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of duloxetine with aluminum- and magnesium-containing antacids (51 mEq) or duloxetine with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption.

Monoamine Oxidase Inhibitors — *See* CONTRAINDICATIONS *and* WARNINGS.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Duloxetine was administered in the diet to mice and rats for 2 years.

In female mice receiving duloxetine at dietary doses of approximately 140 mg/kg/day (11 times the maximum recommended human dose [MRHD] of 60 mg/day on a mg/m^2 basis), there was an increased incidence of hepatocellular adenomas and carcinomas; the no-effect level was approximately 50 mg/kg (4 times the MRHD on a mg/m^2 basis). Tumor incidence was not increased in male mice receiving duloxetine at dietary doses up to approximately 100 mg/kg/day (8 times the MRHD on a mg/m^2 basis).

In rats, dietary doses of duloxetine up to approximately 27 mg/kg/day in females (4 times the MRHD on a mg/m^2 basis) or approximately 36 mg/kg/day in males (6 times the MRHD on a mg/m^2 basis) did not increase the incidence of tumors.

Mutagenesis — Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*.

Impairment of Fertility — Duloxetine administered orally to either male or female rats prior to and throughout mating at daily doses up to 45 mg/kg (7 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) did not alter mating or fertility.

Pregnancy

Pregnancy-Nonteratogenic Effects

Neonates exposed to SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS, Monoamine Oxidase Inhibitors). When treating a pregnant woman with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

Pregnancy Category C — In animal reproduction studies, duloxetine has been shown to have adverse effects on embryo/fetal and postnatal development.

When duloxetine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 and 15 times the maximum recommended human dose [MRHD] on a mg/m^2 basis, in rats and rabbits, respectively). However, fetal weights were decreased at this dose, with a no-effect level of 10 mg/kg (2 and 3 times the MRHD on a mg/m^2 basis, in rats and rabbits, respectively).

When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period were decreased following maternal exposure to 30 mg/kg/day (5 times the MRHD on a mg/m^2 basis), with a no-effect level of 10 mg/kg. Furthermore, behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity, were observed in pups following maternal exposure to 30 mg/kg/day. Post-weaning growth and reproductive performance of the progeny were not affected adversely by maternal duloxetine treatment.

There are no adequate and well-controlled studies in pregnant women; therefore, duloxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of duloxetine on labor and delivery in humans is unknown. Duloxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Duloxetine and/or its metabolites are excreted into the milk of lactating rats. It is unknown whether or not duloxetine and/or its metabolites are excreted into human milk, but nursing while on duloxetine is not recommended.

Pediatric Use

Safety and efficacy in pediatric patients have not been established (*see* WARNINGS, Clinical Worsening and Suicide Risk).

Geriatric Use

Of the 2418 patients in clinical studies of duloxetine, 5.9% (143) were 65 years of age or over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Duloxetine has been evaluated for safety in 2418 patients diagnosed with major depressive disorder who participated in multiple-dose premarketing trials, representing 1099 patient-years of exposure. Among these 2418 duloxetine-treated patients, 1139 patients participated in eight 8- or 9-week, placebo-controlled trials at doses ranging from 40 to 120 mg/day, while the remaining 1279 patients were followed for up to 1 year in an open-label safety study using flexible doses from 80 to 120 mg/day. Two placebo-controlled studies with doses of 80 and 120 mg/day had 6-month maintenance extensions. Of these 2418 patients, 993 duloxetine-treated patients were exposed for at least 180 days and 445 duloxetine-treated patients were exposed for at least 1 year. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Clinical investigators recorded adverse events using descriptive terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing adverse events, grouping similar types of events into a smaller number of standardized event categories is

necessary. In the tables and tabulations that follow, MedDRA terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. Events reported during the studies were not necessarily caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of causality.

The cited figures provide the prescriber with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied. The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators.

Adverse Events Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials

Approximately 10% of the 1139 patients who received duloxetine in the placebo-controlled trials discontinued treatment due to an adverse event, compared with 4% of the 777 patients receiving placebo. Nausea (duloxetine 1.4%, placebo 0.1%) was the only common adverse event reported as reason for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the duloxetine-treated patients and at a rate of at least twice that of placebo).

Adverse Events Occurring at an Incidence of 2% or More Among Duloxetine-Treated Patients in Placebo-Controlled Trials

Table 1 gives the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with duloxetine in the acute phase of MDD placebo-controlled trials and with an incidence greater than placebo. The most commonly observed adverse events in duloxetine-treated MDD patients (incidence of 5% or greater and at least twice the incidence in placebo patients) were: nausea; dry mouth; constipation; decreased appetite; fatigue; somnolence; and increased sweating (*see* Table 1).

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Table 1: Treatment-Emergent Adverse Events Incidence in Placebo-Controlled Trials[1]

System Organ Class / Adverse Event	Percentage of Patients Reporting Event	
	Duloxetine (N=1139)	Placebo (N=777)
Gastrointestinal Disorders		
Nausea	20	7
Dry mouth	15	6
Constipation	11	4
Diarrhea	8	6
Vomiting	5	3
Metabolism and Nutrition Disorders		
Appetite decreased[2]	8	2
Investigations		
Weight decreased	2	1
General Disorders and Administration Site Conditions		
Fatigue	8	4
Nervous System Disorders		
Dizziness	9	5
Somnolence	7	3
Tremor	3	1
Skin and Subcutaneous Tissue Disorders		
Sweating increased	6	2
Vascular Disorders		
Hot flushes	2	1
Eye Disorders		
Vision blurred	4	1
Psychiatric Disorders		
Insomnia[3]	11	6
Anxiety	3	2
Libido decreased	3	1
Orgasm abnormal[4]	3	1
Reproductive System and Breast Disorders		
Erectile dysfunction[5]	4	1
Ejaculation delayed[5]	3	1
Ejaculatory dysfunction[5, 6]	3	1

[1]Events reported by at least 2% of patients treated with duloxetine and more often with placebo. The following events were reported by at least 2% of patients treated with duloxetine and had an incidence equal to or less than placebo: upper abdominal pain, palpitations, dyspepsia, back pain, arthralgia, headache, pharyngitis, cough, nasopharyngitis, and upper respiratory tract infection.
[2]Term includes anorexia.
[3]Term includes middle insomnia.
[4]Term includes anorgasmia.
[5]Male patients only.
[6]Term includes ejaculation disorder and ejaculation failure.

Adverse events seen in men and women were generally similar except for effects on sexual function (described below). Clinical studies of CYMBALTA did not suggest a difference in adverse event rates in people over or under 65 years of age. There were too few non-Caucasian patients studied to determine if these patients responded differently from Caucasian patients.

Effects on Male and Female Sexual Function

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. Table 2 displays the incidence of sexual side effects spontaneously reported by at least 2% of either male or female patients taking duloxetine in placebo-controlled trials.

Table 2: Treatment-Emergent Sexual Dysfunction-Related Adverse Events Incidence in Placebo-Controlled Trials[1]

Adverse Event	Percentage of Patients Reporting Event			
	% Male Patients		% Female Patients	
	Duloxetine (N=378)	Placebo (N=247)	Duloxetine (N=761)	Placebo (N=530)
Orgasm abnormal[2]	4	1	2	0
Ejaculatory dysfunction[3]	3	1	NA	NA
Libido decreased	6	2	1	0
Erectile dysfunction	4	1	NA	NA
Ejaculation delayed	3	1	NA	NA

[1]Events reported by at least 2% of patients treated with duloxetine and more often than with placebo.
[2]Term includes anorgasmia.
[3]Term includes ejaculation disorder and ejaculation failure.
NA= Not applicable.

Because adverse sexual events are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 4 placebo-controlled trials. In these trials, as shown in Table 3 below, patients treated with duloxetine experienced significantly more sexual dysfunction, as measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference occurred only in males. Males treated with duloxetine experienced more difficulty with ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual dysfunction on duloxetine than on placebo as measured by ASEX total

score. These studies did not, however, include an active control drug with known effects on female sexual dysfunction, so that there is no evidence that its effects differ from other antidepressants. Negative numbers signify an improvement from a baseline level of dysfunction, which is commonly seen in depressed patients. Physicians should routinely inquire about possible sexual side effects.

Table 3: Mean Change in ASEX Scores by Gender in Placebo-Controlled Trials

	Male Patients		Female Patients	
	Duloxetine (n=175)	Placebo (n=83)	Duloxetine (n=241)	Placebo (n=126)
ASEX Total (Items 1-5)	0.56*	-1.07	-1.15	-1.07
Item 1 – Sex drive	-0.07	-0.12	-0.32	-0.24
Item 2 – Arousal	0.01	-0.26	-0.21	-0.18
Item 3 – Ability to achieve erection (men); Lubrication (women)	0.03	-0.25	-0.17	-0.18
Item 4 – Ease of reaching orgasm	0.40**	-0.24	-0.09	-0.13
Item 5 – Orgasm satisfaction	0.09	-0.13	-0.11	-0.17

n=Number of patients with non-missing change score for ASEX total.
*p=0.013 versus placebo.
**p<0.001 versus placebo.

Urinary Hesitation

Duloxetine is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with duloxetine, consideration should be given to the possibility that they might be drug-related.

Laboratory Changes

Duloxetine treatment, for up to 9-weeks in placebo-controlled clinical trials, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in duloxetine-treated patients when compared with placebo-treated patients (*see* PRECAUTIONS).

Vital Sign Changes

Duloxetine treatment, for up to 9-weeks in placebo-controlled clinical trials of 40 to 120 mg daily doses caused increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic compared to placebo and an increase in the incidence of at least one measurement of systolic blood pressure over 140 mm Hg (*see* PRECAUTIONS).

Duloxetine treatment, for up to 9-weeks in placebo-controlled clinical trials caused a small increase in heart rate compared to placebo of about 2 beats per minute.

Weight Changes

In placebo-controlled clinical trials, patients treated with duloxetine for up to 9-weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients.

Electrocardiogram Changes

Electrocardiograms were obtained from 321 duloxetine-treated patients with major depressive disorder and 169 placebo-treated patients in clinical trials lasting up to 8-weeks. The rate-corrected QT (QTc) interval in duloxetine-treated patients did not differ from that seen in placebo-

treated patients. No clinically significant differences were observed for QT, PR, and QRS intervals between duloxetine-treated and placebo-treated patients.

Other Adverse Events Observed During the Premarketing Evaluation of Duloxetine

Following is a list of modified MedDRA terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with duloxetine at multiple doses throughout the dose range studied during any phase of a trial within the premarketing database. The events included are those not already listed elsewhere in ADVERSE REACTIONS and not considered in the WARNINGS and PRECAUTIONS sections, that were reported with an incidence of greater than or equal to 0.05%, are not common as background events and were considered possibly drug related (e.g., because of the drug's pharmacology) or potentially important.

It is important to emphasize that, although the events reported occurred during treatment with duloxetine, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Blood and Lymphatic System Disorders — *Infrequent:* anemia, leukopenia, increased white blood cell count, lymphadenopathy, and thrombocytopenia.
Gastrointestinal Disorders — *Frequent:* gastritis; *Infrequent:* blood in stool, colitis, dysphagia, esophageal stenosis acquired, gastric ulcer, gingivitis, irritable bowel syndrome, and lower abdominal pain.
Psychiatric Disorders — *Frequent:* initial insomnia; irritability, lethargy, nervousness, nightmare, restlessness, and sleep disorder; *Infrequent:* completed suicide, mania, mood swings, pressure of speech, sluggishness, and suicide attempt.
Renal and Urinary Disorders — *Frequent:* dysuria; *Infrequent:* micturition urgency,-urinary hesitation, urinary incontinence, urinary retention, and urine flow decreased.
Skin and Subcutaneous Tissue Disorders — *Frequent:* night sweats, pruritus, and rash; *Infrequent:* acne, alopecia, cold sweat, ecchymosis, eczema, erythema, face edema, increased tendency to bruise, and photosensitivity reaction.
Vascular Disorders —*Infrequent:* -peripheral edema and phlebitis.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Duloxetine is not a controlled substance.

Physical and Psychological Dependence

In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential. In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats.

While duloxetine has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to

predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of duloxetine (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

There is limited clinical experience with duloxetine overdose in humans. In premarketing clinical trials, as of November 2002, no cases of fatal acute overdose of duloxetine have been reported. Four non-fatal acute ingestions of duloxetine (300 to 1400 mg), alone or in combination with other drugs, have been reported.

Management of Overdose

There is no specific antidote to duloxetine. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug effective in the treatment of major depressive disorder.

An adequate airway, oxygenation, and ventilation should be assured, and cardiac rhythm and vital signs should be monitored. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients.

Activated charcoal may be useful in limiting absorption of duloxetine from the gastrointestinal tract. Administration of activated charcoal has been shown to decrease AUC and C_{max} by an average of one-third, although some subjects had a limited effect of activated charcoal. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be beneficial.

In managing overdose, the possibility of multiple drug involvement should be considered. A specific caution involves patients who are taking or have recently taken duloxetine and might ingest excessive quantities of a TCA. In such a case, decreased clearance of the parent tricyclic and/or its active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (*see* PRECAUTIONS, Drug Interactions). The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

Initial Treatment

Cymbalta should be administered at a total dose of 40 mg/day (given as 20 mg BID) to 60 mg/day (given either once a day or as 30 mg BID) without regard to meals.

There is no evidence that doses greater than 60 mg/day confer any additional benefit.

Maintenance/Continuation/Extended Treatment

It is generally agreed that acute episodes of major depression require several months or longer of sustained pharmacologic therapy. There is insufficient evidence available to answer the question of how long a patient should continue to be treated with Cymbalta. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

Special Populations

Dosage for Renally Impaired Patients —Cymbalta is not recommended for patients with end stage renal disease (ESRD) (*see* CLINICAL PHARMACOLOGY).

Dosage for Hepatically Impaired Patients —It is recommended that Cymbalta not be administered to patients with any hepatic insufficiency (*see* CLINICAL PHARMACOLOGY *and* PRECAUTIONS).

Dosage for Elderly Patients — No dose adjustment is recommended for elderly patients on the basis of age. As with any drugs effective in the treatment of major depressive disorder, however, caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

Treatment of Pregnant Women During the Third Trimester-Neonates exposed to SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS). When treating pregnant women with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Cymbalta in the third trimester.

Discontinuing Cymbalta (duloxetine hydrochloride)

Symptoms associated with discontinuation of Cymbalta and other SSRIs and SNRIs, have been reported (see **PRECAUTIONS**). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

Switching Patients to or from a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Cymbalta. In addition, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI (*see* CONTRAINDICATIONS *and* WARNINGS).

HOW SUPPLIED

Cymbalta® (duloxetine hydrochloride) capsules are available in 20, 30, and 60 mg strengths.

The 20 mg* capsule has an opaque green body and cap, and is imprinted with "20 mg" on the body and "LILLY 3235" on the cap:

NDC 0002-3235-30 (PU3235) – Bottles of 30
NDC 0002-3235-60 (PU3235) – Bottles of 60
NDC 0002-3235-90 (PU3235) – Bottles of 90
NDC 0002-3235-71 (PU3235) – Bottles of 180
NDC 0002-3235-04 (PU3235) – Bottles of 1000
NDC 0002-3235-33 (PU3235) – (ID†100) Blisters

The 30 mg* capsule has an opaque white body and opaque blue cap, and is imprinted with "30 mg" on the body and "LILLY 3240" on the cap:

NDC 0002-3240-30 (PU3240) – Bottles of 30
NDC 0002-3240-90 (PU3240) – Bottles of 90
NDC 0002-3240-04 (PU3240) – Bottles of 1000
NDC 0002-3240-33 (PU3240) – (ID†100) Blisters

The 60 mg* capsule has an opaque green body and opaque blue cap, and is imprinted with "60 mg" on the body and "LILLY 3237" on the cap:

NDC 0002-3237-30 (PU3237) – Bottles of 30
NDC 0002-3237-90 (PU3237) – Bottles of 90
NDC 0002-3237-04 (PU3237) – Bottles of 1000
NDC 0002-3237-33 (PU3237) – (ID†100) Blisters

---

*equivalent to duloxetine base
†Identi-Dose® (unit dose medication, Lilly)

Store at 25°C (77°F); excursions permitted to 15-30°C (59°-86°F) [see USP Controlled Room Temperature].

Literature issued Month dd, yyyy

Eli Lilly and Company
Indianapolis, IN 46285, USA

www.Cymbalta.com

PRINTED IN USA

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United States Patent and Trademark Office

Maintenance Fee Statement

5023269

ATTENTION: PATENT DIVISION
ELI LILLY AND COMPANY
LILLY CORPORATE CENTER
INDIANAPOLIS IN 46285

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,023,269	1553	3100	0	07/499,940	06/11/91	03/27/90	12	NO	PAID

000000

ITEM NBR	ATTY DKT NUMBER
1	X7042B

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,023,269

DATED : June 11, 1991

INVENTOR(S) : Joseph H. Krushinski, Jr., David W. Robertson, and David T. Wong

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

Column 1, line 40, insert "Ar is" after "thiazolyl;"
Column 2, line 23, change "C_1-C_4 alkyl)thienyl" to — (C_1-C_4 alkyl)thienyl —
Column 3, line 49, change "N-Methyl-3-(4-met naphthalenyloxy)-" to — N-Methyl-3-(4-methyl-1-naphthalenyloxy)- —
Column 3, line 53, change "N,N-Dimethyl-3-6-" to — N,N-Dimethyl-3-(6- —
Column 4, line 35, change "3-4-(Trifluoromethyl)phenoxy" to — 3-[4-(Trifluoromethyl)phenoxy —
Column 6, line 30, change "$C_0H_{14}ClNOS$" to — $C_9H_{14}ClNOS$ —
Column 6, line 34, change "(2-thenyl)" to — (2-thienyl) —
Column 6, line 49, change "$C_9H_{19}NOS$" to — $C_9H_{15}NOS$ —
Column 8, line 51, change "42.S3" to — 42.53 —
Column 9, line 17, change "S6.04" to — 56.04 —
Column 9, line 52, change "S8.34" to — 58.34 —
Column 11, line 37, change "b4.49" to — 64.49 —
Column 13, line 5, change "(2thienyl)-" to — (2-thienyl) —
Column 13, line 23, change "(2thiazolyl)-" to — (2-thiazolyl) —
Column 13, line 47, change "N-Methyl-3-(-naphthalenyloxy)" to — N-Methyl-3-(1-naphthalenyloxy) —
Column 29, line 55, insert "Ar is" after "thiazolyl;"
Column 29, line 63, change "C_1C_4" to — C_1-C_4 —
Column 30, line 20, change "claim 10" to — claim 9 —
Column 30, line 23, change "claim 11" to — claim 10 —
Column 30, line 25, change "claim 12" to — claim 11 —

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,023,269

DATED : June 11, 1991

INVENTOR(S) : Joseph H. Krushinski, Jr., et al.

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

Column 31, line 35, change "claim 38" to -- claim 36 --.

Signed and Sealed this

Tenth Day of November, 1992

Attest:

Attesting Officer

DOUGLAS B. COMER

Acting Commissioner of Patents and Trademarks

EXHIBIT 5

N92
28

April 29, 1992

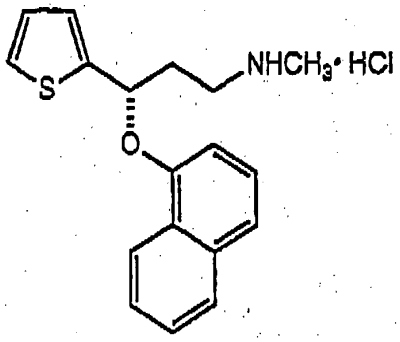
STATEMENT ON A NONPROPRIETARY NAME ADOPTED BY THE USAN COUNCIL:

USAN (EE-18)	DULOXETINE HYDROCHLORIDE
PRONUNCIATION	dū lŏks' ĕ tēn
THERAPEUTIC CLAIM	antidepressant
CHEMICAL NAMES	

1) (S)-N-methyl-γ-(1-naphthalenyloxy)-2-thiophenepropanamine hydrochloride

2) (+)-(S)-N-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride

STRUCTURAL FORMULA



MOLECULAR FORMULA	$C_{18}H_{19}NOS \cdot HCl$
MOLECULAR WEIGHT	236.36
TRADEMARK	Unknown as yet
MANUFACTURER	Eli Lilly and Company
CODE DESIGNATION	LY248686 HCl
CAS REGISTRY NUMBER	136434-34-9
WHO NUMBER	7012

SVF/gat

EXHIBIT 6

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

COPY

June 3, 1991

Food and Drug Administration
Center for Drugs and Biologics
Central Document Room
12420 Parklawn Drive
Room 2-14
Rockville, Maryland 20852

Re: Initial IND for LY248686 Hydrochloride
Serial Number 000

We are submitting herewith a new IND for Compound LY248686 hydrochloride, which is a potent inhibitor of both serotonin and norepinephrine. As discussed in the introduction section of this IND, LY248686 has the potential for treating various forms of depression.

Please call me at (317) 276-2574 or Dr. Al Webber at (317) 276-4255 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

M. W. Talbott, Ph.D.
Director
Medical Regulatory Affairs

Enc.

cc: Mr. P. David - (cover letter and two copies of Vol. 1, without M & C data)

sm

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

Form Approved: OMB No. 0910-0014
Expiration Date: November 30, 1987.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
ELI LILLY AND COMPANY

2. DATE OF SUBMISSION
June 3, 1991

3. ADDRESS *(Number, Street, City, State and Zip Code)*
Lilly Corporate Center
Indianapolis, Indiana 46285

4. TELEPHONE NUMBER *(Include Area Code)*
(317) 276-2000

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Compound LY248686

6. IND NUMBER *(If previously assigned)*

7. INDICATION(S) *(Covered by this submission)*
NA

8. PHASE (S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ■ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9 LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION.

DMFs - 980, 1594, 1936, 5919, 1591, 4343, 8260, 4428, 2256, 4164, 2229, 984, 4007, 1378, 2880, 1466

10. SERIAL NUMBER: 000

IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (i.e., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

■ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)

PROTOCOL AMENDMENT(S):
- ☐ NEW PROTOCOL
- ☐ CHANGE IN PROTOCOL
- ☐ NEW INVESTIGATOR

NFORMATION AMENDMENT(S):
- ☐ CHEMISTRY/MICROBIOLOGY
- ☐ PHARMACOLOGY/TOXICOLOGY
- ☐ CLINICAL

IND SAFETY REPORT(S):
- ☐ INITIAL WRITTEN REPORT
- ☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ RESPONSE TO CLINICAL HOLD

☐ GENERAL CORRESPONDENCE ☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER _____ *(Specify)*

Refer to the designated CFR citations before checking any of the following:

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT:

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 37,071

Date JUN 10 1991

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
Att: M.W. Talbott, Ph.D., Director
Medical Regulatory Affairs

Dear Sir or Madam:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to Section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 37,071

Sponsor: Eli Lilly and Company

Name of Drug: LY248686 HCL

Date of Submission: June 3,1991

Date of Receipt: June 4,1991

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

MWT JUN 14 1991

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations implementing that Act (Title 21 of the Code of Federal Regulations). Those responsibilities include reporting any adverse experience associated with use of the drug that is both serious and unexpected to the FDA as soon as possible and in no event later than 10 working days after initial receipt of the information and reporting any unexpected fatal or life-threatening experience to the FDA by telephone no later than 3 working days after receipt of the information (21 CFR 312.32), and submission of annual progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-120)
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this IND, please contact Mr. Paul David, Consumer Safety Officer (301) 443-3504.

Sincerely yours,

John Purvis

John Purvis
Supervisory Consumer Safety Officer
Division of Neuropharmacologic Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research

cc: Original IND - pink
HFD-120 - yellow
HFD-120/CSO - green

IND ACKNOWLEDGEMENT

IND

Lilly

www.lilly.com

Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.

Phone 317 276 2000

November 12, 2001

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

Original Application NDA 21-427

Re: NDA 21-427, Cymbalta™ (LY248686, duloxetine hydrochloride)- Initial Submission

This letter accompanies submission of an original New Drug Application (NDA) for Cymbalta, a norepinephrine and serotonin reuptake inhibitor, for the indication of Major Depressive Disorder. This NDA is submitted in electronic format according to the January 1999 "Guidance for Industry Providing Regulatory Submissions in Electronic Format-NDAs." As specified in this Guidance, a paper review copy containing 141 Volumes is included in this submission.

Substantial evidence of efficacy supporting the use of Cymbalta for the treatment of Major Depressive Disorder (defined in the DSM IV) is provided in the enclosed application based on six primary randomized, double blind, placebo controlled studies (F1Y-MC-HMAQa, F1Y-MC-HMAQb, F1Y-MC-HMATa, F1Y-MC-HMATb, F1Y-MC-HMBHa, F1Y-MC-HMBHb).

Lilly has met with FDA personnel on a number of occasions to discuss the development program for Cymbalta since the filing of IND 38,838 for depression on 2/5/92. The interactions and agreement from those meetings are outlined in the Application Summary, section 3.H.2.1, Regulatory History and Agreements.

The complete NDA is provided in electronic format on digital tape. The submission size is approximately 6.1 gigabytes. All electronic media have been checked by representatives of Lilly Information Technology and have been verified to be free of known viruses. The virus checking software was Norton AntiVirus, corporate edition version 7.51.847; virus definition version 31031b dated 10/31/2001.

COPY

The User Fee of $309,647.00 for this submission has been paid under User Fee number 4218. Form 3397 has been provided.

A debarment Certification has been provided.

Reference is made to the agreement between FDA and Lilly with respect to the reporting of financial information for investigators who participated in the pivotal efficacy and Bioequivalence trials. This agreement is summarized in the Regulatory History and agreements section of the Application summary of this NDA. Forms 3454 and 3455 have been provided along with accompanying information as requested by the FDA.

To co-ordinate our activities with yours, we suggest that any facsimile (FAX) or other written communications concerning this file, regardless of subject, be directed to:

Gregory T. Brophy, PhD.
Director
U.S. Regulatory Affairs
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

FAX number: (317) 433-2255

Any calls regarding this submission should be directed to:

Sharon L. Hoog, M.D.
Work: (317) 276-5220
Pager: 1-888-431-3591

Alternatively, you may reach Dr. Hoog via e-mail at Hoog_Sharon_L@Lilly.com

In the case of Dr. Hoog's absence, please contact:

Mark Demitrack, M.D.
Work: (317) 277-2443
Pager: 1-888-431-3589

You may also contact:

Gregory T. Brophy, PhD.
Work: (317) 277-3799
Home: (317) 335-7360

COPY

Any calls relating to functionality of the electronic portion of the submission should be made to:

Patrick Q. Mooney
Electronic Submission Coordinator
Work: (317) 276-0586
Home: (317) 272-5528
Cell phone: (317) 331-3096

On holidays, Saturdays or Sundays, call Dr. Hoog or Dr. Brophy at home using the telephone numbers indicated.

Close liason between the representatives of Lilly listed above will result in any messages, no matter how received, being brought to the attention of all concerned.

Sincerely,
Lilly Research laboratories

Gregory T. Brophy, Ph.D.
Director
U.S. Regulatory Affairs

Cc: Doris Bates, Ph.D.

COPY

"Bates, Doris J" <BATESD@cder.fda.gov>

11/13/2001 10:25 AM

To: "'HOOG_SHARON_L@LILLY.COM'" <HOOG_SHARON_L@LILLY.COM>

cc:

Subject: RE: Shipment

Hi Sharon

I'm buried alive - don't worry - clearing some decks so that they are ready for your NDA - but as usual a lot of other things have decided to pile on simultaneously, and I am in the usual phonemail rut.

I have just checked the database and the date shown for the NDA is still the date the number was preassigned - this means that the Central Doc Room has not yet processed it in. We will receive it in the Division Doc Room about one day later. It will take another day, about, to be processed there, before I receive notice to come check it in at my level. That will take me about a day also. So I'd say it will probably be Thursday or Friday, give or take, when I move it out to the Team Leaders.

Be of good cheer: I already scheduled the filing meeting last week, because I knew time would be tight. We will be meeting on December 20, at 10:30.

-----Original Message-----
From: HOOG_SHARON_L@LILLY.COM [mailto:HOOG_SHARON_L@LILLY.COM]
Sent: Monday, November 12, 2001 5:04 PM
To: batesd@cder.fda.gov
Subject: Shipment

Hi Doris,
The team is proud to notify you of the shipment of the Dulox depression NDA.
It should arrive tomorrow.
I will try to call you in the AM.

Thanks very much.

Sharon L. Hoog

COPY

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-427

Eli Lilly and Co., Inc.
Attention: Gregory T. Brophy, Ph.D.
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Brophy:

Please refer to your new drug application (NDA) dated November 12, 2001, received November 13, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CYMBALTA® (duloxetine hydrochloride) 20, 30, and 60 mg capsules.

We acknowledge receipt of your submissions dated December 22, 2003, April 8, 2004, May 13, 2004, June 4, 2004, June 14, 2004, July 1, 2004, July 7, 2004 and July 14, 2004. Your December 22, 2003 submission constituted a complete response to our September 29, 2003 action letter. Your June 4, 2004 submission constituted a major amendment submitted within three months of the review goal date, and our letter of June 22, 2004 extended the review goal date for this submission to September 23, 2004.

This new drug application provides for the use of CYMBALTA (duloxetine hydrochloride) Capsules for the treatment of major depressive disorder (MDD).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text attached to this letter.

OCPB and CMC:
Approved Dissolution Specification and Expiration Date, Methods Validation
Approval of this application includes the following dissolution specification and method, to be used for all three approved strengths of duloxetine hydrochloride capsules:

Apparatus:	USP Apparatus I (Basket) at 100 RPM	
Media:	A: Gastric Challenge:	1000 mL of 0.1 N hydrochloric acid in deionized water at 37±0.5°±
	B: Medium 2:	1000 mL of 50 mM pH 6.8 Phosphate Buffer in deionized water at 37±0.5°±
Specifications:	For Medium A:	(Gastric Challenge) specification: meets USP Requirements of **not more than 10%** dissolved at 120 minutes.
	For Medium B:	specification: meets USP requirement of **Q = 75%** dissolved in 60 minutes.

The approved expiration date for the drug product is 24 months.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

Pediatric Research Equity Act (PREA) Requirements: Phase 4 Commitment: Studies Deferred
All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

We are waiving this requirement for children below the age of 7 years. We are deferring submission of your pediatric studies for ages 7 to 17 years (children and adolescents) until June 30, 2008 (see below). Your deferred pediatric studies required under Section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing commitments shall be reported annually according to 21 CFR 314.81. The associated commitments are listed below.

1. *Deferred pediatric studies under PREA.*
   You are required to assess the safety and effectiveness of CYMBALTA as a treatment for major depressive disorder (MDD) in pediatric patients ages 7 to 17 (children and adolescents).

   Final Report Submission: June 30, 2008

Please submit study protocols to your IND for this product, with a cross-reference letter submitted to the NDA. Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment, whether submitted to the IND or the NDA, must be clearly designated "**Required Pediatric Study Commitments**".

Pediatric Exclusivity
Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity, you should submit a "Proposed Pediatric Study Request" ***in addition to*** your plans for pediatric drug development described above. Please note that satisfaction of the requirements in Section 2 of PREA alone may not qualify you for pediatric exclusivity.

Additional Phase 4 Commitments (by Discipline)
We remind you of your additional postmarketing commitments, agreed upon in your submission dated December 22, 2003. These commitments are listed below.

2. *OCPB: Dissolution study.*
   As agreed, two *in vitro* dissolution experiments will be performed and the results submitted to further demonstrate the stability of the enteric coating:
   (a) 6 hour dissolution testing, using 0.1N HCl as medium
   (b) 2 hour dissolution testing using a solution of 50% ethanolic 0.1N HCl as medium.
   For both experiments, please report the amount of 1-naphthol generated quantitatively, in addition to reporting it as a percentage of duloxetine.

   We have reviewed and accept your previously submitted protocol, with the proviso that results for generation of 1-naphthol will be reported as described above.

   Final Report Submission: On or before October 23, 2004.

3. *Educational Campaign to Educate Practitioners and Patients Concerning the Differences between CYMBALTA and SYMBYAX (olanzapine / fluoxetine hydrochloride).*
   Your proposed trademark, CYMBALTA®, has been reviewed and is acceptable. You have agreed to assure continued differentiation in packaging between CYMBALTA and your approved drug SYMBYAX® (olanzapine / fluoxetine hydrochloride); this is an ongoing commitment, with no specific time limit. You have also agreed to institute an educational campaign that will educate practitioners and patients concerning the differences between CYMBALTA and SYMBYAX.

   Educational Campaign Materials Submission: On or before October 23, 2004.

4. *Clinical Safety: Clinical pharmacology study to evaluate the effect of duloxetine on the QT interval.*
   We are aware that two clinical pharmacology studies are currently underway or have recently been completed, and that the protocols for these investigations have already received detailed feedback from the Division of Reproductive and Urologic Drug Products (HFD-580) and the Division of Scientific Investigations.

   Final Study Report Submission: On or before December 31, 2004.

   Please submit the final study reports to the IND, clearly marked as a "**Postmarketing Study Final Report**". If the study reports are intended to support a change in labeling within this Division, please submit them to the NDA.

5. *Clinical Efficacy: Adult clinical study to address longer-term effectiveness of duloxetine in MDD.*
   You have agreed to submit the results of one adult clinical study of duloxetine in the longer-term treatment of MDD. Per our action letter of September 29, 2003, we note that you have an already ongoing study (not a continuation study) that is expected to meet the requirements of this commitment. We have already received and reviewed the protocol for this study.

   Final Report Submission: On or before June 30, 2006.

6. *Clinical Efficacy: Adult clinical study to address effects of duloxetine on female sexual function in depressed patients.*
   You have agreed to submit the results of one adult clinical study of the effects of duloxetine on female sexual function. This study must include an active control known to have deleterious effects on female sexual function.

   Final Report Submission: On or before June 30, 2008.

Please submit all final study reports other than those intended to support clinical efficacy claims, or changes in labeling, to your IND for this product, with a cross-reference letter submitted to this NDA. Please submit any final reports intended to support clinical efficacy claims or changes in labeling to this NDA. Please submit the educational campaign materials requested under point 3. above to this NDA.

In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary for each commitment in your annual report to this NDA. The status summary should include

- expected final report submission dates,
- any changes in plans since the last annual report,

- and, for clinical studies, the number of patients entered into each study.

All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence.**" This includes IND cross-reference letters submitted to the NDA.

Labeling
The final printed labeling (FPL) must be identical to the enclosed agreed-upon labeling (text for the package insert) and submitted labeling (immediate container and carton labels submitted December 22, 2003). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-427.**" Approval of this submission by FDA is not required before the labeling is used.

Introductory Promotional Materials
In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). In addition, we note your agreement to monitoring and reporting during the postmarketing period of liver-related Adverse Events, as outlined below:

- expedited reporting of all liver-related AEs received during the postmarketing period;
- quarterly summaries of all liver-related AEs along with estimates of drug usage for that specific quarter and an explanation of the method used to estimate drug usage;
- detailed follow-up information on reported cases of hepatotoxicity.

If you have any questions, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}
Robert Temple, M.D.
Director
Office of New Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Agreed-upon labeling (clean copy)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Temple
8/3/04 06:57:25 PM

Registration Number 38,838
Roadmap Information

Sponsor's Serial Number	Sponsor's Submission Date	Description of Submission	CD Serial Number	Paper Only	File or Folder Name
0313	19-AUG-2004	IND Medwatch	N/A	X	N/A
0312	16-AUG-2004	Independent Sponsor Cross-Reference Letter	N/A	X	N/A
0311	12-AUG-2004	IND Medwatch for F1J-US-HMCR-316-2513	N/A	X	N/A
0310	11-AUG-2004	F1J-US-HMBZ Abbreviated Clinical Study Report	N/A	X	N/A
0309	09-AUG-2004	ADME Report 22-292-TC; New Investigators F1J-MC-HMCN and F1J-MC-HMCV	N/A	X	N/A
0308	06-AUG-2004	IND Medwatch for study F1J-JE-HMBC	N/A	X	N/A
0307	29-JUL-2004	IND Medwatch for F1J-US-HMCR	N/A	X	N/A
0306	28-JUL-2004	IND Medwatch for F1J-JE-HMBC	N/A	X	N/A
0305	01-JUL-2004	IND Medwatch	N/A	X	N/A
0304	30-JUN-2004	New Investigators F1J-MC-HMCN and F1J-AA-HMCV	N/A	X	N/A
0303	10-JUN-2004	IND Medwatch	N/A	X	N/A
0302	02-JUN-2004	Cross Reference letter IND 43560 Serial Number 302 regarding US 0405103839 for subject F1J US SBCD 84 8743. Complete submission was enclosed as attachement	N/A	X	N/A
0301	01-JUN-2004	Investigator documents for the following studies: F1J MC HMCN, F1J MC HMCQ, F1J-US-HMBZ and F1J US HMCR	N/A	X	N/A
0300	28-MAY-2004	Toxicology Report INV BTX-034-2	N/A	X	N/A
0299	27-MAY-2004	Toxicology Report No 27 - Final Report Amendment 2	N/A	X	N/A
0298	10-MAY-2004	Protocol and Investigator for study F1J-FW-HMCE	N/A	X	N/A
0297	05-MAY-2004	Annual Report	N/A	X	N/A
0296	22-APR-2004	Medwatch for US 0402100365 F for subject F1J US HMCR 328 3701	N/A	X	N/A
0295	02-APR-2004	Cross Reference to Drug Experience Report submitted to IND 43560, Serial No. 292, dated April 02, 2004, for subject F1J LC HMCG 084 0024	N/A	X	N/A
0294	01-APR-2004	Clinical Investigator's Brochure	N/A	X	N/A
0293	24-MAR-2004	CM&C Briefing Document requesting a meeting with duloxetine Chemistry and Biopharmaceutice review team	N/A	X	N/A
0292	19-MAR-2004	Cross Reference Letter to IND 43560, SN288 dated March 17, 2004. Regarding subject F1J LC HMCG 084 0024	N/A	X	N/A
0291	08-MAR-2004	Cross Reference letter to Addendum submitted to IND 43560, Serial Number 286 on March 03, 2004	N/A	X	N/A
0290	26-FEB-2004	Medwatch Cross Reference Letter to IND 43560 SN285, for US_040100573 Follow-Up to study F1J-LC-HMCG-084	N/A	X	N/A
0289	12-FEB-2004	Medwatch Cross Reference Letter to IND 43560, SN084 for US-0402100573 Initital to study F1J-LC-HMCG-084	N/A	X	N/A
0288	12-FEB-2004	Serial Number 288 was inadvertely omitted	N/A	X	N/A
0287	12-FEB-2004	IND Medwatch Cross Reference letter that was submitted to IND 43560 on a 7-day phone call Drug Experience Report	N/A	X	N/A
0286	12-FEB-2004	Investigators HMCR, HMCV	N/A	X	N/A

0285	22-JAN-2004	Medwatch	N/A	X	N/A
0284	14-JAN-2004	Protocol and Investigators for study F1J AA HMCV	N/A	X	N/A
0283	19-DEC-2003	New Investigator for studies F1J MC HMBV, F1J MC HMCN and F1J US HMCR	N/A	X	N/A
0282	18-DEC-2003	IND Medwatch	N/A	X	N/A
0281	26-NOV-2003	Medwatch	N/A	X	N/A
0280	13-NOV-2003	New Investigators for studies F1J-MC-HMBV, F1J-MC-HMCN and F1J-MC-HMCR	N/A	X	N/A
0279	28-OCT-2003	Correspondence regarding Proposal for Clincial Trial to assess potential effect on growth of depressed pediatric subjects receiving fluoxetine or duloxetine (Briefing Document)	N/A	X	N/A
0278	16-OCT-2003	New Investigators for studies F1J MC HMBU, F1J MC HMCN and F1J US HMCR, CT Labels for study F1J MC HMCN and Pharmacology Report CNS454	N/A	X	N/A
0277	23-SEP-2003	CM&C Amendment	N/A	X	N/A
0276	16-SEP-2003	New Protocol and Investigator for study F1J-US-HMCR, Protocol Amendment and Protocol Amendment Summary for study F1J-MC-HMCR(a) Also Investigators for studies F1J-MC-HMBV, F1J-MC-HMCN and F1J-MC-HMCQ and Clinical Trial Labels for study F1J-MC-HMCN	N/A	X	N/A
0275	05-SEP-2003	ADME Report 105, Pharmacology Reports CNS412, CNS455 and CNS464	N/A	X	N/A
0274	25-AUG-2003	New Investigators for study H8I MC HQAC	N/A	X	N/A
0273	15-AUG-2003	Case Report data forward to FDA as informational report	N/A	X	N/A
0272	14-AUG-2003	New Investigators to studies F1J MC HMAV, F1J MC HMBU, F1J MC HMCN, F1J MC HMCQ and F1J US HMBZ Also CT Labels for study F1J MC HMCN	N/A	X	N/A
0271	03-JUL-2003	Protocol and investigator for study F1J MC HMCN also investigator for study F1J MC HMCQ	N/A	X	N/A
0270	27-JUN-2003	Cross Reference letter to Briefing Document submitted to IND 62,536 on June 26, 2003	N/A	X	N/A
0269	16-JUN-2003	New Investigators for studies F1J-MC-HMBU, F1J-MC-HMBV, F1J-US-HMBZ and F1J-MC-HMCQ, also CT Labels for study F1J-MC-HMBV	N/A	X	N/A
0268	20-MAY-2003	New Investigators for studies F1J MC HMBV, F1J MC HMBU, and F1J MC HMCQ Also Nonclinical Pharmacology Reports 57, 61 and 63	N/A	X	N/A
0267	09-MAY-2003	Cross Reference letter to IND 62536 dated May 07, 2003 requesting a Type B Meeting to discuss content and format of a New Drug Application for Duloxetine for the treatment of Diabetic Neurophatic Pain	N/A	X	N/A
0266	05-MAY-2003	Annual Report	N/A	X	N/A
0265	29-APR-2003	Abbreviated Clinical Study Report for study F1J US HMBY	N/A	X	N/A
0264	24-APR-2003	Medwatch	N/A	X	N/A
0263	23-APR-2003	Protocol, Protocol Amendment, Protocol Amendment Summary and Investigators for study F1J MC HMCQ Also Investigators for study F1J MC HMBV and Clinical Trial Labels	N/A	X	N/A
0262	17-APR-2003	Medwatch	N/A	X	N/A
0261	08-APR-2003	Clinical Investigator's Brochure	N/A	X	N/A
0260	04-APR-2003	Protocol Amendment(submitted as initial protocol),Amendment Summary and Investigator for study H8I MC HQACa	N/A	X	N/A
0259	02-APR-2003	Protocol, Protocol Amendment, Protocol Summary and New Investigators for study F1J MC HMBU also new investigators for study F1J MC HMBV	N/A	X	N/A

0258	27-MAR-2003	New Investigators for studies F1J MC HMBV and F1J MC HMBZ also Pharmacology Reports 55 and 56 and Clinicl Trial Labels	N/A	X	N/A
0257	21-MAR-2003	CM&C Amendment	N/A	X	N/A
0256	20-MAR-2003	Abbreviated Study Report for study F1J US HMCB	N/A	X	N/A
0255	20-MAR-2003	Medwatch	N/A	X	N/A
0254	13-MAR-2003	Clinical Study Main Report and Amendment Summary to study F1J LC HMAXa	N/A	X	N/A
0253	07-MAR-2003	New Protocol for study F1J MC HMBV and new investigators for studies F1J MC HMBV and F1J US HMBZ	N/A	X	N/A
0252	27-JAN-2003	New Investigators to study F1J MC HMBZ and Supplement to Duloxetine Biopharmaceutics Summary	N/A	X	N/A
0251	10-JAN-2003	Abbreviated Clinical Study Report and Final Study Report and Japanese Version to study F1J JE 321G	N/A	X	N/A
0250	06-JAN-2003	Interim Clinical Study Report for study F1J LC SBBN	N/A	X	N/A
0249	02-JAN-2003	New Investigators for studies F1J MC HMBY and F1J US HMBZ	N/A	X	N/A
0248	19-DEC-2002	New Investigators for study F1J MC HMBZ and CT Labels	N/A	X	N/A
0247	11-DEC-2002	Cross Reference for Clinical Study Report for study F1J MC HMBO submitted to IND 63615	N/A	X	N/A
0246	10-DEC-2002	Cross Refence letter to IND 62536 which submitted Abbreviated Clinical Study Report for study F1J MC HMAW	N/A	X	N/A
0245	05-DEC-2002	New Investigators for study F1J US HMBZ and Clinical Synopsis for study F1J LC HMCC Final Reports for studies F1J JE 1006 and F1J JE 324G	N/A	X	N/A
0244	25-NOV-2002	Final Study Reports F1J JE 1002 F1J JE 104G F1J JE 105G and F1J JE 323G	N/A	X	N/A
0243	12-NOV-2002	New Investigators for study F1J US HMBZ ADME Reports 94 and 95 Method Validation Report and Stability Report	N/A	X	N/A
0242	08-NOV-2002	Toxicology Reports 10, 13 and 17	N/A	X	N/A
0241	07-NOV-2002	Medwatch	N/A	X	N/A
0240	01-NOV-2002	Final Reports for studies F1J JE 221G and F1J JE 313G	N/A	X	N/A
0239	31-OCT-2002	Medwatch	N/A	X	N/A
0238	15-OCT-2002	CM&C Amendment	N/A	X	N/A
0237	01-OCT-2002	Abbreviated Clinical Study Report for study F1J JE 102G English and Japanese version	N/A	X	N/A
0236	19-SEP-2002	Cross Reference Letter to Correspondence submitted to NDA 21-427	N/A	X	N/A
0235	05-SEP-2002	Final Study Reports F1J JE 105G and F1J JE 312G Also Abbreivated Clinical Study Reports F1J MC HMAY Group A and B F1J US HMBY and F1J US HMCB and Interim Abbreviated Clinical Study Report F1J US HMBC	N/A	X	N/A
0234	26-AUG-2002	Clinical Synopsis Report	N/A	X	N/A
0233	19-AUG-2002	Protocol and Investigators to study F1J US HMBZ	N/A	X	N/A
0232	08-AUG-2002	Final Study Report to study F1J JE 1008 and CT Labels	N/A	X	N/A
0231	24-JUL-2002	ADME Report 91 and New Investigator	N/A	X	N/A
0230	15-JUL-2002	New Investigator for studies F1J MC HMBC and F1J US HMBY also final study reports for studies F1J JE 103G and F1J JE 311G and Clinical Trial Labels	N/A	X	N/A

0229	11-JUL-2002	Medwatch	N/A	X	N/A
0228	26-JUN-2002	Protocol Addeneum F1J MC HMBC2	N/A	X	N/A
0227	12-JUN-2002	IRB Supplement 1 (F1J US HMBY) New Protocol F1J US HMBY and New Investigators to studies F1J MC HMBC and F1J US HMBY	N/A	X	N/A
0226	24-MAY-2002	CM&C Amendment	N/A	X	N/A
0225	23-MAY-2002	Medwatch	N/A	X	N/A
0224	15-MAY-2002	Protocol Addendum 1 to study F1J US HMCB and Investigators to study F1J MC HMBC	N/A	X	N/A
0223	30-APR-2002	Annual Report	N/A	X	N/A
0222	29-APR-2002	New Investigators for study F1J-US-HMCB and CT Labels	N/A	X	N/A
0221	04-APR-2002	Clinical Investigator's Brochure	N/A	X	N/A
0220	03-APR-2002	New Protocol and investigator for study F1J MC HMCC and investigators for study F1J US HMCB	N/A	X	N/A
0219	06-MAR-2002	Study Report Abbreviated F1J LC SAAZa, Study Report Amendment Summary F1J LC SAAZa, Study Report Synopsis F1J LC HMBI and Overview Safety Pharmacology Report	N/A	X	N/A
0218	08-MAR-2002	New Protocol and Investigators for study F1J US HMCB	N/A	X	N/A
0217	07-MAR-2002	New Protocol and Amendments (a and b) for study F1J-MC-HMBC	N/A	X	N/A
0216	07-FEB-2002	Medwatch	N/A	X	N/A
0215	05-FEB-2002	Tox Report 50, Tox Report 50 Amend 01	N/A	X	N/A
0214	28-JAN-2002	Final Report	N/A	X	N/A
0213	18-JAN-2002	Final Report (F1J-LC-HMAN)	N/A	X	N/A
0212	18-DEC-2001	CM&C	N/A	X	N/A
0211	17-DEC-2001	Final Report: F1J-JE-105G, F1J-LC-HMAX & F1J-LC HMBI	N/A	X	N/A
0210	17-DEC-2001	CM&C	N/A	X	N/A
0207	16-NOV-2001	ADME Reports: 65, 66, 74, 75, and 75	N/A	X	N/A
0206	04-OCT-2001	Medwatch	N/A	X	N/A
0205	02-OCT-2001	Medwatch	N/A	X	N/A
0204	02-OCT-2001	Medwatch (Correction)	N/A	X	N/A
0203	01-OCT-2001	Medwatch	N/A	X	N/A
0202	13-SEP-2001	Medwatch	N/A	X	N/A
0201	06-SEP-2001	Medwatch	N/A	X	N/A
0200	05-SEP-2001	Sub-Investigators, Inv. Changes and Final Reports (F1J-LC-HMBA & F1J-LC-HMBJ)	N/A	X	N/A
0199	29-AUG-2001	CM&C Briefing Document	N/A	X	N/A
0198	29-AUG-2001	Medwatch	N/A	X	N/A
0197	15-AUG-2001	ADME Reports 77 & 78, Final Reports F1J-BD-HMBD, F1J-FW-HMBB, F1J-MC-SAAW	N/A	X	N/A
0196	15-AUG-2001	Protocol Amendment (F1J-LC-SBBN (a)) Sub-Inv. (F1J-MC-HMAU, HMBH, HMBG) & CT Labels	N/A	X	N/A

0195	09-AUG-2001	CM&C	N/A	X	N/A
0194	30-JUL-2001	CM&C Supplement	N/A	X	N/A
0193	27-JUL-2001	Correspondence for Doris Bates IND38,838 and IND 43,560	N/A	X	N/A
0192	20-JUL-2001	Briefing Document	N/A	X	N/A
0191	12-JUL-2001	Correspondence - Response to Biopharmaceutics Concerns Raised at 06/12/01 Meeting	N/A	X	N/A
0190	28-JUN-2001	New Protocol & Investigator (F1J-LC-SBBN)	N/A	X	N/A
0189	26-JUN-2001	Correspondence	N/A	X	N/A
0188	25-JUN-2001	Correspondence Proposed Pediatric Study Request	N/A	X	N/A
0187	25-JUN-2001	CM&C Amendment	N/A	X	N/A
0186	21-JUN-2001	Correspondence - Meeting Minutes	N/A	X	N/A
0185	14-JUN-2001	Protocol Amend., Investigators, & CT Labels	N/A	X	N/A
0184	25-MAY-2001	Protocol Amendment, Investigators (F1J-LC-HMBI(a) Address Changes	N/A	X	N/A
0183	24-MAY-2001	Correspondence - (Type B Meeting Request)	N/A	X	N/A
0182	22-MAY-2001	Briefing Document	N/A	X	N/A
0181	04-MAY-2001	Annual Report	N/A	X	N/A
0180	02-MAY-2001	New Protocol and Invest. (F1J-LC-HMBI) Sub-Inv. F1J-MC-HMBH) & Changes F1J-MC-HMAT, HMAU & HMBH	N/A	X	N/A
0179	19-APR-2001	General Correspondence	N/A	X	N/A
0178	05-APR-2001	Final Report and Pharmacology Report	N/A	X	N/A
0176	20-MAR-2001	New Protocol (F1J-LC-HMBN)	N/A	X	N/A
0175	06-MAR-2001	New & Sub-Investigators, IRB and Site Address changes (F1J-MC-HMAU, F1J-MC-HMAT & F1J-MC-HMBM)	N/A	X	N/A
0172	31-JAN-2001	ADME Report 60, Tox Rpts. 46, 47, & 48	N/A	X	N/A
0171	05-JAN-2001	New & Sub-Investigators	N/A	X	N/A
0170	04-JAN-2001	CM&C	N/A	X	N/A
0169	22-NOV-2000	Protocol & Protocol Amend (a) (F1J-LC-HMBJ, New Investigators (F1J-MC-HMBH) & Sub-Inv. (F1J-MC-HMAT)	N/A	X	N/A
0168	01-NOV-2000	New Protocol & New Investigators (F1J-MC-HMBH) Sub-Inv. F1J-MC-HMBH	N/A	X	N/A
0167	27-OCT-2000	CM&C Briefing Document	N/A	X	N/A
0166	28-SEP-2000	Amended Protocol F1J-LC-HMAX(a), Subinvestigator documents (F1J-MC-HMAU)	N/A	X	N/A
0165	21-SEP-2000	Final Report (F1J-MC-HMAZ)	N/A	X	N/A
0164	15-SEP-2000	Correction Letter to FDA re: Biopsy Issues	N/A	X	N/A
0163	13-SEP-2000	Final Report (F1J-LC-SAAZ), Investigator & Subinvestigator documents	N/A	X	N/A
0162	11-SEP-2000	Final Report (F1J-BD-HMAR)	N/A	X	N/A
0161	06-SEP-2000	General Correspondence re: Discontinuation of Investigator	N/A	X	N/A
0160	21-AUG-2000	Final Summary Report (F1J-LC-HMAJ) Investigator documents, CT lLabels	N/A	X	N/A
0159	10-AUG-2000	Final Report ???????? and New Investigators	N/A	X	N/A
0158	01-AUG-2000	Investigator documents for studies F1J-MC-HMAT & F1J-MC-HMAU	N/A	X	N/A
0157	27-JUL-2000	Protocol F1J-LC-HMBG, Investigator documents	N/A	X	N/A

0156	23-JUN-2000	Protocol F1J-MC-HMAU, Investigator documents	N/A	X	N/A
0155	16-JUN-2000	Investigator & Subinvestigator documents, Investigator Site Changes (F1J-MC-HMAW & F1J-MC-HMAT) and Final Study Report (F1J-MC-SAAB)	N/A	X	N/A
0154	09-MAY-2000	Revised CIB	N/A	X	N/A
0153	01-MAY-2000	Letter to FDA re: ??????????	N/A	X	N/A
0152	02-MAY-2000	Annual Report	N/A	X	N/A
0151	21-APR-2000	Investigator documents for: F1J-MC-HMAT, ADME Report 64	N/A	X	N/A
0150	14-APR-2000	Investigator documents, Final Reports: F1J-LC-HMAA, F1J-LC-HMAB, F1J-LC-HMAF & F1J-LC-HMAO	N/A	X	N/A
0149	03-APR-2000	Cross -reference letter re: Submission of White Paper to IND 58,832	N/A	X	N/A
0148	29-MAR-2000	Briefing Document	N/A	X	N/A
0147	23-MAR-2000	Investigator & Subinvestigator documents for F1J-MC-HMAT, ADME Report 58, and CT lLabels	N/A	X	N/A
0146	10-MAR-2000	Protocol F1J-LC-HNBA, Investigator & Subinvestigator documents, ADME Report 62	N/A	X	N/A
0145	15-FEB-2000	Final Reports Abbreviated: F1J-LC-HMAE, F1J-MC-SAAH and F1J-MC-SAAI	N/A	X	N/A
0144	14-FEB-2000	CM&C Amendment	N/A	X	N/A
0143	08-FEB-2000	Protocol F1J-MC-HMAT	N/A	X	N/A
0142	07-FEB-2000	Investigator Document - F1J-MC-HMAX, ADME Reports: 2 Amend-1, 9 Amend-1, 10 Amend-1, 18 Amend-1, 19 Amend-1, 34 Amend-1, 59 Amend, Pharmacology Report 4, and CT labels	N/A	X	N/A
0141	06-JAN-2000	CM&C Amendment	N/A	X	N/A
0140	15-DEC-1999	Investigator documents- F1J-MC-HMAQ	N/A	X	N/A
0139	30-NOV-1999	Briefing Document	N/A	X	N/A
0138	22-NOV-1999	Investigator documents- F1J-MC-HMAQ	N/A	X	N/A
0137	02-NOV-1999	Protocol F1J-LC-HMAZ & Investigator Doc.	N/A	X	N/A
0136	29-OCT-1999	Letter to FDA re: Meeting Request	N/A	X	N/A
0135	29-SEP-1999	Letter to FDA re: ???????????	N/A	X	N/A
0134	22-SEP-1999	Protocol F1J-LC-HMAX, Investigator documents	N/A	X	N/A
0133	21-SEP-1999	Toxicology Report 45	N/A	X	N/A
0132	13-JUL-1999	ADME Report 56, CT labels, and Final Report F1J-LC-SAAY (and New pagination letter)	N/A	X	N/A
0131	17-JUN-1999	Toxicology Reports 43, 44 - Dose Justification Studies in Mice & Rats	N/A	X	N/A
0130	05-MAY-1999	Annual Report (Includes Revised CIB)	N/A	X	N/A
0129	10-MAR-1999	Letter too FDA re: ????????	N/A	X	N/A
0128	03-MAR-1999	Investigator & Subinvestigator documents, CT labels, Final Report F1J-LC-HMAJ	N/A	X	N/A
0127	08-FEB-1999	Amended Protocol F1J-MC-HMAQ(a)	N/A	X	N/A
0126	22-DEC-1998	CM&C Amendment	N/A	X	N/A
0125	03-DEC-1998	Protocol F1J-MC-HMAQ, Investigator documents	N/A	X	N/A

0124	24-NOV-1998	ADME Report 55, Amendment 1	N/A	X	N/A
0123	16-OCT-1998	Protocol F1J-LC-SAAZ, Investigator documents	N/A	X	N/A
0122	14-OCT-1998	CM&C Amendment	N/A	X	N/A
0121	28-SEP-1998	ADME Report 55	N/A	X	N/A
0120	21-AUG-1998	Letter to FDA re: response to questions on protocol F1J-LC-SBAA	N/A	X	N/A
0119	10-AUG-1998	Protocol F1J-MC-SAAY, Investigator documents	N/A	X	N/A
0118	08-JUN-1998	Protocol F1J-LC-SBAA, Investigator documents, ADME Report 54	N/A	X	N/A
0117	05-MAY-1998	Annual Report (Includes Revised CIB)	N/A	X	N/A
0116	04-MAY-1998	ADME Report 53	N/A	X	N/A
0115	25-MAR-1998	Summaries for Toxicology Reports 36, 37, 40, 41, 42, 43, 44 & ADME Reports 46-52	N/A	X	N/A
0114	18-FEB-1998	Final Report F1J-LC-HMAP	N/A	X	N/A
0113	07-JAN-1998	Medwatch Form	N/A	X	N/A
0112	03-JUN-1997	Letter to FDA re: Laboratory Name Change	N/A	X	N/A
0111	05-MAY-1997	Annual Report (Includes Revised CIB)	N/A	X	N/A
0110	10-MAR-1996	Cross-reference letter for submission of Toxicology Reports 36 & 37	N/A	X	N/A
0109	17-DEC-1996	Cross-reference letter for submission of Toxicology Report 44	N/A	X	N/A
0108	13-DEC-1996	Cross-reference letter for submission of Toxicology Report 43	N/A	X	N/A
0107	08-OCT-1996	Cross-reference letter for submission of Toxicology Reports 40, 41 & 42	N/A	X	N/A
0106	07-OCT-1996	Final Report F1J-MC-HMAH	N/A	X	N/A
0105	18-JUN-1996	Cross-reference letter to FDA re: submission of Pharmacology Report CNS134	N/A	X	N/A
0104	04-MAY-1996	Pharmacology Report CNS137	N/A	X	N/A
0103	03-MAY-1996	Annual Report (Includes Revised CIB)	N/A	X	N/A
0102	21-MAR-1996	ADME Reports 42 & 45	N/A	X	N/A
0101	20-DEC-1995	Toxicology Reports 35, 36, 37, 38, & 39	N/A	X	N/A
0100	06-NOV-1995	Revised Toxicology Report 27	N/A	X	N/A
0099	01-NOV-1995	Correction of Toxicology Report 27	N/A	X	N/A
0098	31-AUG-1995	Letter to FDA re: ?????????	N/A	X	N/A
0097	14-AUG-1995	IND Safety Report	N/A	X	N/A
0096	12-JUN-1995	ADME Report 41, Pharmacology Report 52, Pharmacology Report 63	N/A	X	N/A
0095	01-MAY-1995	Annual Report	N/A	X	N/A
0094	25-APR-1995	FD-1639 Form	N/A	X	N/A
	18-APR-1995				

0093		FD-1639 Form	N/A	X	N/A
0092	11-APR-1995	FD-1639 Form	N/A	X	N/A
0091	04-APR-1995	FD-1639 Form	N/A	X	N/A
0090	07-MAR-1995	FD-1639 Form	N/A	X	N/A
0089	28-FEB-1995	ADME Report 40	N/A	X	N/A
0088	24-JAN-1995	FD-1639 Form	N/A	X	N/A
0087	17-JAN-1995	FD-1639 Form	N/A	X	N/A
0086	10-JAN-1995	FD-1639 Form	N/A	X	N/A
0085	23-DEC-1994	FD-1639 Form	N/A	X	N/A
0084	25-NOV-1994	ADME Reports, 27, 28 & 39, Non-Clinical Pharmacology Report 4, CT labels	N/A	X	N/A
0083	17-NOV-1994	Revised CIB	N/A	X	N/A
0082	04-OCT-1994	FD-1639 Form	N/A	X	N/A
0081	28-AUG-1994	Letter to FDA re: ???????	N/A	X	N/A
0080	19-AUG-1994	General Pharmacology Report 4, Subinvestigator documents, CT labels	N/A	X	N/A
0079	16-AUG-1994	FD-1639 Form	N/A	X	N/A
0078	24-JUN-1994	Protocol Addendum F1J-MC-HMAK(1)	N/A	X	N/A
0077	16-JUN-1994	CM&C Amendment	N/A	X	N/A
0076	15-JUN-1994	Protocol F1J-MC-HMAK	N/A	X	N/A
0075	13-JUN-1994	Protocol F1J-MC-HMAO, Investigator documents	N/A	X	N/A
0074	06-JUN-1994	CM&C Amendment	N/A	X	N/A
0073	02-JUN-1994	Subinvestigator documents	N/A	X	N/A
0072	23-APR-1994	Annual Report	N/A	X	N/A
0071	11-APR-1994	CM&C Amendment	N/A	X	N/A
0070	17-MAR-1994	FD-1639 Form	N/A	X	N/A
0069	15-MAR-1994	FD-1639 Form	N/A	X	N/A
0068	11-MAR-1994	Revised CIB (Safety Section)	N/A	X	N/A
0067	07-MAR-1994	Subinvestigator documents	N/A	X	N/A
0066	22-FEB-1994	FD-1639 Form	N/A	X	N/A
0065	18-FEB-1994	Cross-reference letter to FDA re: submission of study report HMAB	N/A	X	N/A
0064	22-DEC-1993	Amended Protocol HMAH(a), Subinvestigator documents, Preclinical Pharmacology Report 36	N/A	X	N/A
0063	15-DEC-1993	Letter to FDA re: Update of Section 4.1 in Protocol HMAH	N/A	X	N/A
0062	10-DEC-1993	Blinded Document	N/A	X	N/A
0061	09-DEC-1993	Revised CIB	N/A	X	N/A
0060	01-DEC-1993	Nonclinical Pharmacology Report	N/A	X	N/A

0059	24-NOV-1993	Amended Protocol F1J-MC-HMAG(b), CT labels	N/A	X	N/A
0058	28-OCT-1993	Protocol F1J-LC-HMAJ, Investigator documents	N/A	X	N/A
0057	21-OCT-1993	????????????????	N/A	X	N/A
0056	12-OCT-1993	CM&C Amendment	N/A	X	N/A
0055	17-SEP-1993	Toxicology Report 33, Preclinical Pharmacology Report	N/A	X	N/A
0054	14-SEP-1993	CM&C Amendment	N/A	X	N/A
0053	13-SEP-1993	Letter to FDA re: Revision to Annual Report due to error in number of patients	N/A	X	N/A
0052	01-SEP-1993	FD-1639 Form	N/A	X	N/A
0051	19-AUG-1993	Revised CIB	N/A	X	N/A
0050	12-AUG-1993	Letter to FDA re: WCBP Treatment	N/A	X	N/A
0049	03-AUG-1993	FD-1639 Form	N/A	X	N/A
0048	27-JUL-1993	FD-1639 Form	N/A	X	N/A
0047	22-JUL-1993	Amended Protocol F1J-MC-HMAG(a), Subinvestigator documents	N/A	X	N/A
0046	21-JUL-1993	CM&C Amendment	N/A	X	N/A
0045	13-JUL-1993	FD-1639 Form	N/A	X	N/A
0044	08-JUL-1993	Pharmacology Report 26, Subinvestigator documents, CT labels	N/A	X	N/A
0043	07-JUL-1993	FD-1639 Form	N/A	X	N/A
0042	22-JUN-1993	FD-1639 Form	N/A	X	N/A
0041	08-JUN-1993	FD-1639 Form	N/A	X	N/A
0040	02-JUN-1993	FD-1639 Form	N/A	X	N/A
0039	25-MAY-1993	Pharmacology Report 3	N/A	X	N/A
0038	27-APR-1993	FD-1639 Form	N/A	X	N/A
0037	26-APR-1993	Annual Report (Includes Abstracts for studies JE-1001, 1002 & 1003)	N/A	X	N/A
0036	23-APR-1993	Toxicology Report 31, ADME Reports 35 & 36, CT labels	N/A	X	N/A
0035	01-APR-1993	Toxicology Report 32	N/A	X	N/A
0034	25-MAR-1993	CM&C Amendment	N/A	X	N/A
0033	22-FEB-1993	Toxicology Report 29, Subinvestigator documents	N/A	X	N/A
0032	19-FEB-1993	Protocol F1J-JE-1007	N/A	X	N/A
0031	25-JAN-1993	Toxicology Report 30	N/A	X	N/A
0030	19-JAN-1993	Protocol F1J-MC-HMAG, Investigator documents	N/A	X	N/A
0028	22-DEC-1992	Protocol F1J-JE-1002	N/A	X	N/A
0027	18-DEC-1992	CM&C Letter to FDA re: response to FDA questions	N/A	X	N/A
0026	18-DEC-1992	CM&C Amendment	N/A	X	N/A
0025	17-DEC-1992	Revised CIB	N/A	X	N/A
0024	03-DEC-1992	Pharmacology Report 2	N/A	X	N/A
	30-OCT-1992				

0023		Protocol F1J-LC-HMAF, Investigator documents	N/A	X	N/A
0022	27-OCT-1992	Interim Reports on F1J-LC-HMAB & F1J-LC-HMAD	N/A	X	N/A
0021	22-OCT-1992	CM&C Amendment	N/A	X	N/A
0020	02-OCT-1992	Amended Protocol F1J-LC-HMAE(a)	N/A	X	N/A
0019	30-SEP-1992	Protocol F1J-LC-HMAE, Investigator documents, CT labels	N/A	X	N/A
0018	29-SEP-1992	Pharmacology Report 1	N/A	X	N/A
0017	16-SEP-1992	CM&C Amendment	N/A	X	N/A
0016	02-SEP-1992	Nonclinical Pharmacology Report, ADE Report 33	N/A	X	N/A
0015	26-AUG-1992	Letter to FDA re: Adjusting Annual Report date to coincide with IND 31,171	N/A	X	N/A
0014	21-AUG-1992	Toxicology Report 28, Nonclinical Pharmacology Report	N/A	X	N/A
0013	04-AUG-1992	Nonclinical Pharmacology Report	N/A	X	N/A
0012	22-JUL-1992	Toxicology Reports 26 & 27	N/A	X	N/A
0011	20-JUL-1992	CM&C Briefing Document	N/A	X	N/A
0010	14-JUL-1992	Letter to FDA re: Nonproprietory name assignment, Toxicology Report 24, CT labels	N/A	X	N/A
0009	25-JUN-1992	Letter to FDA re: ????????	N/A	X	N/A
0008	22-JUN-1992	Protocol F1J-LC-HMAD, Investigator documents	N/A	X	N/A
0007	11-MAY-1992	Protocol F1J-JE-1001, Investigator documents	N/A	X	N/A
0006	30-APR-1992	CM&C Amendment	N/A	X	N/A
0005	21-APR-1992	Toxicology Report 19, ADME Report 32	N/A	X	N/A
0004	16-APR-1992	Toxicology Reports 20, 21, 22, & 25	N/A	X	N/A
0003	03-APR-1992	Amended Protocol F1J-LC-HMAB(b), CT labels	N/A	X	N/A
0002	19-MAR-1992	ADME Report 31, Pharmacology & Preclinical Pharmacology Reports	N/A	X	N/A
0001	09-MAR-1992	Amended Protocol F1J-LC-HMAB(a)	N/A	X	N/A
0000	05-FEB-1992	Initial IND Submission, included Protocol F1J-LC-HMAB, Revised CIB	N/A	X	N/A
			N/A	X	N/A
			N/A	X	N/A
			N/A	X	N/A
			N/A	X	N/A
			N/A	X	N/A
			N/A	X	N/A

Registration Number 21-427
Roadmap Information

Sponsor's Serial Number	Sponsor's Submission Date	Description of Submission	CD Serial Number	Paper Only	File or Folder Name
	19-Aug-2004	Final Printed Labeling	N/A	X	N/A
	05-AUG-2004	MQ28163 Cymbalta Rep Name Badge Template MQ28162 Cymbalta Business Card Template	N/A	X	N/A
	14-JUL-2004	Response to Reviewer's Questions of July 12, 2004 Regarding Hepatic Safety	N/A	X	N/A
	01-JUL-2004	Response to Reviewer's Questions of June 27, 2004 Regarding Hepatic Safety	N/A	X	N/A
	07-JUL-2004	Response to Reviewer's Questions of July 1, 2004 Regarding Hepatic Safety	N/A	X	N/A
	13-MAY-2004	General Correspondence - Cross-Refererence	N/A	X	N/A
	14-JUN-2004	Response to Reviewer's questions of June 10, 2004, regarding Hepatic Safety.	N/A	X	N/A
	08-APR-2004	Response to Reviewer's questions of March 15, 2004, regarding Hepatic Enzymes.	N/A	X	N/A
	22-DEC-2003	Response to FDA Approvable Letter (Second Cycle)	N/A	X	N/A
	06-OCT-2003	Notification of Intent to file an amendment in response to approvable letter	N/A	X	N/A
	22-SEP-2003	Response to Clarification to Questions from Chemistry Reviewers and Meetings Minutes	N/A	X	N/A
	07-AUG-2003	Response to reviewer's questions of July 29, 2003 regarding Cases of Syncope	N/A	X	N/A
	29-JUL-2003	Responses and Clarifications to Questions from Complete Response to FDA Approvable Letter	N/A	X	N/A
	23-JUL-2003	Response to FDA communication regarding feedback on trademark, medication error issues	N/A	X	N/A
	24-MAR-2003	Complete Response to FDA Approvable Letter	N/A	X	N/A
			N/A	X	N/A
		Correspondence - Copies of printed packaging mock-ups	N/A	X	N/A
	15-NOV-2002	Briefing Document	N/A	X	N/A
	31-OCT-2002	Request for Type A Meeting CM&C Briefing Document	N/A	X	N/A
	19-SEP-2002	Notification of Intent to Amend NDA 21-427	N/A	X	N/A
	29-AUG-2002	Amendment with data and summary statistics for a pivotal dissolution study in hard copy and electronic format	N/A	X	N/A
	19-AUG-2002	Responses to FDA Request which includes Pre-Clinical, Clinical and Safety Update	N/A	X	N/A
	07-JUN-2002	Two posters from scientific meetings to the previously submitted updated literature search.	N/A	X	N/A
	24-APR-2002	Electronic copy of response to questions received by email from Dr. Doris Bates, FDA on April 08, 2002	N/A	X	N/A
	04-APR-2002	Response to Dr. Andreason's request of February 28, 2002 regarding lack of baseline EKG data for patient F1J JE 324G	N/A	X	N/A
	29-MAR-2002	During CMC Pre-NDA meeting on September 28, 2002, we're providing updated supportive information to Item 4, CM&C	N/A	X	N/A
	28-MAR-2002	Response to reviewer's questionf of March 06, 2002 regarding Adverse Events and Study Dropouts	N/A	X	N/A
	15-MAR-2002	Response to FDA request to questions received by email from Dr. Paul Andreason on February 28, 2002	N/A	X	N/A
	12-MAR-2002	120 Day Safety Update for treatment of Major Depressive	N/A	X	N/A

		Disorder			
	26-FEB-2002	Response to questions received by email from Dr. Paul Andreason on February 11, 2002	N/A	X	N/A
	26-FEB-2002	Amendment provides the data and summary statistics for pivotal dissolution studies	N/A	X	N/A
	26-FEB-2002	A revised version of a White Paper	N/A	X	N/A

EXHIBIT 12

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285
(317) 276-2000

August 26, 1992

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Attn.: Document Control Room 10B-20
5600 Fishers Lane
Rockville, Maryland 20857-1706

Re: IND 37,071 - Duloxetine Hydrochloride (LY248686), capsules. Serial No.: 018
IND 38,838 - Duloxetine Hydrochloride (LY248686), enteric coated tablets
Serial No.: 015

On August 26, 1992, the annual progress report for IND 37,071 was submitted. The IND effective date for IND 38,838 is March 7, 1992, therefore an annual progress report will be due May 5, 1993.

The study of duloxetine hydrochloride using the capsule form has been discontinued. Trials for duloxetine hydrochloride are currently being conducted using the enteric coated tablets under IND 38,838. Therefore, we have designated IND 38,838 as the primary IND file for duloxetine hydrochloride .

At the time we file the next annual report for IND 38,838 on May 5, 1993, we intend to also include information relative to IND 37,071. The combined annual report will be submitted to IND 38,838 and cross-referenced to IND 37,071. By doing so, the due date for the subsequent annual reports for IND 37,071 is adjusted to May 5 of each calendar year. This will allow for a more thorough reviewing and efficient reporting process. We would appreciate your concurrence with this adjustment of the annual report schedule for IND 37,071.

Please call me at (317) 276-2574 or Dr. Al Webber at (317) 276-4255 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,

ELI LILLY AND COMPANY

M. W. Talbott, Ph.D.
Director
Medical Regulatory Affairs

SM

4380.2

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: December 31, 1991.
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1 NAME OF SPONSOR
ELI LILLY AND COMPANY

2. DATE OF SUBMISSION
August 26, 1992

3. ADDRESS *(Number, Street, City, State and Zip Code)*
Lilly Corporate Center
Indianapolis, Indiana 46285

4. TELEPHONE NUMBER *(Include Area Code)*
(317) 276-2000

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Duloxetine Hydrochloride, Compound LY248686

6. IND NUMBER *(If previously assigned)*
IND 37,071

7. INDICATION(S) *(Covered by this submission)*
NA

8. PHASE (S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☒ PHASE 3 ☐ OTHER NA *(Specify)*

9 LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION.
NA

10. IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.

SERIAL NUMBER: 018

11. THIS SUBMISSION CONTAINS THE FOLLOWING *(Check all that apply)*:

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☒ CHEMISTRY/MICROBIOLOGY
☒ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION
☐ ANNUAL REPORT
■ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT:

FORM FDA 1571 (6/91) PREVIOUS EDITION IS OBSOLETE.

12

CONTENTS OF APPLICATION

This application contains the following items: *(check all that apply)*

- ☐ 1. Form FDA 1571 *[21 CFR 312.23 (a) (1)]*
- ☐ 2. Table of contents *[21 CFR 312.23 (a) (2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23 (a) (3)]*
- ☐ 4. General investigational plan *[21 CFR 312.23 (a) (3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23 (a) (5)]*
- 6. Protocol(s) *[21 CFR 312.23 (a) (6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23 (a) (6)]*
  - ☐ b. Investigator data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23 (a) (7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23 (a) (7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23 (a) (8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23 (a) (9)]*
- ☐ 10. Additional information *[21 CFR 312.23 (a) (10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☒ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

J. H. Heiligenstein, M.D.
U. S. Schwertschlag, M.D.
R. G. Thompson, M.D.

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Same as 14 above

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
M. W. Talbott, Ph.D., Director, Medical Regulatory Affairs		
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
Eli Lilly and Company (MC598) (11/3) Lilly Corporate Center Indianapolis, Indiana 46285	(317) 276-2574	8/26/92

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Reports Clearance Officer, PHS
Hubert H. Humphrey Building, Room 721-B
200 Independence Avenue, S.W.
Washington, DC 20201
Attn: PRA

and to:

Office of Management and Budget
Paperwork Reduction Project (0910-0014)
Washington, DC 20503

Please DO NOT RETURN this application to either of these addresses.