Customer No. 28880

Confirmation No.

PTO/SB/17 (10-04)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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FEE TRANSMITTAL for FY 2005

Effective 10/01/2004. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 1,120.00

Complete if Known	
Application Number	
Filing Date	
First Named Inventor	Richard B. Silverman, et al
Examiner Name	
Art Unit	
Attorney Docket No.	4362 (PC16424)

OIPE JC13 FEB 2 5 2005 TRADEMARK OFFICE
RECEIVED MAR 0 8 2005 OFFICE OF PETITIONS
022505

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☑ Deposit Account:

Deposit Account Number: 23-0455

Deposit Account Name: Warner-Lambert Company LLC

The Director is authorized to: *(check all that apply)*

☑ Charge fee(s) indicated below ☑ Credit any overpayments

☑ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	790	2001	395	Utility filing fee	
1002	350	2002	175	Design filing fee	
1003	550	2003	275	Plant filing fee	
1004	790	2004	395	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) 0.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below	Fee Paid
Total Claims		-20** =	x 18.00	= $0.00
Independent Claims		- 3** =	x 88.00	= $0.00
Multiple Dependent				=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	88	2201	44	Independent claims in excess of 3
1203	300	2203	150	Multiple dependent claim, if not paid
1204	88	2204	44	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0.00

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	430	2252	215	Extension for reply within second month	
1253	980	2253	490	Extension for reply within third month	
1254	1,530	2254	765	Extension for reply within fourth month	
1255	2,080	2255	1,040	Extension for reply within fifth month	
1401	340	2401	170	Notice of Appeal	
1402	340	2402	170	Filing a brief in support of an appeal	
1403	300	2403	150	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,370	2501	685	Utility issue fee (or reissue)	
1502	490	2502	245	Design issue fee	
1503	660	2503	330	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	790	2809	395	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	790	2810	395	For each additional invention to be examined (37 CFR 1.129(b))	
1801	790	2801	395	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	
Other fee (specify) 37 CFR 1.20(j)(1) Patent Term Ext.					1,120.00

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($)1,120.00

EXPRESS MAIL NO. EV545392610US
DOCKET NO. 4362 (PC16424)

SUBMITTED BY				(Complete *(if applicable)*)	
Name *(Print/Type)*	Karen DeBenedictis	Registration No. *(Attorney/Agent)*	32,977	Telephone	734-622-3374
Signature	Karen DeBenedictis			Date	02/25/05

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

This collection of information is required by 37 CFR 1.17 and 1.27. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Customer No. 28880

FEB 2 5 2005 PATENT & TRADEMARK OFFICE

Confirmation No.

PTO/SB/21 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	
Filing Date	
First Named Inventor	Richard B. Silverman, et al
Art Unit	
Examiner Name	
Attorney Docket Number	4362 (PC16424)
Total Number of Pages in This Submission	

RECEIVED MAR 1 3 2005 OFFICE OF PETITIONS

ENCLOSURES *(Check all that apply)*

- [✓] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [✓] Other Enclosure(s) (please Identify below):
  - Transmittal of Application for Extension of Patent Term Under 35 U.S.C. § 156
  - Application for Extension of Patent Term Under 35 U.S.C. § 156 w/Exhibitis
  - Certificate of Express Mail
  - Return Postcard

Remarks

Authorization to charge the fee and any additional fees as necessary or credit any overpayment to Deposit Account 23-0455 is hereby given.

EXPRESS MAIL NO. EV545392610US
DOCKET NO. 4362 (PC16424)

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Warner-Lambert Company LLC		
Signature	Karen DeBenedictis		
Printed name	Karen DeBenedictis		
Date	2/25/05	Reg. No.	32,977

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

Signature	Linda A. Zerby		
Typed or printed name	Linda A. Zerby	Date	2/25/2005

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and1.14. This collection is estimated to 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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USPTO Fax No. 703-872-9306

Customer No. 28880

CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10) Applicant(s): Richard B. Silverman, et al	Docket No. 4362 (PC16424)

Serial No	Filing Date	Examiner	Group Art

OIPE
FEB 2 5 2005
PATENT & TRADEMARK OFFICE

Invention:
GAMMA AMINO BUTYRIC ACID ANALOGS AND OPTICAL ISOMERS

RECEIVED
MAR 0 3 2005
OFFICE OF PETITIONS

I hereby certify that this Application for Extension of Patent Term Under 35 U.S.C. § 156
(Identify type of correspondence)

Is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

on Feb. 25 2005
(Date)

Linda A. Zerby
(Typed or Printed Name of Person Mailing Correspondence)

(Signature of Person Mailing Correspondence)

EV545392610US
("Express Mail" Mailing Label Number)

EXPRESS MAIL NO. EV545392610US
DOCKET NO. 4362 (PC16424)

Note: Each paper must have its own certificate of mailing

OIPE
FEB 2 5 2005
TRADEMARK OFFICE

Customer No. 28880 4362 (PC16424)

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE: U. S. PATENT NO. 6,197,819 B1
ISSUED: MARCH 6, 2001
TO: RICHARD B. SILVERMAN
FOR: GAMMA AMINO BUTYRIC ACID ANALOGS AND OPTICAL ISOMERS
ASSIGNEE: NORTHWESTERN UNIVERSITY

Transmittal of Application for Extension of Patent Term Under 35 U.S.C. § 156

Mail Stop Patent Ext.
Commissioner for Patents
P.O. BOX 1450
Alexandria, VA 22313-1450

03/02/2005 HGUTEMA1 00000002 230455 6197719
01 FC:1457 1120.00 DA

EXPRESS MAIL NO. EV545392610US
DOCKET NO. 4362 (PC16424)

Dear Sir:

Transmitted herewith is the application of Warner-Lambert Company LLC for extension of the term of United States Patent No. 6,197,819 B1 under 35 U.S.C. § 156, together with four identical copies thereof. United States Patent 6,197,819 B1 contains product claims to the pregabalin, the active ingredient in LYRICA™. LYRICA™ received permission for commercial marketing or use under subsection 505(b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(b)) on December 30, 2004. Two NDA's relating to LYRICA™ were approved on December 30, 2004 - NDA No. 21-446, which relates to the treatment of neuropathic pain associated with diabetic peripheral neuropathy with LYRICA™, and NDA No. 21-723, which relates to the treatment of neuropathic pain associated with herpes zoster (post herpetic neuralgia) with LYRICA™.

This application for patent term extension of United States Patent 6,197,819 B1 is based on the regulatory review period that ended with the approval of NDA No. 21-446 on December 30, 2004. Applicant, Warner-Lambert Company LLC, is also submitting to the United States Patent and Trademark Office (the Office), concurrently with this application, an application for extension of the term of U.S. Patent 6,001,876, which contains claims to the treatment of pain by administering pregabalin, based on the regulatory review period ending with the approval of NDA No. 21-723 on December 30, 2004.

Applicant asserts that it has the right, under 35 U.S.C. §156, to extend both of the foregoing patents relating to LYRICA™ (pregabalin) because both NDA's relating to LYRICA™ were approved on December 30, 2004 and there were no approvals relating to LYRICA™ prior to December 30, 2004. Applicant respectfully requests that if the Commissioner does not share Applicant's view regarding its right to extend both patents, the Office contact Applicant's undersigned attorney.

Please charge Deposit Account 23-0455 the amount of $1,120.00. The Commissioner is hereby authorized to charge any additional fees that may be required to ensure prosecution of this application, or to credit any overpayment, to Deposit Account 23-0455.

Respectfully submitted,

Dated: 2/24/05

Karen DeBenedictis
Registration No. 32,977
Warner-Lambert Company LLC
2800 Plymouth Road
Ann Arbor, MI 48105
Telephone: (734) 622-3374
Facsimile: (734) 622-1553

Customer No. 28880 4362 (PC16424)

OIPE JC161 FEB 2 5 2005 PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE: U. S. PATENT NO. 6,197,819 B1
ISSUED: MARCH 6, 2001
TO: RICHARD B. SILVERMAN
FOR: GAMMA AMINO BUTYRIC ACID ANALOGS AND OPTICAL ISOMERS
ASSIGNEE: NORTHWESTERN UNIVERSITY

OIPE JC161 FEB 2 5 2005 PATENT & TRADEMARK OFFICE

Transmittal of Application for Extension of Patent Term Under 35 U.S.C. § 156

Mail Stop Patent Ext.
Commissioner for Patents
P.O. BOX 1450
Alexandria, VA 22313-1450

Dear Sir:

Transmitted herewith is the application of Warner-Lambert Company LLC for extension of the term of United States Patent No. 6,197,819 B1 under 35 U.S.C. § 156, together with four identical copies thereof. United States Patent 6,197,819 B1 contains product claims to the pregabalin, the active ingredient in LYRICA™. LYRICA™ received permission for commercial marketing or use under subsection 505(b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(b)) on December 30, 2004. Two NDA's relating to LYRICA™ were approved on December 30, 2004 - NDA No. 21-446, which relates to the treatment of neuropathic pain associated with diabetic peripheral neuropathy with LYRICA™, and NDA No. 21-723, which relates to the treatment of neuropathic pain associated with herpes zoster (post herpetic neuralgia) with LYRICA™.

This application for patent term extension of United States Patent 6,197,819 B1 is based on the regulatory review period that ended with the approval of NDA No. 21-446 on December 30, 2004. Applicant, Warner-Lambert Company LLC, is also submitting to the United States Patent and Trademark Office (the Office), concurrently with this application, an application for extension of the term of U.S. Patent 6,001,876, which contains claims to the treatment of pain by administering pregabalin, based on the regulatory review period ending with the approval of NDA No. 21-723 on December 30, 2004.

EXPRESS MAIL NO. EV545392610US
DOCKET NO. 4362 (PC16424)

Applicant asserts that it has the right, under 35 U.S.C. §156, to extend both of the foregoing patents relating to LYRICA™ (pregabalin) because both NDA's relating to LYRICA™ were approved on December 30, 2004 and there were no approvals relating to LYRICA™ prior to December 30, 2004. Applicant respectfully requests that if the Commissioner does not share Applicant's view regarding its right to extend both patents, the Office contact Applicant's undersigned attorney.

Please charge Deposit Account 23-0455 the amount of $1,120.00. The Commissioner is hereby authorized to charge any additional fees that may be required to ensure prosecution of this application, or to credit any overpayment, to Deposit Account 23-0455.

Respectfully submitted,

Dated: 2/24/05

Karen DeBenedictis
Registration No. 32,977
Warner-Lambert Company LLC
2800 Plymouth Road
Ann Arbor, MI 48105
Telephone: (734) 622-3374
Facsimile: (734) 622-1553

Customer No. 28880 4362 (PC16424)

OIPE FEB 25 2005 PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE: U. S. PATENT NO. 6,197,819 B1

ISSUED: MARCH 6, 2001

TO: RICHARD B. SILVERMAN, *ET AL.*

FOR: GAMMA AMINO BUTYRIC ACID ANALOGS AND OPTICAL ISOMERS

ASSIGNEE: NORTHWESTERN UNIVERSITY

OIPE FEB 25 2005 PATENT & TRADEMARK OFFICE

Application for Extension of the Term of United States Patent No. 6,197,819 B1 Under 35 U.S.C. § 156

EXPRESS MAIL NO. EV545392610US
DOCKET NO. 4362 (PC16424)

Mail Stop Patent Ext.
Commissioner for Patents
P.O. BOX 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicant, Warner-Lambert Company LLC, a corporation of the State of New Jersey having a place of business at 201 Tabor Road, Morris Plains, New Jersey 07950, represents that it is the exclusive licensee of rights in Letters Patent of the United States No. 6,197,819 B1, granted to Richard B. Silverman and Ryszard Andruszkiewicz on the 6th day of March, 2001, for Gamma Amino Butyric Acid Analogs and Optical Isomers. Such patent is owned by Northwestern University by virtue of the assignment recorded in the United States Patent and Trademark Office on April 20, 1995 at Reel 7441, Frame 0079, and the assignment recorded in the United States Patent and Trademark Office on December 12, 2000 at Reel 011354, Frame 0059. Applicant further represents that it has been authorized by Northwestern University to apply for an extension of the term of United States No. 6,197,819 B1 by virtue of a letter dated May 25, 2004, which is appended hereto as Exhibit A.

Pursuant to the provisions of 35 U.S.C. § 156, and based on the materials set forth herein and in the accompanying papers, Applicant hereby applies for an extension of the term of United States Patent No. 6,197,819 B1, which is currently set

to expire on March 6, 2018, of 299 days. If this extension is granted, such patent would not expire until December 30, 2018. In the materials that follow, numbered paragraphs "1" through "15" correspond to paragraph numbers "1" through "15" of 37 C.F.R. § 1.740(a).

(1) The approved product is the active ingredient, including any salt of the active ingredient, in LYRICA, *i.e.*, pregabalin, which is the generic name of the active ingredient in LYRICA™ (LYRICA is a trademark of Parke Davis & Company LLC LTD LIAB CO Michigan), and any pharmaceutically acceptable salts of pregabalin. Pregabalin, the active ingredient in LYRICA™, is identified further as follows:

Chemical Name

S-(+)-4-amino-3-(2-methylpropyl)butanoic acid

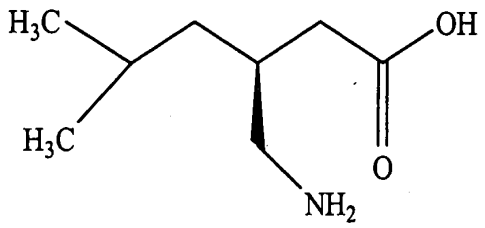
Generic Name

Pregabalin

Molecular Formula

$C_8H_{18}O_2N$

Structural Formula



Physical Form

LYRICA™ (pregabalin) capsules contain 25, 50, 75, 100, 150, 200, 225, or 300 mg of pregabalin. Pregabalin is a white to off-white crystalline

solid with a pk_{a1} of 4.2 and a pk_{a2} of 10.6. It is freely soluble in water and in both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is -1.35.

(2) LYRICA™ (pregabalin) was subject to regulatory review under subsection 505(b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(b)).

(3) LYRICA™ (pregabalin) received permission for commercial marketing or use under subsection 505(b) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(b)) on December 30, 2004. The FDA's letter dated December 30, 2004, reporting the approval of NDA No. 21-446, which relates to the treatment of neuropathic pain associated with diabetic peripheral neuropathy with LYRICA™, and the attachments to such letter, are appended hereto as Exhibit B. The FDA's letter dated December 30, 2004, reporting the approval of NDA No. 21-723, which relates to the treatment of neuropathic pain associated with herpes zoster (postherptic neuralgia) with LYRICA™, and the attachments to such letter, are appended hereto as Exhibit C. This application for patent term extension is based on the regulatory review period that ended with the approval of NDA No. 21-446 on December 30, 2004. An application for extension of the term of U.S. Patent 6,001,876, which contains claims to the treatment of pain by administering pregabalin or a pharmaceutically acceptable salt of pregabalin to a mammal in need of such treatment is being filed concurrently with this application and is based on the regulatory review period ending with the approval of NDA No. 21-723 on December 30, 2004.

(4) The active ingredient in LYRICA™ is S-(+)-4-amino-3-(2-methylpropyl)butanoic acid (pregabalin). Neither pregabalin nor any salt of pregabalin has 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.

(5) This application is being submitted within the sixty day period permitted for its submission pursuant to 37 C.F.R. § 1.720(f). The last day on which this application could be submitted is February 28, 2005.

(6) The patent for which an extension is being sought is identified as follows:

Inventors: RICHARD B. SILVERMAN
RYSZARD ANDRUSZKIEWICZ

Patent No.: 6,197,819 B1

Title: GAMMA AMINO BUTYRIC ACID ANALOGS AND OPTICAL ISOMERS

Issued: MARCH 6, 2001

Expires: MARCH 6, 2018

(7) A copy of United States Patent No. 6,197,819 B1, the patent for which an extension is sought, is appended as Exhibit D.

(8) No disclaimer, certificate of correction, or reexamination certificate has issued for United States Patent No. 6,197,819 B1. One receipt for a maintenance fee payment has issued for this patent, and a copy of such receipt is attached hereto as Exhibit E.

(9) United States Patent No. 6,197,819 B1 claims the approved product and pharmaceutical compositions comprising the approved product. Claim 1 embraces the optically active approved product *per se*. Claim 2 embraces 4-amino-3-(2-methylpropyl)butanoic acid, which is a genus that includes pregabalin, its opposite enantiomer, R-(-)-(4)-amino-3-(2-methylpropyl)butanoic acid, and all mixtures thereof. Claim 3 embraces pharmaceutically acceptable salts of pregabalin. Claim 4 embraces pharmaceutical compositions comprising pregabalin, or a pharmaceutically acceptable salt of pregabalin, and a pharmaceutically acceptable carrier.

A listing of each applicable patent claim and the manner in which each such claim reads on the approved product follows:

Claim 1 of U.S. Patent 6,197,819 B1 reads "A compound of the formula S-(+)-4-amino-3-(2-methylpropyl)butanoic acid as a single optical isomer". Claim 1 therefore claims pregabalin, which is S-(+)-4-amino-3-(2-methylpropyl)butanoic acid. Claim 1 therefore reads on the approved product.

Claim 2 of U.S. Patent 6,197,819 B1 reads "4-amino-3-(2-methylpropyl)butanoic acid, or a pharmaceutically acceptable salt thereof". 4-Amino-3-(2-methylpropyl)butanoic acid is a genus that includes pregabalin, its opposite enantomer, R-(-)-(4)-amino-3-(2-methylpropyl)butanoic acid, and all mixtures thereof. Claim 2 therefore embraces pregabalin, which is the S-(+) enantiomer of 4-amino-3-(2-methylpropyl)butanoic acid, and its pharmaceutically acceptable salts. Claim 2 therefore reads on the approved product.

Claim 3 of U.S. Patent 6,197,819 B1 reads "A pharmaceutically acceptable salt of S-(+)-4-amino-3-(2-methylpropyl)butanoic acid, said salt being present as a single optical isomer." S-(+)-4-amino-3-(2-methylpropyl)butanoic acid is pregabalin. Claim 3 therefore embraces all pharmaceutically acceptable salts of pregabalin as single optical isomers. Claim 3 therefore reads on the approved product.

Claim 4 of U.S. Patent 6,197,819 B1 reads "A pharmaceutical composition comprising a compound any one of claims 1 or 3, together with a pharmaceutically acceptable carrier." Claim 4 therefore embraces all pharmaceutical compositions that comprise pregabalin or a pharmaceutically acceptable salt of pregabalin and a pharmaceutically acceptable carrier. Claim 4 therefore reads on the approved product.

(10) The relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to permit the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

- An exemption under subsection (i) of section 505 of the Federal Food, Drug and Cosmetic Act became effective for LYRICA™ (pregabalin) on August 24, 1997, *i.e.,* thirty days following receipt by the FDA of Investigational New Drug ("IND") Application No. 53,763 on July 25, 1997.

- A new Drug Application ("NDA") under subsection (b) of section 505 of the Federal Food, Drug and Cosmetic Act for LYRICA™ (pregabalin) was initially submitted on October 30, 2003 as NDA No. 21-446. This NDA was submitted by Pfizer Inc ("Pfizer"), a company incorporated in Delaware and having its headquarters in New York, NY, and of which Applicant, Warner-Lambert Company LLC, is a wholly owned subsidiary. By a letter dated November 25, 2003, the FDA informed Pfizer that it had split NDA No. 21-446 into separate NDA's according to indication. These NDA's were: NDA No. 21-446, relating to the treatment of neuropathic pain associated with diabetic peripheral neuropathy with LYRICA™; and NDA No. 21-723, relating to the treatment of neuropathic pain associated with herpes zoster (postherpetic neuralgia) with LYRICA™.

- NDA No. 21-446 was approved on December 30, 2004. This application for patent term extension is based on the regulatory review period that ended with the approval of NDA No. 21-446 on December 30, 2004. An application for patent term extension of U.S. Patent 6,001,876, which contains claims that embrace methods of treating pain by administering pregabalin or a pharmaceutically acceptable salt of

pregabalin to a mammal in need of such treatment, is being submitted concurrently with this application and is based on the regulatory review period ending with the approval of NDA No. 21-723, which was also approved on December 30, 2004.

(11) A brief description 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 is appended as Exhibit F.

(12) It is Applicant's opinion that United States Patent No. 6,197819 B1 is eligible, under 35 U.S.C. §156, for an extension of its term. The length of the extension claimed is 299 days. If this extension is granted, the term of such patent, which is currently set to expire on March 6, 2018, would not expire until December 30, 2018.

The requirements of 35 U.S.C. § 156(a) and 156(c)(4) have been satisfied as follows:

- U.S. Patent No. 6,197, 819 B1 claims a product, LYRICA™ (pregabalin).

- U.S. Patent No. 6,197, 819 B1 has not yet expired. It is currently set to expire on March 6, 2018.

- The term of U.S. Patent No. 6,197,819 B1 has never been extended.

- This application for extension is being submitted by Warner-Lambert Company LLC, the exclusive licensee of rights in U.S. Patent No. 6,197,819 B1, as authorized by Northwestern University, the owner of the patent, in accordance with the requirements of 35 U.S.C. § 156(d).

- The product, LYRICA™ (pregabalin), has been subject to a regulatory review period under section 505 of the Federal Food, Drug and Cosmetic Act before its commercial marketing or use, and permission for said commercial marketing or use is the first permitted commercial marketing or use under section 505 of the Federal Food, Drug and Cosmetic Act.

- No patent that claims pregabalin or a method of making or using pregabalin has been extended, and no application for extension of such a patent has been filed for the regulatory review period which forms the basis for this application.

The length of extension of the term of U.S. Patent No. 6,197,819 B1 of 299 days claimed by Applicant was determined according to the provisions of 35 U.S.C. § 156(c) and § 156(g) as follows:

- According to 35 U.S.C. § 156(c), the length of extension is equal to the regulatory review period for the approved product, as defined in 35 U.S.C. § 156(g), which occurred after the patent issued, subject to the provisions of paragraphs (1) to (4) of 35 U.S.C. § 156(c) and the limitations of 35 U.S.C. § 156(g)(6).

- Under 35 U.S.C. § 156(g), the regulatory review period is the sum of (I) the number of days in the period beginning on the date on which an exemption under subsection 505(i) of the Federal Food, Drug and Cosmetic Act became effective for the approved product and ending on the date the NDA for the approved product was initially submitted under subsection 505 of the Federal Food, Drug and Cosmetic Act, and (II) the number of days in the period beginning on the date the NDA was initially submitted under subsection 505 of the Federal Food, Drug and Cosmetic Act and ending on the date the NDA was approved. As indicated in paragraph 10 of this application, the exemption under subsection 505 (i) became effective on August 24, 1997. As also indicated in paragraph 10, NDA No. 21-446 was submitted to the FDA on October 30, 2003, and was later divided by the FDA into separate NDA's according to indication – NDA No. 21-446 (neuropathic

pain associated with diabetic peripheral neuropathy) and NDA No. 21-723 (neuropathic pain associated with herpes zoster (postherpetic neuralgia)). As also indicated in paragraph 10, NDA No. 21-446 was approved on December 30, 2004. This application for extension of the term of U.S. Patent 6,197,819B1 is based on the regulatory review period that ended with the approval of NDA No. 21-446 on December 30, 2004. Therefore, the length of the regulatory review period is the sum of 2258 days and 427 days. This is 2685 days.

- U.S. Patent No. 6,197,819B1, issued on March 6, 2001. The portion of the regulatory review period that occurred after issuance of the patent is, therefore, 1395 days.

- Paragraphs (1) and (4) of 35 U.S.C. § 156(c) do not apply.

- Under 35 U.S.C. § 156(c)(2), the regulatory review period must be reduced by one-half of the period determined under 35 U.S.C. § 156 (g)(1)(B)(i) that occurred after the patent issued. As indicated in above in paragraph 12 of this application, the period determined under 35 U.S.C. § 156(g)(1)(B)(i) is 2258 days. The portion of this period that occurred after March 6, 2001, the date of issuance of the patent, is 968 days. One-half of 968 days is 484 days. Subtracting this amount, 484 days, from 1395 days (the portion of the regulatory review period that occurred after issuance of the patent) leaves a reduced extension of 911 days.

- According to 35 U.S.C. § 156(c)(3), if the period remaining in the term of a patent after the date of approval of the approved product plus the regulatory review period as revised in

accordance with 35 U.S.C. § 156(c)(1) and (2) exceeds fourteen years, the period of extension shall be reduced so that the total of both periods does not exceed fourteen years. Adding the 911 day period determined in subsection 12(B)(e) above to March 6, 2018, the expiration date of U.S. Patent 6, 197,819 B1, gives a date of September 2, 2020. This date, September 2, 2020, is later than December 30, 2018, the date obtained by adding 14 years to the date of approval of the approved product. Therefore, in compliance with 35 U.S.C. § 156(c)(3), Applicant is claiming an extension period of 299 days rather than 911 days. When the extension period of 299 days being claimed by Applicant is added to March 6, 2018, the current expiration date of U.S. Patent No. 6,197,819 B1, the date obtained is December 30, 2018, the same date obtained by adding 14 years to the date of approval of the approved product. Hence, Applicant is in compliance with 35 U.S.C. § 156(c)(3).

- Because U.S. Patent No. 6, 197,819 B1 issued after the date of enactment of 35 U.S.C. § 156, the five-year limitation of § 156(g)(6)(A) applies. The extension period of 299 days claimed by Applicant does not exceed the five-year limitation on the extension period imposed by 35 U.S.C. § 156(g)(6)(A).

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patent and Trademarks and the Secretary of Health and Human Services any information, which is material to the determination of entitlement to the 299 day extension being sought to the term of the United States Patent No. 6,197,819 B1.

(14) The prescribed fee for receiving and acting on this application for extension is to be charged to Deposit Account 23-0455, as authorized in the enclosed transmittal letter.

(15) Please address all inquires and correspondence relating to this application for patent term extension to:

Karen DeBenedictis
Warner-Lambert Company LLC
2800 Plymouth Road, 016/410E/PAT/6
Ann Arbor, MI 48105

Pursuant to 37 C.F.R. § 1.740(b), two identical copies of this application, with accompanying exhibits, are enclosed herewith. Pursuant to M.P.E.P. § 2753, an additional two copies of this application, with accompanying exhibits, are enclosed herewith. Accordingly, a total of four copies of these application papers and one original application for patent term extension of United States Patent No. 6,197,819B1 are submitted herewith.

Respectfully submitted,

Dated: 2/24/05

Karen DeBenedictis

Karen DeBenedictis
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Warner-Lambert Company LLC
2800 Plymouth Road
Ann Arbor, MI 48105
Telephone: (734) 622-3374
Facsimile: (734) 622-1553

Technology Transfer Program
Northwestern University
1880 Oak Avenue, Suite 100
Evanston, Illinois 60201-5937

Phone 847-491-3005
Fax 847-491-3625
www.northwestern.edu/ttp

Received in
JUN 0 3 2004
AA Patent Dept.

NORTHWESTERN
UNIVERSITY

(A)

May 25, 2004

Pfizer, Inc.
2800 Plymouth Road
Ann Arbor, Michigan 48105

RE: U. S. Patent No. 6,197,819 issued March 6, 2001
Pfizer Reference No. 4362
Northwestern Reference No. NU 8912

To Whom It May Concern:

Northwestern, as the assignee and owner of the rights in U. S. Patent 6,197,819, which claims pregabalin and the foreign equivalents of such patent, does hereby grant Pfizer Inc. and its affiliates and agents the authority to prepare and file any and all applications and petitions that need to be filed worldwide in order to request extension of the term of any patent claiming pregabalin, and, specifically, U. S. Patent 6,197,819 and its foreign equivalents, in the United States and in any country in which an application that is a foreign equivalent of U. S. Patent 6,197,819 has issued as a patent or issues as a patent in the future.

"Foreign equivalents of U. S. Patent 6,187,819" refers to any patent that has issued or that issues in the future in a country that is not the United States of America from an application owned by Northwestern University, which, as originally filed, claimed the compound pregabalin, and which claims priority from one or more of the following U. S. patent applications: Serial No. 08/064,285, filed on May 18, 1993; Serial No. 07/886,080, filed on May 20, 1992; and Serial No. 07/618,692, filed on November 27, 1990.

If you have any questions, please do not hesitate to contact me at (847)491-2105 or by e-mail at indrani@northwestern.edu.

Sincerely,

Indrani Mukharji

Indrani Mukharji, Ph.D.
Executive Director

/c/license/pfizerpermission

(B)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

RECEIVED
JAN 11 2005
WORLDWIDE REGULATORY AFFAIRS

NDA 21-446

Pfizer Global Research and Development
2800 Plymouth Road
Ann Arbor, Michigan 48105

Attention: Jonathan M. Parker, RPh, MS
Global Regulatory Leader, Regulatory Affairs

Dear Mr. Parker:

Please refer to your new drug application (NDA) dated October 30, 2003, received October 31, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LYRICA™ (pregabalin) Capsules, 25/50/75/100/150/200/225/300 mg.

We acknowledge receipt of your submissions dated November 7 and 20, 2003, and January 8, 12, 16, and 30, February 5, 12, 13, 16, 17, 20, 23, 25(3), 26, and 27, March 3, 17, 19, 30, and 31, April 6, 8, 9, 12, 19, 20, 21, 22, and 28, May 3, 4, 13, 17, 18, 19, 25, 26, and 27, June 2, 3, 4, 7, 9, 14, 18, 21, 22, 24, 25, 28, and 29, July 1, 2, 6, 7, 9, 14, 16, 20, 22, 26, and 27, and August 3, 5, 12, 18, 19, 20, 23, 24, and 25, September 3, 7 and 8, October 26, November 1(2), and December 30(2), 2004.

The November 1, 2004, submission constituted a complete response to our July 29, 2004, action letter.

This new drug application provides for the use of LYRICA™ (pregabalin) Capsules for the management of neuropathic pain associated with diabetic peripheral neuropathy.

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

The final printed labeling (FPL) must be identical to the submitted labeling (text for the package insert and for the patient package insert submitted December 30, 2004). Immediate container and carton labels must be identical to those submitted July 9, 2004, with the addition of the word "Capsules" to the established name as agreed upon in the November 3, 2004, teleconference. 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 these submissions "**FPL for approved NDA 21-446.**" Approval of this submission by FDA is not required before the labeling is used.

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 the pediatric study requirement for this application.

The final scheduling of this product under the Controlled Substances Act is currently proceeding, but not yet complete as of the date of this letter. We note your commitment of December 30, 2004, not to market this drug until the scheduling is finalized. We further note that, when finalized, appropriate revisions will be made to the package insert, the patient-package insert and the product labeling through supplementation of your NDA. This would include the statements detailing the scheduling of Lyrica in the labeling, as required under 21 CFR 201.57 (h)(1).

We remind you of your postmarketing study commitments in your submission dated December 30, 2004. These commitments are listed below.

1. Complete an adequate and well-controlled clinical study or studies to better assess the ophthalmologic effects of pregabalin

   Protocol Submission: by 08/05
   Study Start: by 07/06
   Final Report Submission: by 01/09

2. Complete an in vitro study of the propensity of pregabalin to induce CYP-enzyme metabolism

   Protocol Submission: by 02/05
   Study Start: by 03/05
   Final Report Submission: by 12/05

3. Complete adequate and well-controlled clinical studies to assess the effect of pregabalin on nerve conduction velocity (NCV)

   Protocol Submission: by 04/04
   Study Start: by 09/04
   Final Report Submission: by 03/06

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports 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 of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, 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**."

In addition, 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 the Division of Anesthetic, Critical Care and Addiction Drug Products and two copies of both the promotional materials and the package insert directly to:

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

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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.

If you have any questions, call Lisa Malandro, Regulatory Project Manager, at (301) 827-7416.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures

PROPOSED LABELING TEXT (NEUROPATHIC PAIN – DPN INDICATION-PHN INDICATION)

DRAFT US PACKAGE INSERT

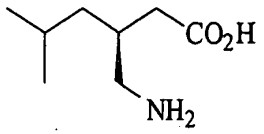
PRODUCT NAME

LYRICA™ (pregabalin) 25, 50, 75, 100, 150, 200, 225, and 300-mg Capsules

Version Date: **December 30, 2004**

DESCRIPTION

Pregabalin is described chemically as (*S*)-3-(aminomethyl)-5-methylhexanoic acid. The molecular formula is $C_8H_{17}NO_2$ and the molecular weight is 159.23. The chemical structure of pregabalin is:



Pregabalin is a white to off-white, crystalline solid with a pK_{a1} of 4.2 and a pK_{a2} of 10.6. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is – 1.35.

LYRICA (pregabalin) Capsules are supplied as imprinted hard-shell capsules containing 25, 50, 75, 100, 150, 200, 225, and 300 mg of pregabalin, along with lactose monohydrate, cornstarch, and talc as inactive ingredients. The capsule shells contain gelatin and titanium dioxide. In addition, the orange capsule shells contain red iron oxide and the white capsule shells contain sodium lauryl sulfate and colloidal silicon dioxide. Colloidal silicon dioxide is a manufacturing aid that may or may not be present in the capsule shells. The imprinting ink contains shellac, black iron oxide, propylene glycol, and potassium hydroxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

LYRICA (pregabalin) binds with high affinity to the alpha$_2$-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin is unknown, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the alpha$_2$-delta subunit may be involved in pregabalin's antinociceptive effects in animal models. *In vitro*, pregabalin reduces the calcium-dependent release of several neurotransmitters, possibly by modulation of calcium channel function.

While pregabalin is a structural derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), it does not bind directly to $GABA_A$, $GABA_B$, or benzodiazepine receptors, does not augment $GABA_A$ responses in cultured neurons, does not alter rat brain GABA concentration or have acute effects on GABA uptake or degradation. In vitro, pregabalin, like gabapentin, may affect the GABA transporter protein. Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenaline reuptake.

Pharmacokinetics

Pregabalin is well absorbed after oral administration, is eliminated largely by renal excretion, and has an elimination half-life of about 6 hours.

Absorption and Distribution

Following oral administration of pregabalin capsules under fasting conditions, peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is ≥90% and is independent of dose. Following single- (25 to 300 mg) and multiple- dose (75 to 900 mg/day) administration, maximum plasma concentrations (Cmax) and area under the plasma concentration-time curve (AUC) values increase linearly. Following repeated administration, steady state is achieved within 24 to 48 hours. Multiple-dose pharmacokinetics can be predicted from single-dose data.

The rate of pregabalin absorption is decreased when given with food, resulting in a decrease in Cmax of approximately 25% to 30% and an increase in T_{max} to approximately 3 hours. However, administration of pregabalin with food has no clinically relevant effect on the total absorption of pregabalin. Therefore, pregabalin can be taken with or without food.

Pregabalin does not bind to plasma proteins. The apparent volume of distribution of pregabalin following oral administration is approximately 0.5 L/kg. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood brain barrier. Although there are no data in humans, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. In addition, pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats.

Metabolism and Elimination

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 90% of the administered dose was recovered in the urine as unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, pregabalin (S-enantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits, or monkeys.

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug with a mean elimination half-life of 6.3 hours in subjects with normal renal function. Mean renal clearance was estimated to be 67.0 to 80.9 mL/min in young healthy subjects. Because pregabalin is not bound to plasma proteins this clearance rate indicates that renal tubular reabsorption is involved. Pregabalin elimination is nearly proportional to creatinine clearance (CLcr) (see **Special Populations, Renal Impairment and DOSAGE AND ADMINISTRATION, Patients with Impaired Renal Function**).

Special Populations

Race: In population pharmacokinetic analyses of the clinical studies in various populations, the pharmacokinetics of pregabalin were not significantly affected by race (Caucasians, Blacks, and Hispanics).

Gender: Population pharmacokinetic analyses of the clinical studies showed that the relationship between daily dose and pregabalin drug exposure is similar between genders.

Renal Impairment and Hemodialysis: Pregabalin clearance is nearly proportional to creatinine clearance (CLcr). Dosage reduction in patients with renal dysfunction is necessary. Pregabalin is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients on hemodialysis, dosing must be modified (see **DOSAGE AND ADMINISTRATION, Patients with Renal Impairment**).

Elderly: Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in CLcr. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function (see **DOSAGE AND ADMINISTRATION, Patients with Renal Impairment**).

Pediatric Pharmacokinetics: Pharmacokinetics of pregabalin have not been adequately studied in pediatric patients.

Drug Interactions:

In Vitro Studies: Pregabalin, at concentrations that were, in general, 10-times those attained in clinical trials, does not inhibit human CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzyme systems. The potential of pregabalin to induce these enzymes has not been studied in vitro.

In Vivo Studies: The drug interaction studies described in this section were conducted in healthy adults, and across various patient populations.

Gabapentin: The pharmacokinetic interactions of pregabalin and gabapentin were investigated in 12 healthy subjects following concomitant single-dose administration of 100-mg pregabalin and 300-mg gabapentin and in 18 healthy subjects following concomitant multiple-dose administration of 200-mg pregabalin every 8 hours and 400-mg gabapentin every 8 hours. Gabapentin pharmacokinetics following single- and multiple-dose administration were unaltered by pregabalin coadministration. The extent of pregabalin absorption was unaffected by gabapentin coadministration, although there was a small reduction in rate of absorption.

Oral Contraceptive: Pregabalin coadministration (200 mg three times a day) had no effect on the steady-state pharmacokinetics of norethindrone and ethinyl estradiol (1 mg/35 μg, respectively) in healthy subjects.

Lorazepam: Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of lorazepam single-dose pharmacokinetics and single-dose administration of lorazepam (1 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Oxycodone: Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of oxycodone single-dose pharmacokinetics. Single-dose administration of oxycodone (10 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Ethanol: Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of ethanol single-dose pharmacokinetics and single-dose administration of ethanol (0.7 g/kg) had no effect on the steady-state pharmacokinetics of pregabalin.

Phenytoin, carbamazepine, valproic acid, and lamotrigine: Steady-state trough plasma concentrations of phenytoin, carbamazepine and carbamazepine 10,11 epoxide, valproic acid, and lamotrigine were not affected by concomitant pregabalin (200 mg three times a day) administration.

Population pharmacokinetic analyses in patients treated with pregabalin and various concomitant medications suggest the following:

Therapeutic class	Specific concomitant drug studied
Concomitant drug has no effect on the pharmacokinetics of pregabalin	
Hypoglycemics	Glyburide, insulin, metformin,
Diuretics	Furosemide
Antiepileptic Drugs	Tiagabine
Concomitant drug has no effect on the pharmacokinetics of pregabalin and pregabalin has no effect on the pharmacokinetics of concomitant drug	
Antiepileptic Drugs	Carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, valproic acid

CLINICAL STUDIES

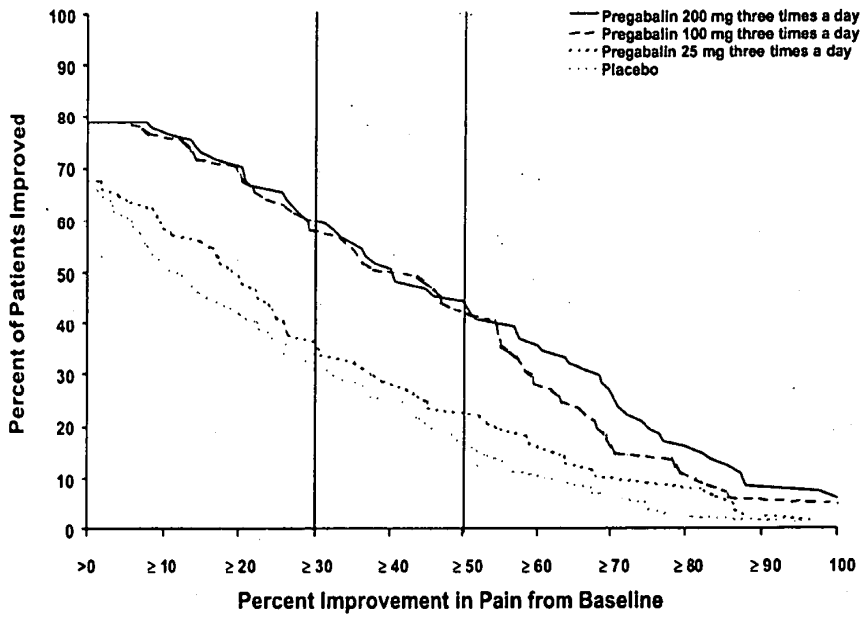
Neuropathic pain associated with diabetic peripheral neuropathy

The efficacy of the maximum recommended dose of LYRICA for the management of neuropathic pain associated with diabetic peripheral neuropathy was established in three double-blind, placebo-controlled, multicenter studies that enrolled 729 patients with three times a day dosing, two of which studied the maximum recommended dose.
Studies DPN 1 and DPN 2 enrolled a total of 483 patients of which 89% completed the studies. Patients enrolled had Type 1 or 2 diabetes mellitus with a diagnosis of painful distal symmetrical sensorimotor polyneuropathy for 1 to 5 years. The patients had a minimum mean baseline pain score of ≥4 on an 11-point numerical pain rating scale ranging from 0 (no pain) to 10 (worst possible pain). The baseline mean pain scores across the two studies ranged from 6.1 to 6.7. Patients were permitted up to 4 grams of acetaminophen per day as needed for pain, in addition to pregabalin. Patients recorded their pain daily in a diary.

Study DPN 1: This 5-week study of 337 patients (240 pregabalin and 97 placebo) compared LYRICA 25, 100, or 200 mg three times a day with placebo. Treatment with LYRICA 100 and 200 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. There was no evidence of a greater effect on pain scores of the 200 mg three times a day dose than the 100 mg three times a day dose, but

there was evidence of dose dependent adverse effects (see ADVERSE REACTIONS). For various degrees of improvement in pain from baseline to study endpoint, Figure 1 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

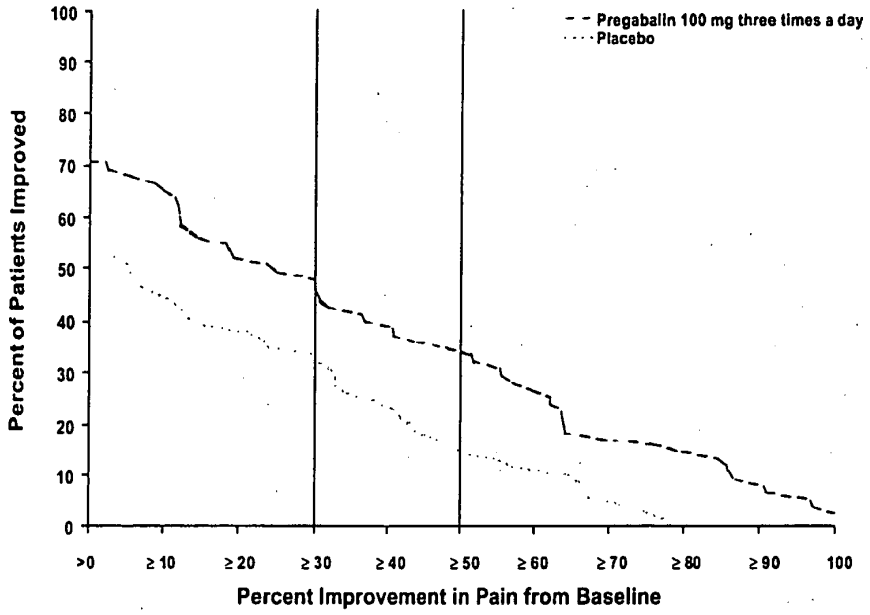
Figure 1: Patients Achieving Various Levels of Pain Relief



Study DPN 2: This 8-week study of 146 patients (76 pregabalin and 70 placebo) compared LYRICA 100 mg three times a day with placebo. Treatment with LYRICA 100 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. For various degrees of improvement in pain from baseline to study endpoint, Figure 2 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not

complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 2: Patients Achieving Various Levels of Pain Relief

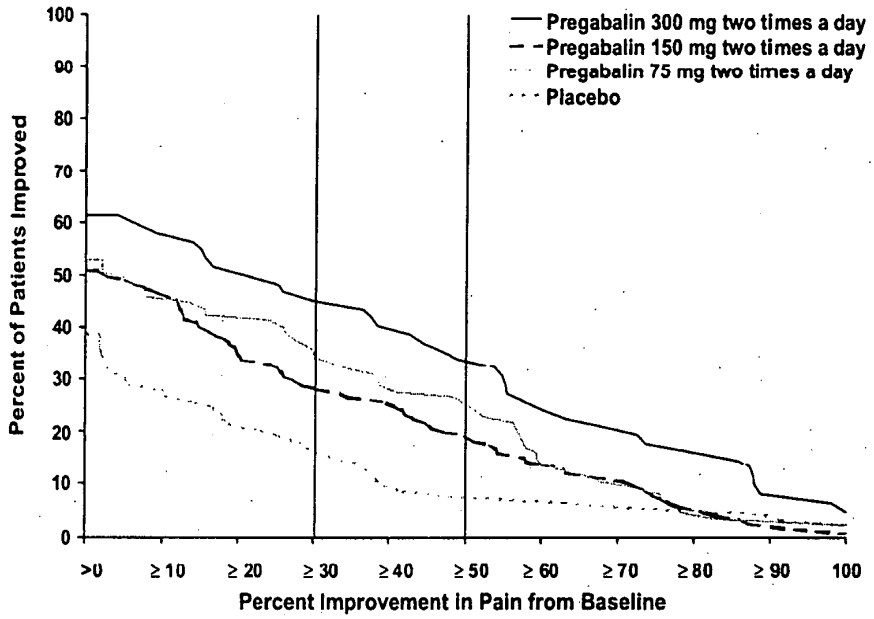


Postherpetic Neuralgia

The efficacy of LYRICA for the management of postherpetic neuralgia was established in three double-blind, placebo-controlled, multicenter studies. These studies enrolled 779 patients, of whom 566 completed the studies. These patients had neuralgia persisting for at least 3 months following healing of herpes zoster rash and a minimum baseline score of ≥4 on an 11-point numerical pain rating scale ranging from 0 (no pain) to 10 (worst possible pain). The baseline mean pain scores across the 3 studies ranged from 6 to 7. Patients were permitted up to 4 grams of acetaminophen per day as needed for pain, in addition to pregabalin. Patients recorded their pain daily in a diary.

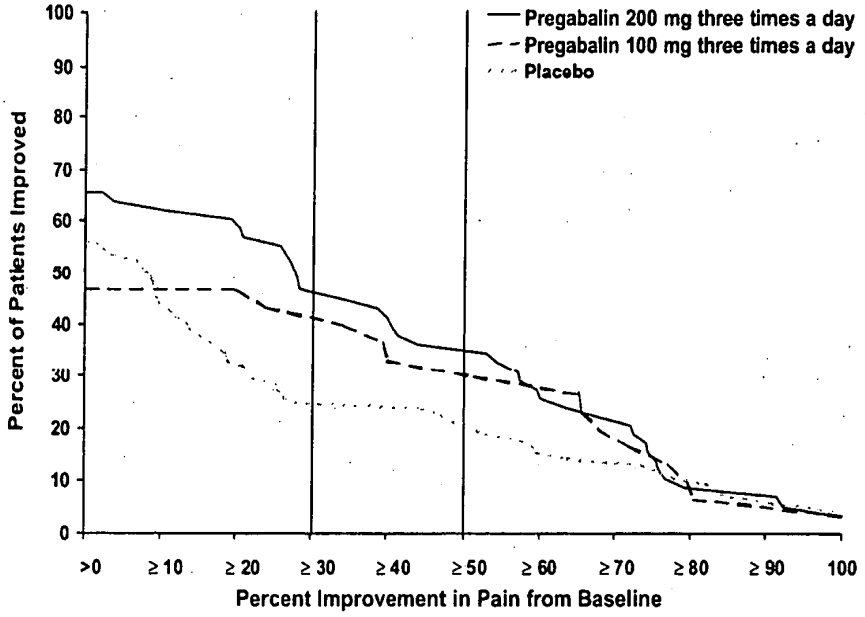
Study PHN 1: This 13-week study of 368 patients (275 pregabalin and 93 placebo) compared LYRICA 75, 150, and 300 mg twice daily with placebo. Patients with creatinine clearance (CLcr) between 30 to 60 mL/min were randomized to 75 mg, 150 mg, or placebo twice daily. Patients with creatinine clearance greater than 60 mL/min were randomized to 75 mg, 150 mg, 300 mg or placebo twice daily. In patients with creatinine clearance greater than 60 mL/min treatment with all doses of LYRICA statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. Despite differences in dosing based on renal function, patients with creatinine clearance between 30 to 60 mL/min tolerated LYRICA less well than patients with creatinine clearance greater than 60 mL/min as evidenced by higher rates of discontinuation due to adverse events. For various degrees of improvement in pain from baseline to study endpoint, Figure 3 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 3: Patients Achieving Various Levels of Pain Relief



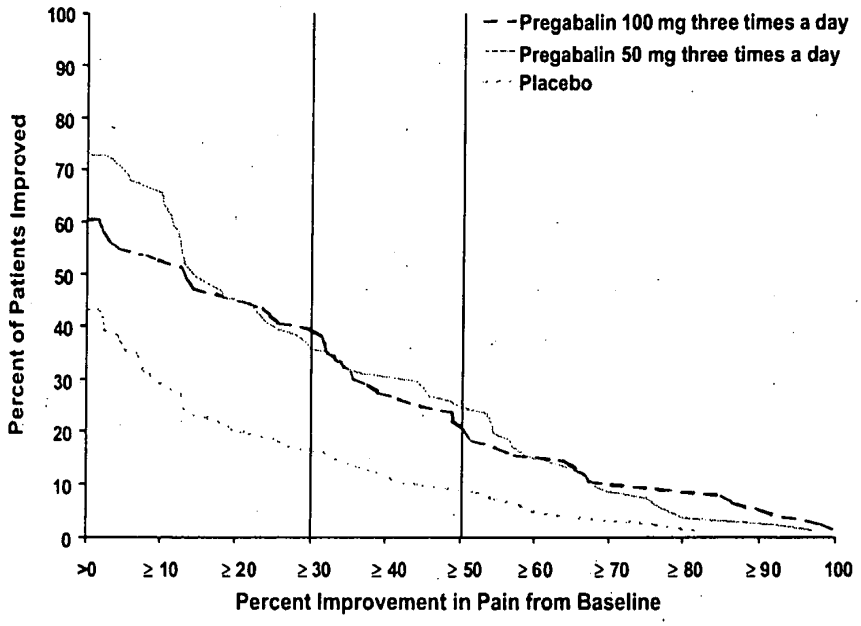
Study PHN 2: This 8-week study of 173 patients (89 pregabalin and 84 placebo) compared LYRICA 100 or 200 mg three times a day with placebo, with doses assigned based on creatinine clearance. Patients with creatinine clearance between 30 to 60 mL/min were treated with 100 mg three times a day, and patients with creatinine clearance greater than 60 mL/min were treated with 200 mg three times daily. Treatment with LYRICA statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. For various degrees of improvement in pain from baseline to study endpoint, Figure 4 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 4: Patients Achieving Various Levels of Pain Relief



Study PHN 3: This 8-week study of 238 patients (157 pregabalin and 81 placebo) compared LYRICA 50 or 100 mg three times a day with placebo with doses assigned regardless of creatinine clearance. Treatment with LYRICA 50 and 100 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. Patients with creatinine clearance between 30 to 60 mL/min tolerated LYRICA less well than patients with creatinine clearance greater than 60 mL/min as evidenced by markedly higher rates of discontinuation due to adverse events. For various degrees of improvement in pain from baseline to study endpoint, Figure 5 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 5: Patients Achieving Various Levels of Pain Relief



INDICATIONS AND USAGE

LYRICA is indicated for management of

- Neuropathic pain associated with diabetic peripheral neuropathy
- Postherpetic neuralgia

CONTRAINDICATIONS

LYRICA is contraindicated in patients with known hypersensitivity to pregabalin or any of its components.

WARNINGS

Tumorigenic Potential

In standard preclinical *in vivo* lifetime carcinogenicity studies of pregabalin, an unexpectedly high incidence of hemangiosarcoma was identified in two different strains of mice. (See **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility**). The clinical significance of this finding is unknown. Clinical experience during pregabalin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies across various patient populations, comprising 6396 patient-years of exposure in patients >12 years of age, new or worsening-preexisting tumors were reported in 57 patients. Without knowledge of the background incidence and recurrence in similar populations not treated with LYRICA, it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment.

PRECAUTIONS

Dizziness and Somnolence

Pregabalin causes dizziness and somnolence. Patients should be informed that pregabalin-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery (See **PRECAUTIONS-Information for Patients**).

In the pregabalin controlled trials, dizziness was experienced by 29% of pregabalin-treated patients compared to 9% of placebo-treated patients; somnolence was experienced by 22% of pregabalin-treated patients compared to 8% of placebo-treated patients. Dizziness and somnolence generally began shortly after the initiation of pregabalin therapy and occurred more frequently at higher doses. Dizziness and somnolence were the adverse events most frequently leading to withdrawal (4% each) from controlled studies. In pregabalin-treated patients reporting these adverse events in short-term, controlled studies, dizziness persisted until the last dose in 31% and somnolence persisted until the last dose in 46% of patients.

Ophthalmological Effects

In controlled studies, a higher proportion of patients treated with pregabalin reported blurred vision (6%) than did patients treated with placebo (2%), which resolved in a majority of cases with continued dosing. Less than 1% of patients discontinued pregabalin treatment due to vision-related events (primarily blurred vision).

Prospectively planned ophthalmologic testing, including visual acuity testing, formal visual field testing and dilated funduscopic examination, was performed in over 3600 patients. In these patients, visual acuity was reduced in 7% of patients treated with pregabalin, and 5% of placebo-treated patients. Visual field changes were detected in 13% of pregabalin-treated, and 12% of placebo-treated patients. Funduscopic changes were observed in 2% of pregabalin-treated and 2% of placebo-treated patients.

Although the clinical significance of the ophthalmologic findings is unknown, patients should be informed that if changes in vision occur, they should notify their physician. If visual disturbance persists, further assessment should be considered. More frequent

assessment should be considered for patients who are already routinely monitored for ocular conditions (See **PRECAUTIONS-Information for Patients**).

Abrupt or Rapid Discontinuation

Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, and diarrhea. Pregabalin should be tapered gradually over a minimum of 1 week rather than discontinued abruptly.

Weight Gain

Pregabalin treatment caused weight gain. In pregabalin controlled clinical trials of up to 13 weeks, a gain of 7% or more over baseline weight was observed in 8% of pregabalin-treated patients and 2% of placebo-treated patients. Few patients treated with pregabalin (0.2%) withdrew from controlled trials due to weight gain. Pregabalin associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender, or age. Weight gain was not limited to patients with edema (See **Precautions-Peripheral Edema**).

Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown.

Among diabetic patients, pregabalin-treated patients gained an average of 1.6 kg (range: -16 to 16 kg), compared to an average 0.3 kg (range: -10 to 9 kg) weight gain in placebo patients. In a cohort of 333 diabetic patients who received pregabalin for at least 2 years, the average weight gain was 5.2 kg.

While the effects of pregabalin-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open label clinical trials with diabetic patients, pregabalin treatment did not appear to be associated with loss of glycemic control (as measured by HbA_{1C}).

Peripheral Edema

Pregabalin treatment caused edema, primarily described as peripheral edema. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. Peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

In controlled clinical trials the incidence of peripheral edema was 6% in the pregabalin group compared with 2% in the placebo group. In controlled clinical trials, 0.6% of pregabalin patients and no placebo patients withdrew due to peripheral edema.

Higher frequencies of weight gain and peripheral edema were observed in patients taking both LYRICA and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. The majority of patients using thiazolidinedione antidiabetic agents in the overall safety database were participants in studies of pain associated with diabetic peripheral neuropathy. In this population, peripheral edema was reported in 3% (2/60) of patients who were using thiazolidinedione antidiabetic agents only, 8% (69/859) of patients who were treated with pregabalin only, and 19% (23/120) of patients who were on both pregabalin and thiazolidinedione antidiabetic agents. Similarly, weight gain was reported in 0% (0/60) of patients on thiazolidinediones only; 4% (35/859) of patients on pregabalin only; and 7.5% (9/120) of patients on both drugs.

As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, care should be taken when co-administering LYRICA and these agents.

Because there are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status, LYRICA should be used with caution in these patients.

Creatine Kinase Elevations

Pregabalin treatment was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for pregabalin-treated patients and 28 U/L for the placebo patients. In all controlled trials across multiple patient populations, 2% of patients on pregabalin and 1% of placebo patients had a value

of creatine kinase at least three times the upper limit of normal. Three pregabalin treated subjects had events reported as rhabdomyolysis in premarketing clinical trials. The relationship between these myopathy events and pregabalin is not completely understood because the cases had documented factors that may have caused or contributed to these events. Prescribers should instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Pregabalin treatment should be discontinued if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Laboratory Changes

Decreased Platelet Count

Pregabalin treatment was associated with a decrease in platelet count. Pregabalin-treated subjects experienced a mean maximal decrease in platelet count of 20 x $10^3/\mu L$, compared to 11 x $10^3/\mu L$ in placebo patients. In the overall database of controlled trials, 2% of placebo patients and 3% of pregabalin patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and < 150 x $10^3/\mu L$. In randomized controlled trials, pregabalin was not associated with an increase in bleeding related adverse events.

ECG Changes

PR Interval Prolongation

Pregabalin treatment was associated with mild PR interval prolongation. In analyses of clinical trial ECG data, the mean PR interval increase was 3-6 msec at pregabalin doses =300 mg/day. This mean change difference was not associated with an increased risk of PR increase =25% from baseline, an increased percentage of subjects with on-treatment PR >200 msec, or an increased risk of adverse events of second or third degree AV block.

Information for Patients

Patients should be counseled that LYRICA may cause dizziness, somnolence, blurred vision and other CNS signs and symptoms. Accordingly, they should be advised not to drive, operate complex machinery, or engage in other hazardous activities until they have

gained sufficient experience on pregabalin to gauge whether or not it affects their mental, visual, and/or motor performance adversely.

Patients should be counseled that LYRICA may cause visual disturbances. Patients should be informed that if changes in vision occur, they should notify their physician (See **PRECAUTIONS**).

Patients should be advised to take LYRICA as prescribed. Abrupt or rapid discontinuation may result in insomnia, nausea, headache, or diarrhea.

Patients should be counseled that LYRICA may cause edema and weight gain.

Patients should be advised that concomitant treatment with LYRICA and a thiazolidinedione antidiabetic agent may lead to an additive effect on edema and weight gain. For patients with preexisting cardiac conditions, this may increase the risk of heart failure.

Patients should be instructed to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Patients who require concomitant treatment with central nervous system depressants such as opiates or benzodiazepines should be informed that they may experience additive CNS side effects, such as somnolence.

Patients should be told to avoid consuming alcohol while taking LYRICA, as LYRICA may potentiate the impairment of motor skills and sedation of alcohol.

Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding or intend to breast feed during therapy.

Men being treated with LYRICA who plan to father a child should be informed of the potential risk of male-mediated teratogenicity. In preclinical studies in rats, pregabalin was associated with an increased risk of male-mediated teratogenicity. The clinical significance of this finding is uncertain (see PRECAUTIONS - Carcinogenesis and Impairment of Fertility).

Diabetic patients should be instructed to pay particular attention to skin integrity while being treated with LYRICA. Some animals treated with pregabalin developed skin ulcerations, although no increased incidence of skin lesions associated with LYRICA was observed in clinical trials (see **Animal Toxicology**).

Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking LYRICA.

Drug Interactions

Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. In vitro and in vivo studies showed that LYRICA is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, there are no pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between pregabalin and commonly used antiepileptic drugs (See **CLINICAL PHARMACOLOGY**).

Pharmacodynamics

Multiple oral doses of pregabalin were co-administered with oxycodone, lorazepam, or ethanol. Although no pharmacokinetic interactions were seen, additive effects on cognitive and gross motor functioning were seen when pregabalin was co-administered with those drugs. No clinically important effects on respiration were seen (See **PRECAUTIONS, Dizziness and Somnolence and Information for Patients**).

Animal Toxicology

Dermatopathy

Skin lesions ranging from erythema to necrosis were seen in repeated-dose toxicology studies in both rats and monkeys. The etiology of these skin lesions is unknown. At the maximum recommended human dose (MRD) of 600 mg/day, there is a 2-fold safety

margin for the dermatological lesions. The more severe dermatopathies involving necrosis were associated with pregabalin exposures (as expressed by plasma AUCs) of approximately 3 to 8 times those achieved in humans given the MRD. No increase in incidence of skin lesions was observed in clinical studies.

Ocular lesions

Ocular lesions (characterized by retinal atrophy [including loss of photoreceptor cells] and/or corneal inflammation/mineralization) were observed in two lifetime carcinogenicity studies in Wistar rats. These findings were observed at plasma pregabalin exposures (AUC) =2 times those achieved in humans given the maximum recommended dose of 600 mg/day. A no-effect dose for ocular lesions was not established. Similar lesions were not observed in lifetime carcinogenicity studies in two strains of mice or in monkeys treated for 1 year. The clinical significance of this finding in rats is unknown.

Effects in Juvenile Animals

In studies in which pregabalin (50 to 500 mg/kg) was orally administered to young rats from early in the postnatal period (Postnatal Day 7) through sexual maturity, neurobehavioral abnormalities (deficits in learning and memory, altered locomotor activity, decreased auditory startle responding and habituation) and reproductive impairment (delayed sexual maturation and decreased fertility in males and females) were observed at doses = 50 mg/kg. The neurobehavioral changes (except for locomotor activity) persisted in animals tested after cessation of dosing and, thus, were considered to represent long-term effects. The low effect dose for developmental neurotoxicity and reproductive impairment in juvenile rats (50 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately equal to human exposure at the maximum recommended dose of 600 mg/day. A no-effect dose was not established.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

A dose-dependent increase in the incidence of malignant vascular tumors (hemangiosarcomas) was observed in two strains of mice (B6C3F1 and CD-1) given pregabalin (200, 1000, or 5000 mg/kg) in the diet for two years. Plasma pregabalin

exposure (AUC) in mice receiving the lowest dose that increased hemangiosarcomas was approximately equal to the human exposure at the maximum recommended dose (MRD) of 600 mg/day. A no-effect dose for induction of hemangiosarcomas in mice was not established. No evidence of carcinogenicity was seen in two studies in Wistar rats following dietary administration of pregabalin for two years at doses (50, 150, or 450 mg/kg in males and 100, 300, or 900 mg/kg in females) that were associated with plasma exposures in males and females up to approximately 14 and 24 times, respectively, human exposure at the MRD. The clinical significance of this finding in mice is unknown.

Mutagenesis

Pregabalin was not mutagenic in bacteria or in mammalian cells *in vitro*, was not clastogenic in mammalian systems in vitro and in vivo, and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes.

Impairment of Fertility

In fertility studies in which male rats were orally administered pregabalin (50 to 2500 mg/kg) prior to and during mating with untreated females, a number of adverse reproductive and developmental effects were observed. These included decreased sperm counts and sperm motility, increased sperm abnormalities, reduced fertility, increased preimplantation embryo loss, decreased litter size, decreased fetal body weights, and an increased incidence of fetal abnormalities. Effects on sperm and fertility parameters were reversible in studies of this duration (3-4 months). The no-effect dose for male reproductive toxicity in these studies (100 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately 3 times human exposure at the maximum recommended dose (MRD) of 600 mg/day.

In addition, adverse effects on reproductive organ (testes, epididymides) histopathology were observed in male rats exposed to pregabalin (500 to 1250 mg/kg) in general toxicology studies of four weeks or greater duration. The no-effect dose for male reproductive organ histopathology in rats (250 mg/kg) was associated with a plasma exposure approximately 8 times human exposure at the MRD.

In a fertility study in which female rats were given pregabalin (500, 1250, or 2500 mg/kg) orally prior to and during mating and early gestation, disrupted estrous cyclicity and an increased number of days to mating were seen at all doses, and embryolethality occurred at the highest dose. The low dose in this study produced a plasma exposure approximately 9 times that in humans receiving the MRD. A no-effect dose for female reproductive toxicity in rats was not established. The clinical significance of female fertility findings in animals is unknown.

Human Data

In a double-blind, placebo-controlled clinical trial to assess the effect of pregabalin on sperm motility, 30 healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment (one complete sperm cycle), the difference between placebo- and pregabalin-treated subjects in mean percent sperm with normal motility was <4% and neither group had a mean change from baseline of more than 2%. Effects on other male reproductive parameters in humans have not been adequately studied.

Pregnancy

Pregnancy Category C

Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity, including lethality, growth retardation, and nervous and reproductive system functional impairment, were observed in the offspring of rats and rabbits given pregabalin during pregnancy, at doses that produced plasma pregabalin exposures (AUC) ≥5 times human exposure at the maximum recommended dose (MRD) of 600 mg/day.

When pregnant rats were given pregabalin (500, 1250, or 2500 mg/kg) orally throughout the period of organogenesis, incidences of specific skull alterations attributed to abnormally advanced ossification (premature fusion of the jugal and nasal sutures) were increased at =1250 mg/kg, and incidences of skeletal variations and retarded ossification were increased at all doses. Fetal body weights were decreased at the highest dose. The low dose in this study was associated with a plasma exposure (AUC) approximately 17

times human exposure at the MRD of 600 mg/day. A no-effect dose for rat embryo-fetal developmental toxicity was not established.

When pregnant rabbits were given pregabalin (250, 500, or 1250 mg/kg) orally throughout the period of organogenesis, decreased fetal body weight and increased incidences of skeletal malformations, visceral variations, and retarded ossification were observed at the highest dose. The no-effect dose for developmental toxicity in rabbits (500 mg/kg) was associated with a plasma exposure approximately 16 times human exposure at the MRD.

In a study in which female rats were dosed with pregabalin (50, 100, 250, 1250, or 2500 mg/kg) throughout gestation and lactation, offspring growth was reduced at = 100 mg/kg and offspring survival was decreased at = 250 mg/kg. The effect on offspring survival was pronounced at doses =1250 mg/kg, with 100% mortality in high-dose litters. When offspring were tested as adults, neurobehavioral abnormalities (decreased auditory startle responding) were observed at =250 mg/kg and reproductive impairment (decreased fertility and litter size) was seen at 1250 mg/kg. The no-effect dose for pre- and postnatal developmental toxicity in rats (50 mg/kg) produced a plasma exposure approximately 2 times human exposure at the MRD.

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

Labor and Delivery: The effects of pregabalin on labor and delivery in pregnant women are unknown. In the prenatal-postnatal study in rats, pregabalin prolonged gestation and induced dystocia at exposures ≥50 times the mean human exposure ($AUC_{(0-24)}$ of 123 μg·hr/mL) at the maximum recommended clinical dose of 600 mg/day.

Use in Nursing Mothers: It is not known if pregabalin is excreted in human milk; it is, however, present in the milk of rats. Because many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for pregabalin in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and efficacy of pregabalin in pediatric patients have not been established.

Geriatric Use

In controlled clinical studies of LYRICA in neuropathic pain associated with diabetic peripheral neuropathy, 306 patients were 65 to 74 years of age, and 88 patients were 75 years of age or older.

In controlled clinical studies of LYRICA in neuropathic pain associated with postherpetic neuralgia, 282 patients were 65 to 74 years of age, and 379 patients were 75 years of age or older.

No overall differences in safety and efficacy were observed between these patients and younger patients. Even though the incidence of adverse events did not increase with age, greater sensitivity of some older individuals cannot be ruled out. LYRICA is known to be substantially excreted by the kidney, and the risk of toxic reactions to LYRICA may be greater in patients with impaired renal function.

Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for elderly patients with renal impairment, as noted in the **DOSAGE AND ADMINISTRATION** section.

ADVERSE REACTIONS

In all controlled and uncontrolled trials across various patient populations during the premarketing development of pregabalin, more than 9000 patients have received pregabalin. Approximately 4300 patients were treated for 6 months or more, over 2700 patients were treated for 1 year or longer, and over 1000 patients were treated for at least 2 years.

Adverse Events Most Commonly Leading to Discontinuation in All Controlled Clinical Studies

In controlled trials of all populations combined, 14% of patients treated with pregabalin and 7% of patients treated with placebo discontinued prematurely due to adverse events. In the pregabalin treatment group, the adverse events most frequently leading to discontinuation were dizziness (4%) and somnolence (3%). In the placebo group, 1% of patients withdrew due to dizziness and <1% withdrew due to somnolence. Other adverse events that led to discontinuation from controlled trials more frequently in the pregabalin group compared to the placebo group were ataxia, confusion, asthenia, thinking abnormal, blurred vision, incoordination, and peripheral edema (1% each)

Most Common Adverse Events in All Controlled Clinical Studies

In controlled trials of all patient populations combined, dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and "thinking abnormal" (primarily difficulty with concentration/attention) were more commonly reported by subjects treated with pregabalin than by subjects treated with placebo (≥5% and twice the rate of that seen in placebo).

Controlled Studies with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

Adverse Events Leading to Discontinuation

In clinical trials in patients with neuropathic pain associated with diabetic peripheral neuropathy, 9% of patients treated with pregabalin and 4% of patients treated with placebo discontinued prematurely due to adverse events. In the pregabalin treatment group, the most common reasons for discontinuation due to adverse events were dizziness (3 %) and somnolence (2 %). In comparison, <1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring with greater frequency in the pregabalin group than in the placebo group, were asthenia, confusion, and peripheral edema. Each of these events led to withdrawal in approximately 1% of patients.

Most Common Adverse Events

Table 1 lists all adverse events, regardless of causality, occurring in = 1% of patients with neuropathic pain associated with diabetic neuropathy in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group. A majority of pregabalin-treated patients in clinical studies had adverse events with a maximum intensity of "mild" or "moderate".

Table 1. Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body system - Preferred term	75 mg/day [N=77] %	150 mg/day [N=212] %	300 mg/day [N=321] %	600 mg/day [N=369] %	All PGB* [N=979] %	Placebo [N=459] %
Body as a whole						
Asthenia	4	2	4	7	5	2
Accidental injury	5	2	2	6	4	3
Back pain	0	2	1	2	2	0
Chest pain	4	1	1	2	2	1
Face edema	0	1	1	2	1	0
Digestive system						
Dry mouth	3	2	5	7	5	1
Constipation	0	2	4	6	4	2
Flatulence	3	0	2	3	2	1
Metabolic and nutritional disorders						
Peripheral edema	4	6	9	12	9	2
Weight gain	0	4	4	6	4	0
Edema	0	2	4	2	2	0
Hypoglycemia	1	3	2	1	2	1
Nervous system						
Dizziness	8	9	23	29	21	5
Somnolence	4	6	13	16	12	3
Neuropathy	9	2	2	5	4	3
Ataxia	6	1	2	4	3	1
Vertigo	1	2	2	4	3	1
Confusion	0	1	2	3	2	1
Euphoria	0	0	3	2	2	0
Incoordination	1	0	2	2	2	0
Thinking abnormal[1]	1	0	1	3	2	0
Tremor	1	1	1	2	1	0
Abnormal gait	1	0	1	3	1	0
Amnesia	3	1	0	2	1	0
Nervousness	0	1	1	1	1	0
Respiratory system						
Dyspnea	3	0	2	2	2	1

Table 1. Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body system - Preferred term	75 mg/day [N=77] %	150 mg/day [N=212] %	300 mg/day [N=321] %	600 mg/day [N=369] %	All PGB* [N=979] %	Placebo [N=459] %
Special senses						
Blurry vision[b]	3	1	3	6	4	2
Abnormal vision	1	0	1	1	1	0

*PGB: pregabalin

[a] Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.

[b] Investigator term; summary level term is amblyopia

Controlled Studies in Postherpetic Neuralgia

Adverse Events Leading to Discontinuation

In clinical trials in patients with postherpetic neuralgia, 14% of patients treated with pregabalin and 7% of patients treated with placebo discontinued prematurely due to adverse events. In the pregabalin treatment group, the most common reasons for discontinuation due to adverse events were dizziness (4%) and somnolence (3%). In comparison, less than 1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring in greater frequency in the pregabalin group than in the placebo group, were confusion (2%), as well as peripheral edema, asthenia, ataxia, and abnormal gait (1% each).

Most Common Adverse Events

Table 2 lists all adverse events, regardless of causality, occurring in = 1% of patients with neuropathic pain associated with postherpetic neuralgia in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group. In addition, an event is included, even if the incidence in the all pregabalin group is not greater than in the placebo group, if the incidence of the event in the 600 mg/day group is more than twice that in the placebo group. A majority of

pregabalin-treated patients in clinical studies had adverse events with a maximum intensity of "mild" or "moderate".

Table 2. Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body system - Preferred term	75 mg/d [N=84] %	150 mg/d [N=302] %	300 mg/d [N=312] %	600 mg/d [N=154] %	All PGB* [N=852] %	Placebo [N=398] %
Body as a whole						
Infection	14	8	6	3	7	4
Headache	5	9	5	8	7	5
Pain	5	4	5	5	5	4
Accidental injury	4	3	3	5	3	2
Flu syndrome	1	2	2	1	2	1
Face edema	0	2	1	3	2	1
Digestive system						
Dry mouth	7	7	6	15	8	3
Constipation	4	5	5	5	5	2
Flatulence	2	1	2	3	2	1
Vomiting	1	1	3	3	2	1
Metabolic and nutritional disorders						
Peripheral edema	0	8	16	16	12	4
Weight gain	1	2	5	7	4	0
Edema	0	1	2	6	2	1
Musculoskeletal system						
Myasthenia	1	1	1	1	1	0
Nervous system						
Dizziness	11	18	31	37	26	9
Somnolence	8	12	18	25	16	5
Ataxia	1	2	5	9	5	1
Abnormal gait	0	2	4	8	4	1
Confusion	1	2	3	7	3	0
Thinking abnormal[a]	0	2	1	6	2	2
Incoordination	2	2	1	3	2	0
Amnesia	0	1	1	4	2	0
Speech disorder	0	0	1	3	1	0
Respiratory system						
Bronchitis	0	1	1	3	1	1

Table 2. Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body system - Preferred term	75 mg/d [N=84] %	150 mg/d [N=302] %	300 mg/d [N=312] %	600 mg/d [N=154] %	All PGB* [N=852] %	Placebo [N=398] %
Special senses						
Blurry vision[b]	1	5	5	9	5	3
Diplopia	0	2	2	4	2	0
Abnormal vision	0	1	2	5	2	0
Eye Disorder	0	1	1	2	1	0
Urogenital System						
Urinary Incontinence	0	1	1	2	1	0

*PGB: pregabalin

[a] Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.

[b] Investigator term; summary level term is amblyopia

Other Adverse Events Observed During the Clinical Studies of LYRICA (pregabalin)

Following is a list of treatment-emergent adverse events reported by patients treated with LYRICA during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: **frequent** adverse events are those occurring on one or more occasions in at least 1/100 patients; **infrequent** adverse events are those occurring in 1/100 to 1/1000 patients; **rare** events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are described in the **WARNINGS** and **PRECAUTIONS** sections.

Body as a Whole – *Frequent:* Abdominal pain, Allergic reaction, Fever, *Infrequent:* Abscess, Cellulitis, Chills, Malaise, Neck rigidity, Overdose, Pelvic pain, Photosensitivity reaction, Suicide attempt, *Rare:* Anaphylactoid reaction, Ascites, Hangover effect, Shock, Suicide

Cardiovascular System –*Infrequent:* Deep thrombophlebitis, Heart failure, Hypotension, Postural hypotension, Retinal vascular disorder, Syncope

Digestive System – *Frequent*: Gastroenteritis, Increased appetite; *Infrequent:* Cholecystitis, Cholelithiasis, Colitis, Dysphagia, Esophagitis, Gastritis, Gastrointestinal hemorrhage, Melena, Mouth ulceration, Pancreatitis, Rectal hemorrhage, Tongue edema; *Rare:* Aphthous stomatitis

Hemic and Lymphatic System – *Frequent:* Ecchymosis; *Infrequent:* Anemia, Eosinophilia, Hypochromic anemia, Leukocytosis, Leukopenia, Lymphadenopathy, Thrombocytopenia; *Rare:* Polycythemia, Prothrombin decreased, Purpura, Thrombocythemia

Musculoskeletal System – *Frequent*: Arthralgia, Leg cramps, Myalgia, Myasthenia; *Infrequent:* Arthrosis

Nervous System – *Frequent:* Anxiety, Depersonalization, Hypertonia, Hypesthesia, Libido decreased, Nystagmus, Paresthesia, Stupor, Twitching; *Infrequent:* Abnormal dreams, Agitation, Apathy, Aphasia, Circumoral paresthesia, Dysarthria, Hallucinations, Hostility, Hyperalgesia, Hyperesthesia, Hyperkinesia, Hypokinesia, Hypotonia, Libido increased, Myoclonus, Neuralgia, *Rare:* Addiction, Cerebellar syndrome, Cogwheel rigidity, Coma, Delirium, Dyskinesia, Dystonia, Encephalopathy, Extrapyramidal syndrome, Guillain barre syndrome, Hypalgesia, Intracranial hypertension, Manic reaction, Paranoid reaction, Peripheral neuritis, Psychotic depression, Schizophrenic reaction, Torticollis, Trismus

Respiratory System –*Rare:* Apnea, Atelectasis, Bronchiolitis, Hiccup, Laryngismus, Lung edema, Lung fibrosis, Yawn

Skin and Appendages – *Frequent:* Pruritus, *Infrequent:* Alopecia, Dry skin, Eczema, Hirsutism, Skin ulcer, Urticaria, Vesiculobullous rash; *Rare:* Angioedema, Exfoliative dermatitis, Lichenoid dermatitis, Melanosis, Petechial rash, Purpuric rash, Pustular rash, Skin atrophy, Skin necrosis, Skin nodule, Stevens-Johnson syndrome, Subcutaneous nodule

Special senses– *Frequent:* Conjunctivitis, Diplopia, Otitis media, Tinnitus; *Infrequent:* Abnormality of accommodation, Blepharitis, Dry eyes, Eye hemorrhage, Hyperacusis, Photophobia, Retinal edema, Taste loss, Taste perversion; *Rare:* Anisocoria, Blindness, Corneal ulcer, Exophthalmos, Extraocular palsy, Iritis, Keratitis, Keratoconjunctivitis, Miosis, Mydriasis, Night blindness, Ophthalmoplegia, Optic atrophy, Papilledema, Parosmia, Ptosis

Urogenital System – *Frequent*: Anorgasmia, Impotence, Urinary frequency, Urinary incontinence, *Infrequent*: Abnormal ejaculation, Albuminuria, Amenorrhea, Dysmenorrhea, Dysuria, Hematuria, Kidney calculus, Leukorrhea, Menorrhagia, Metrorrhagia, Nephritis, Oliguria, Urinary retention, *Rare*: Acute kidney failure, Balanitis, Cervicitis, Dyspareunia, Epididymitis, Female lactation, Glomerulitis

Comparison of Gender and Race

The overall adverse event profile of pregabalin was similar between women and men There are insufficient data to support a statement regarding the distribution of adverse experience reports by race.

DRUG ABUSE AND DEPENDENCE

In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, Lyrica (450mg, single dose) received subjective ratings of "good drug effect," "high" and

"liking" to a degree that was similar to diazepam (30mg, single dose). In controlled clinical studies in over 5500 patients, 4 % of Lyrica-treated patients and 1 % of placebo-treated patients overall reported euphoria as an adverse event, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%. In clinical studies, following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache or diarrhea (See PRECAUTIONS, Abrupt Discontinuation), suggestive of physical dependence.

Pregabalin is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior).

OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans

There is limited experience with overdose of pregabalin. The highest reported accidental overdose of pregabalin during the clinical development program was 8000 mg, and there were no notable clinical consequences. In clinical studies, some patients took as much as 2400 mg/day. The types of adverse events experienced by patients exposed to higher doses (= 900 mg) were not clinically different from those of patients administered recommended doses of pregabalin.

Treatment or Management of Overdose

There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with pregabalin.

Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

DOSAGE AND ADMINISTRATION

LYRICA™ is given orally with or without food.

Neuropathic pain associated with diabetic peripheral neuropathy

The maximum recommended dose of LYRICA is 100 mg three times a day (300 mg/day) in patients with creatinine clearance of at least 60 mL/min. Dosing should begin at 50 mg three times a day (150mg/day) and may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for patients with reduced renal function (see **Patients with Renal Impairment**).

Although LYRICA was also studied at 600 mg/day, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse effects, treatment with doses above 300 mg/day are not recommended (see ADVERSE REACTIONS).

When discontinuing LYRICA, taper gradually over a minimum of 1 week.

Postherpetic neuralgia

The recommended dose of LYRICA is 75 to 150 mg two times a day, or 50 to 100 mg three times a day (150 to 300 mg/day) in patients with creatinine clearance of at least 60 mL/min. Dosing should begin at 75 mg two times a day, or 50 mg three times a day (150 mg/day) and may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for patients with reduced renal function (see **Patients with Renal Impairment**).

Patients who do not experience sufficient pain relief following 2 to 4 weeks of treatment with 300 mg/day, and who are able to tolerate LYRICA, may be treated with up to 300 mg two times a day, or 200 mg three times a day (600 mg/day). In view of the dose-dependent adverse effects and the higher rate of treatment discontinuation due to adverse events, dosing above 300 mg/day should be reserved only for those patients who have on-going pain and are tolerating 300 mg daily (see **Adverse Reactions**).

When discontinuing LYRICA, taper gradually over a minimum of 1 week.

Patients with Renal Impairment:

In view of dose-dependent adverse events and since Lyrica is eliminated primarily by renal excretion, the dose should be adjusted in patients with reduced renal function. Dosage adjustment in patients with renal impairment should be based on CLcr, as indicated in Table 3. To use this dosing table, an estimate of the patient's CLcr in mL/min is needed. CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the Cockcroft and Gault equation:

$$CLcr = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times\ 0.85 \text{ for female patients})$$

For patients undergoing hemodialysis, pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose adjustment, a supplemental dose should be given immediately following every 4-hour hemodialysis treatment (see Table 3).

Table 3: Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CLcr) (mL/min)	Total Pregabalin Daily Dose (mg/day)[a]			Dose Regimen
≥60	150	300	600	BID or TID
30-60	75	150	300	BID or TID
15-30	25-50	75	150	QD or BID
<15	25	25-50	75	QD
Supplementary dosage following hemodialysis (mg)[b]				
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg Patients on the 25-50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg				

TID = Three divided doses; BID = Two divided doses; QD = Single daily dose.

[a] Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.

[b] Supplementary dose is a single additional dose.

HOW SUPPLIED

25-mg capsules:

White, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 25" on the body; available in:

Bottles of 90 capsules: NDC0071-1012-68

Unit-Dose Blister Packages of 100: NDC0071-1012-41

50-mg capsules:

White, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 50" and an ink band on the body, available in:

Bottles of 90: NDC0071-1013-68

Unit-Dose Blister Packages of 100: NDC0071-1013-41

75-mg capsules:

White/orange hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 75" on the body; available in:

Bottles of 90:	NDC0071-1014-68
Unit-Dose Blister Packages of 100:	NDC0071-1014-41

100-mg capsules:

Orange, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 100" on the body, available in:

Bottles of 90:	NDC0071-1015-68
Unit-Dose Blister Packages of 100:	NDC0071-1015-41

150-mg capsules:

White hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 150" on the body, available in:

Bottles of 90 capsules:	NDC0071-1016-68
Unit-Dose Blister Packages of 100:	NDC0071-1016-41

200-mg capsules:

Light orange hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 200" on the body, available in:

Bottles of 90:	NDC0071-1017-68
Unit-Dose Blister Packages of 100:	NDC0071-1017-41

225-mg capsules:

White/light orange hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 225" on the body; available in:

Bottles of 90:	NDC0071-1019-68
Unit-Dose Blister Packages of 100:	NDC0071-1019-41

300-mg capsules:

White/orange hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 300" on the body, available in:

Bottles of 90:	NDC0071-1018-68
Unit-Dose Blister Packages of 100:	NDC0071-1018-41

Storage

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

Rx Only

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PATIENT INFORMATION

LYRICA (LEER-ik-ah)
PREGABALIN

Read the Patient Information that comes with LYRICA before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or treatment. If you have any questions about LYRICA, ask your doctor or pharmacist.

What is the most important information I should know about LYRICA?

1. **LYRICA may cause dizziness and sleepiness.**
   - **Do not drive a car, work with machines, or do other dangerous activities until you know how LYRICA affects how alert you are.** Ask your doctor when it is okay to do these activities.
2. **LYRICA may cause problems with your eyesight, including blurry vision.**
   - Call your doctor if you have any changes in your eyesight.

What is LYRICA?

LYRICA is a prescription medicine used in adults, 18 years and older, to treat pain from damaged nerves (neuropathic pain) that:

- happens with diabetes, or
- follows healing of shingles (a painful rash that comes after a herpes zoster infection)

Diabetes and shingles can damage your nerves. Pain from damaged nerves may feel sharp, burning, tingling, shooting, or numb. If you have diabetes, the pain can be in your arms, hands, fingers, legs, feet, or toes. If you have shingles, the pain is in the area of your rash. You may experience this kind of pain even with a very light touch. LYRICA can help relieve the pain. Some people taking LYRICA had less pain by the end of the first week of LYRICA therapy. LYRICA may not work for everyone.

LYRICA has not been studied for nerve pain in children under 18 years of age.

Who Should Not Take LYRICA?

Do not take LYRICA if you are allergic to any of its ingredients. The active ingredient is pregabalin. See the end of this leaflet for a complete list of ingredients in LYRICA.

What should I tell my doctor before taking LYRICA?

Tell your doctor about all your medical conditions, including if you:

- **have any kidney problems or get kidney dialysis**
- **have heart problems including heart failure**
- **have a bleeding problem or a low blood platelet count**
- **are pregnant or plan to become pregnant.** It is not known if LYRICA may harm your unborn baby. You and your doctor will have to decide if LYRICA is right for you while you are pregnant.
- **are breastfeeding.** It is not known if LYRICA passes into breast milk and if it can harm your baby. You and your doctor should decide whether you should take LYRICA or breastfeed, but not both.

Tell your doctor about all the medicines you take including prescription or non-prescription medicines, vitamins or herbal supplements. LYRICA and other medicines may affect each other. Especially tell your doctor if you take:

- rosiglitazone (Avandia®) or pioglitazone (Actos®) for diabetes. You may have a higher chance of weight gain or swelling if these medicines are taken with LYRICA. See "What are the possible side effects of LYRICA."
- any narcotic pain medicine (such as oxycodone), tranquilizers or medicines for anxiety (such as lorazepam). You may have a higher chance for dizziness and sleepiness if these medicines are taken with LYRICA. See "What is the most important information I should know about LYRICA?"
- any medicines that make you sleepy

Know all the medicines you take. Keep a list of them with you to show your doctor and pharmacist each time you get a new medicine.

Tell your doctor if you plan to father a child. Animal studies showed that pregabalin, the active ingredient in LYRICA, made male animals less fertile. Also, in animal studies, birth defects occurred in the offspring of male animals who were treated with pregabalin. It is not known if these effects would happen in people.

How should I take LYRICA?

- Take LYRICA exactly as prescribed. Your doctor may adjust your dose during treatment. Do not change your dose without talking to your doctor.
- Do not stop taking LYRICA suddenly without talking to your doctor. If you stop taking LYRICA suddenly, you may have headaches, nausea, diarrhea or trouble sleeping. Talk with your doctor about how to slowly stop LYRICA.
- LYRICA is usually taken 2 or 3 times a day, depending on your medical condition. Your doctor will tell you how much LYRICA to take and when to take it. Take LYRICA at the same times each day.
- LYRICA may be taken with or without food.
- If you miss a dose by a few hours, take it as soon as you remember. If it is close to your next dose, just take LYRICA at your next regular time. **Do not** take two doses at the same time.
- If you take too much LYRICA, call your doctor or poison control center or go to the nearest emergency room right away.

What Should I Avoid While Taking LYRICA?

- **Do not drive a car, work with machines, or do other dangerous activities until you know how LYRICA affects how alert you are.** See "What is the most important information I should know about LYRICA?"
- **Do not drink alcohol while taking LYRICA.** LYRICA and alcohol can affect each other and increase side effects such as sleepiness and dizziness. This can be dangerous.
- **Do not take other medicines without talking to your doctor.** Other medicines include prescription and non-prescription medicines, vitamins, and herbal supplements. LYRICA and other medicines may affect each other and increase the side effects of sleepiness and dizziness. Be especially careful about medicines that make you sleepy (such as sleeping pills, anxiety medicines, tranquilizers and some antihistamines, pain relievers and seizure medicines).

Version Date: December 30, 2004

What are the possible side effects of LYRICA?

LYRICA may cause side effects including:

- **dizziness and sleepiness.** See "What is the most important information I should know about LYRICA?"
- **eyesight problems.** See "What is the most important information I should know about LYRICA?"
- **weight gain and swelling of the hands and feet (edema).** Weight gain may affect the management of diabetes. Weight gain and swelling can also be a serious problem for people with heart problems.
- **unexplained muscle problems,** such as muscle pain, soreness, or weakness. If you develop these symptoms, especially if you also feel sick and have a fever, tell your doctor right away.

The most common side effects of LYRICA are:

- dizziness
- blurry vision
- weight gain
- sleepiness
- trouble concentrating
- swelling of hands and feet
- dry mouth

LYRICA caused skin sores in animals. Although skin sores were not seen in studies in people, if you have diabetes, you should pay extra attention to your skin while taking LYRICA and tell your doctor of any sores or skin problems.

LYRICA may cause some people to feel "high." Tell your doctor, if you have abused prescription medicines, street drugs, or alcohol in the past.

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the side effects of LYRICA. For more information, ask your doctor or pharmacist.

How should I store LYRICA?

- Store LYRICA at room temperature, 59 to 86° F (15 to 30°C) in its original package.
- Safely throw away LYRICA that is out of date or no longer needed.
- **Keep LYRICA and all medicines out of the reach of children.**.

General information about LYRICA

Medicines are sometimes prescribed for conditions other than those listed in patient information leaflets. Do not use LYRICA for a condition for which it was not prescribed. Do not give LYRICA to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about LYRICA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about LYRICA that is written for health professionals.
You can also visit the LYRICA website at www.LYRICA.com or call 1-866-4LYRICA.

What are the ingredients in LYRICA?

Active ingredient: pregabalin
Inactive ingredients: lactose monohydrate, cornstarch, talc; **Capsule shell:** gelatin and titanium dioxide; Orange capsule shell: red iron oxide; White capsule shell: sodium lauryl sulfate, colloidal silicon dioxide. Colloidal silicon dioxide is a manufacturing aid that may or may not be present in the capsule shells.
Imprinting ink: shellac, black iron oxide, propylene glycol, potassium hydroxide.

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Version Date: December 30, 2004

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/s/

Robert Meyer
12/30/04 04:33:10 PM

(C)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

RECEIVED
JAN 11 2005
WORLDWIDE REGULATORY AFFAIRS

NDA 21-723

Pfizer Global Research and Development
2800 Plymouth Road
Ann Arbor, Michigan 48105

Attention: Jonathan M. Parker, RPh, MS
Global Regulatory Leader, Regulatory Affairs

Dear Mr. Parker:

Please refer to your new drug application (NDA) dated October 30, 2003, received October 31, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LYRICA™ (pregabalin) Capsules, 25/50/75/100/150/200/225/300 mg.

We acknowledge receipt of your submissions dated November 20, 2003, and January 8, 12, 16, and 30, February 5, 12, 13, 16, 17, 20, 23, 25(3), 26, and 27, March 3, 17, 19, 30, and 31, April 6, 8, 9, 12, 19, 20, 21, 22, and 28, May 3, 4, 13, 17, 18, 19, 25, 26, and 27, June 2, 3, 4, 7, 9, 14, 18, 21, 22, 24, 25, 28, and 29, July 1, 2, 6, 7, 9, 14, 16, 20, 22, 26, and 27, and August 3, 5, 12, 18, 19, 20, 23, 24, and 25, September 3, 7, 8, and 13, October 26, November 1(2) and December 30(2), 2004.

The November 1, 2004, submission constituted a complete response to our August 31, 2004, action letter.

This new drug application provides for the use of LYRICA™ (pregabalin) Capsules for the management of postherpetic neuralgia.

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

The final printed labeling (FPL) must be identical to the submitted labeling (text for the package insert and for the patient package insert submitted December 30, 2004). Immediate container and carton labels must be identical to those submitted July 9, 2004, with the addition of the word "Capsules" to the established name as agreed upon in the November 3, 2004, teleconference. 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 these submissions "**FPL for approved NDA 21-723.**" Approval of this submission by FDA is not required before the labeling is used.

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 the pediatric study requirement for this application.

The final scheduling of this product under the Controlled Substances Act is currently proceeding, but not yet complete as of the date of this letter. We note your commitment of December 30, 2004, not to market this drug until the scheduling is finalized. We further note that, when finalized, appropriate revisions should be made to the package insert, the patient-package insert and the product labeling through supplementation of your NDA. This would include the statements detailing the scheduling of Lyrica in the labeling, as required under 21 CFR 201.57 (h)(1).

We remind you of your postmarketing study commitments in your submission to NDA 21-446 dated December 30 2004.

In addition, 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 the Division of Anesthetic, Critical Care and Addiction Drug Products and two copies of both the promotional materials and the package insert directly to:

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

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field a21-446 for this drug product, not to this NDA. In the future, do not make submissions to this NDA except for the final printed labeling requested above.

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.

If you have any questions, call Lisa Malandro, Regulatory Project Manager, at (301) 827-7416.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures

PROPOSED LABELING TEXT (NEUROPATHIC PAIN – DPN INDICATION-PHN INDICATION)

DRAFT US PACKAGE INSERT

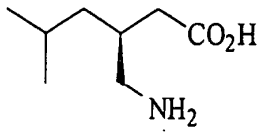
PRODUCT NAME

LYRICA™ (pregabalin) 25, 50, 75, 100, 150, 200, 225, and 300-mg Capsules

Version Date: **December 30, 2004**

DESCRIPTION

Pregabalin is described chemically as (*S*)-3-(aminomethyl)-5-methylhexanoic acid. The molecular formula is $C_8H_{17}NO_2$ and the molecular weight is 159.23. The chemical structure of pregabalin is:



Pregabalin is a white to off-white, crystalline solid with a pK_{a1} of 4.2 and a pK_{a2} of 10.6. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is – 1.35.

LYRICA (pregabalin) Capsules are supplied as imprinted hard-shell capsules containing 25, 50, 75, 100, 150, 200, 225, and 300 mg of pregabalin, along with lactose monohydrate, cornstarch, and talc as inactive ingredients. The capsule shells contain gelatin and titanium dioxide. In addition, the orange capsule shells contain red iron oxide and the white capsule shells contain sodium lauryl sulfate and colloidal silicon dioxide. Colloidal silicon dioxide is a manufacturing aid that may or may not be present in the capsule shells. The imprinting ink contains shellac, black iron oxide, propylene glycol, and potassium hydroxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

LYRICA (pregabalin) binds with high affinity to the alpha$_2$-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin is unknown, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the alpha$_2$-delta subunit may be involved in pregabalin's antinociceptive effects in animal models. *In vitro*, pregabalin reduces the calcium-dependent release of several neurotransmitters, possibly by modulation of calcium channel function.

While pregabalin is a structural derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), it does not bind directly to $GABA_A$, $GABA_B$, or benzodiazepine receptors, does not augment $GABA_A$ responses in cultured neurons, does not alter rat brain GABA concentration or have acute effects on GABA uptake or degradation. In vitro, pregabalin, like gabapentin, may affect the GABA transporter protein. Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenaline reuptake.

Pharmacokinetics

Pregabalin is well absorbed after oral administration, is eliminated largely by renal excretion, and has an elimination half-life of about 6 hours.

Absorption and Distribution

Following oral administration of pregabalin capsules under fasting conditions, peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is ≥90% and is independent of dose. Following single- (25 to 300 mg) and multiple- dose (75 to 900 mg/day) administration, maximum plasma concentrations (Cmax) and area under the plasma concentration-time curve (AUC) values increase linearly. Following repeated administration, steady state is achieved within 24 to 48 hours. Multiple-dose pharmacokinetics can be predicted from single-dose data.

The rate of pregabalin absorption is decreased when given with food, resulting in a decrease in Cmax of approximately 25% to 30% and an increase in T_{max} to approximately 3 hours. However, administration of pregabalin with food has no clinically relevant effect on the total absorption of pregabalin. Therefore, pregabalin can be taken with or without food.

Pregabalin does not bind to plasma proteins. The apparent volume of distribution of pregabalin following oral administration is approximately 0.5 L/kg. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood brain barrier. Although there are no data in humans, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. In addition, pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats.

Metabolism and Elimination

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 90% of the administered dose was recovered in the urine as unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, pregabalin (S-enantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits, or monkeys.

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug with a mean elimination half-life of 6.3 hours in subjects with normal renal function. Mean renal clearance was estimated to be 67.0 to 80.9 mL/min in young healthy subjects. Because pregabalin is not bound to plasma proteins this clearance rate indicates that renal tubular reabsorption is involved. Pregabalin elimination is nearly proportional to creatinine clearance (CLcr) (see **Special Populations, Renal Impairment and DOSAGE AND ADMINISTRATION, Patients with Impaired Renal Function**).

Special Populations

Race: In population pharmacokinetic analyses of the clinical studies in various populations, the pharmacokinetics of pregabalin were not significantly affected by race (Caucasians, Blacks, and Hispanics).

Gender: Population pharmacokinetic analyses of the clinical studies showed that the relationship between daily dose and pregabalin drug exposure is similar between genders.

Renal Impairment and Hemodialysis: Pregabalin clearance is nearly proportional to creatinine clearance (CLcr). Dosage reduction in patients with renal dysfunction is necessary. Pregabalin is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients on hemodialysis, dosing must be modified (see **DOSAGE AND ADMINISTRATION, Patients with Renal Impairment**).

Elderly: Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in CLcr. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function (see **DOSAGE AND ADMINISTRATION, Patients with Renal Impairment**).

Pediatric Pharmacokinetics: Pharmacokinetics of pregabalin have not been adequately studied in pediatric patients.

Drug Interactions:

In Vitro Studies: Pregabalin, at concentrations that were, in general, 10-times those attained in clinical trials, does not inhibit human CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzyme systems. The potential of pregabalin to induce these enzymes has not been studied in vitro.

In Vivo Studies: The drug interaction studies described in this section were conducted in healthy adults, and across various patient populations.

Gabapentin: The pharmacokinetic interactions of pregabalin and gabapentin were investigated in 12 healthy subjects following concomitant single-dose administration of 100-mg pregabalin and 300-mg gabapentin and in 18 healthy subjects following concomitant multiple-dose administration of 200-mg pregabalin every 8 hours and 400-mg gabapentin every 8 hours. Gabapentin pharmacokinetics following single- and multiple-dose administration were unaltered by pregabalin coadministration. The extent of pregabalin absorption was unaffected by gabapentin coadministration, although there was a small reduction in rate of absorption.

Oral Contraceptive: Pregabalin coadministration (200 mg three times a day) had no effect on the steady-state pharmacokinetics of norethindrone and ethinyl estradiol (1 mg/35 μg, respectively) in healthy subjects.

Lorazepam: Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of lorazepam single-dose pharmacokinetics and single-dose administration of lorazepam (1 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Oxycodone: Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of oxycodone single-dose pharmacokinetics. Single-dose administration of oxycodone (10 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Ethanol: Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of ethanol single-dose pharmacokinetics and single-dose administration of ethanol (0.7 g/kg) had no effect on the steady-state pharmacokinetics of pregabalin.

Phenytoin, carbamazepine, valproic acid, and lamotrigine: Steady-state trough plasma concentrations of phenytoin, carbamazepine and carbamazepine 10,11 epoxide, valproic acid, and lamotrigine were not affected by concomitant pregabalin (200 mg three times a day) administration.

Population pharmacokinetic analyses in patients treated with pregabalin and various concomitant medications suggest the following:

Therapeutic class	Specific concomitant drug studied
Concomitant drug has no effect on the pharmacokinetics of pregabalin	
Hypoglycemics Diuretics	Glyburide, insulin, metformin, Furosemide
Antiepileptic Drugs	Tiagabine
Concomitant drug has no effect on the pharmacokinetics of pregabalin and pregabalin has no effect on the pharmacokinetics of concomitant drug	
Antiepileptic Drugs	Carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, valproic acid

CLINICAL STUDIES

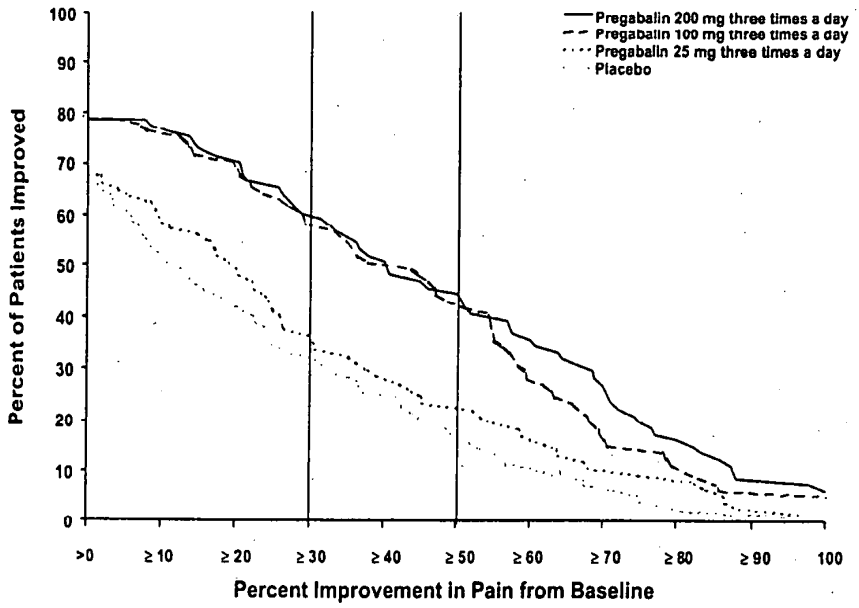
Neuropathic pain associated with diabetic peripheral neuropathy

The efficacy of the maximum recommended dose of LYRICA for the management of neuropathic pain associated with diabetic peripheral neuropathy was established in three double-blind, placebo-controlled, multicenter studies that enrolled 729 patients with three times a day dosing, two of which studied the maximum recommended dose.
Studies DPN 1 and DPN 2 enrolled a total of 483 patients of which 89% completed the studies. Patients enrolled had Type 1 or 2 diabetes mellitus with a diagnosis of painful distal symmetrical sensorimotor polyneuropathy for 1 to 5 years. The patients had a minimum mean baseline pain score of ≥4 on an 11-point numerical pain rating scale ranging from 0 (no pain) to 10 (worst possible pain). The baseline mean pain scores across the two studies ranged from 6.1 to 6.7. Patients were permitted up to 4 grams of acetaminophen per day as needed for pain, in addition to pregabalin. Patients recorded their pain daily in a diary.

Study DPN 1: This 5-week study of 337 patients (240 pregabalin and 97 placebo) compared LYRICA 25, 100, or 200 mg three times a day with placebo. Treatment with LYRICA 100 and 200 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. There was no evidence of a greater effect on pain scores of the 200 mg three times a day dose than the 100 mg three times a day dose, but

there was evidence of dose dependent adverse effects (see ADVERSE REACTIONS). For various degrees of improvement in pain from baseline to study endpoint, Figure 1 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

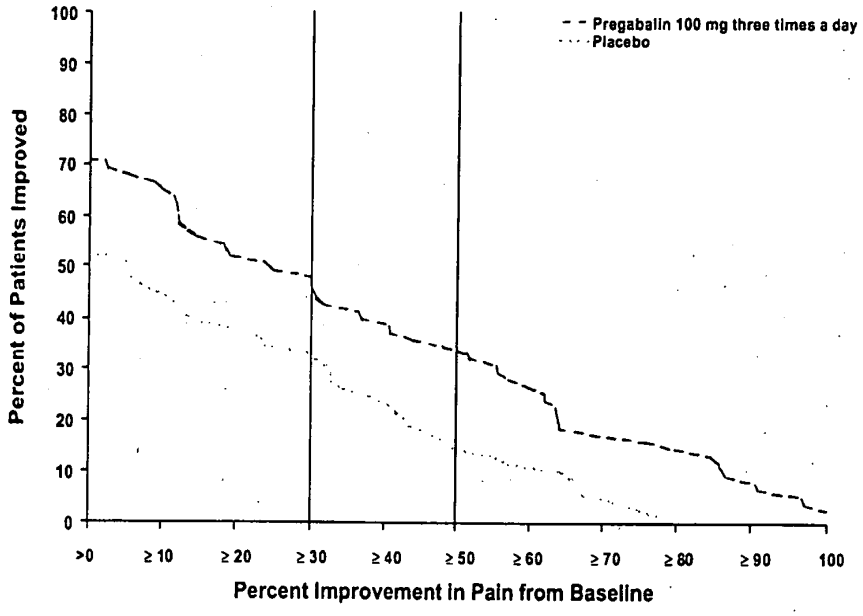
Figure 1: Patients Achieving Various Levels of Pain Relief



Study DPN 2: This 8-week study of 146 patients (76 pregabalin and 70 placebo) compared LYRICA 100 mg three times a day with placebo. Treatment with LYRICA 100 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. For various degrees of improvement in pain from baseline to study endpoint, Figure 2 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not

complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 2: Patients Achieving Various Levels of Pain Relief

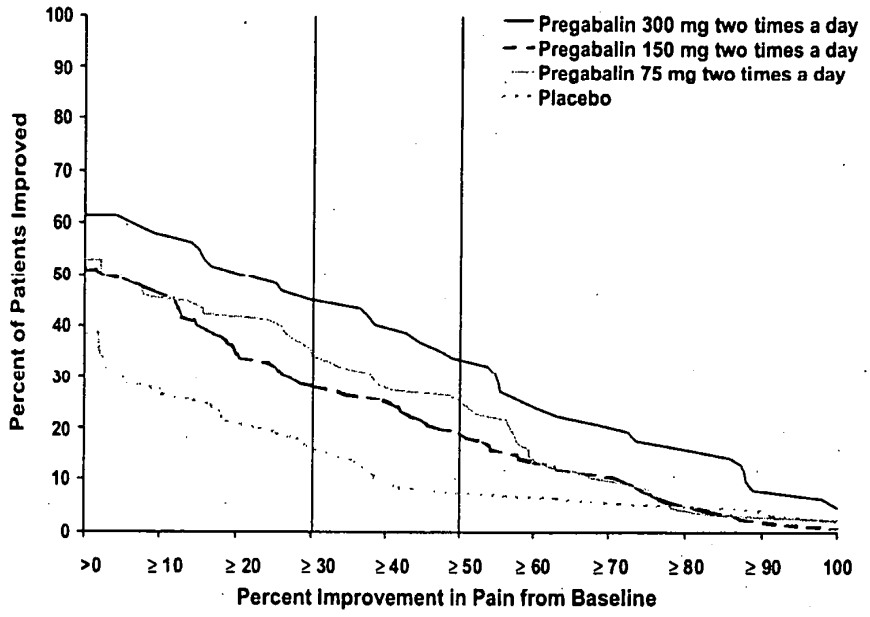


Postherpetic Neuralgia

The efficacy of LYRICA for the management of postherpetic neuralgia was established in three double-blind, placebo-controlled, multicenter studies. These studies enrolled 779 patients, of whom 566 completed the studies. These patients had neuralgia persisting for at least 3 months following healing of herpes zoster rash and a minimum baseline score of ≥4 on an 11-point numerical pain rating scale ranging from 0 (no pain) to 10 (worst possible pain). The baseline mean pain scores across the 3 studies ranged from 6 to 7. Patients were permitted up to 4 grams of acetaminophen per day as needed for pain, in addition to pregabalin. Patients recorded their pain daily in a diary.

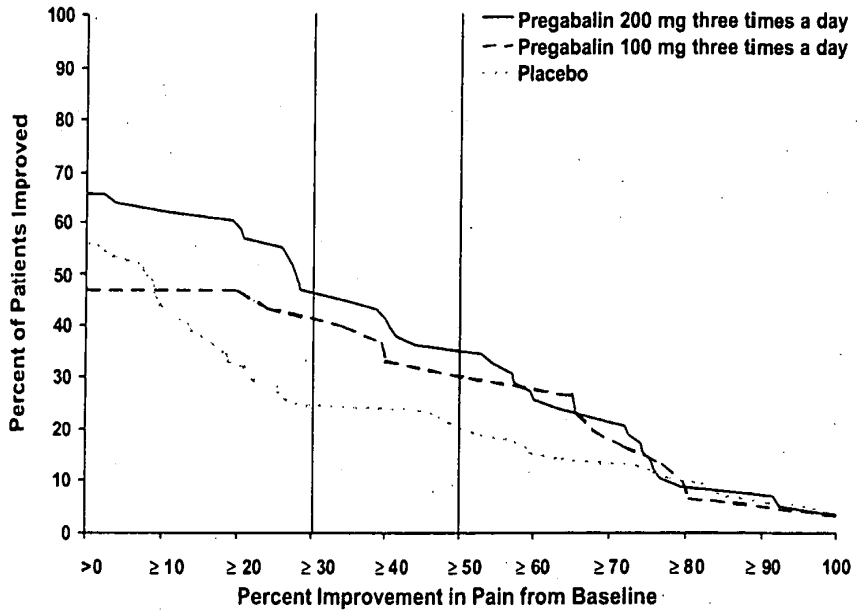
Study PHN 1: This 13-week study of 368 patients (275 pregabalin and 93 placebo) compared LYRICA 75, 150, and 300 mg twice daily with placebo. Patients with creatinine clearance (CLcr) between 30 to 60 mL/min were randomized to 75 mg, 150 mg, or placebo twice daily. Patients with creatinine clearance greater than 60 mL/min were randomized to 75 mg, 150 mg, 300 mg or placebo twice daily. In patients with creatinine clearance greater than 60 mL/min treatment with all doses of LYRICA statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. Despite differences in dosing based on renal function, patients with creatinine clearance between 30 to 60 mL/min tolerated LYRICA less well than patients with creatinine clearance greater than 60 mL/min as evidenced by higher rates of discontinuation due to adverse events. For various degrees of improvement in pain from baseline to study endpoint, Figure 3 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 3: Patients Achieving Various Levels of Pain Relief



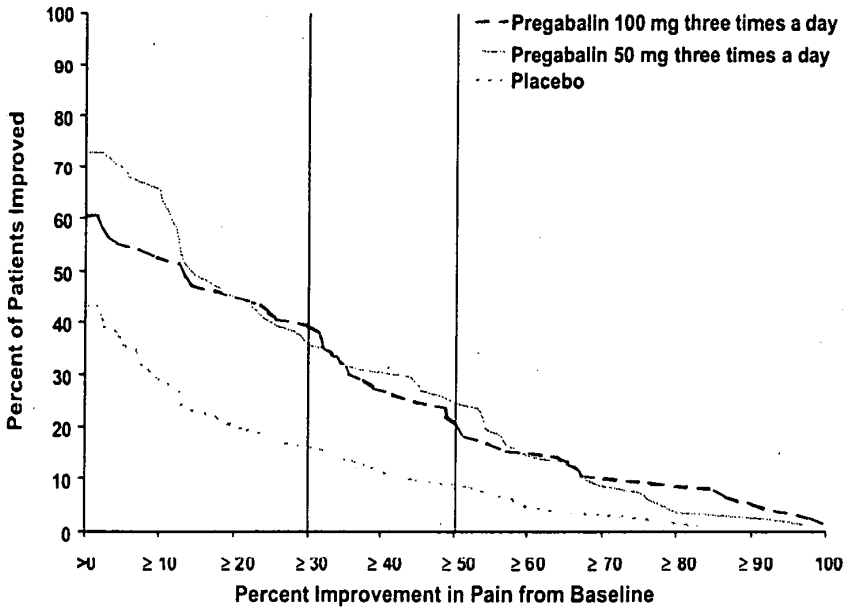
Study PHN 2: This 8-week study of 173 patients (89 pregabalin and 84 placebo) compared LYRICA 100 or 200 mg three times a day with placebo, with doses assigned based on creatinine clearance. Patients with creatinine clearance between 30 to 60 mL/min were treated with 100 mg three times a day, and patients with creatinine clearance greater than 60 mL/min were treated with 200 mg three times daily. Treatment with LYRICA statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. For various degrees of improvement in pain from baseline to study endpoint, Figure 4 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 4: Patients Achieving Various Levels of Pain Relief



Study PHN 3: This 8-week study of 238 patients (157 pregabalin and 81 placebo) compared LYRICA 50 or 100 mg three times a day with placebo with doses assigned regardless of creatinine clearance. Treatment with LYRICA 50 and 100 mg three times a day statistically significantly improved the endpoint mean pain score and increased the proportion of patients with at least a 50% reduction in pain score from baseline. Patients with creatinine clearance between 30 to 60 mL/min tolerated LYRICA less well than patients with creatinine clearance greater than 60 mL/min as evidenced by markedly higher rates of discontinuation due to adverse events. For various degrees of improvement in pain from baseline to study endpoint, Figure 5 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study.

Figure 5: Patients Achieving Various Levels of Pain Relief



INDICATIONS AND USAGE

LYRICA is indicated for management of

- Neuropathic pain associated with diabetic peripheral neuropathy
- Postherpetic neuralgia

CONTRAINDICATIONS

LYRICA is contraindicated in patients with known hypersensitivity to pregabalin or any of its components.

WARNINGS

Tumorigenic Potential

In standard preclinical *in vivo* lifetime carcinogenicity studies of pregabalin, an unexpectedly high incidence of hemangiosarcoma was identified in two different strains of mice. (See **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility**). The clinical significance of this finding is unknown. Clinical experience during pregabalin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies across various patient populations, comprising 6396 patient-years of exposure in patients >12 years of age, new or worsening-preexisting tumors were reported in 57 patients. Without knowledge of the background incidence and recurrence in similar populations not treated with LYRICA, it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment.

PRECAUTIONS

Dizziness and Somnolence

Pregabalin causes dizziness and somnolence. Patients should be informed that pregabalin-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery (See **PRECAUTIONS-Information for Patients**).

In the pregabalin controlled trials, dizziness was experienced by 29% of pregabalin-treated patients compared to 9% of placebo-treated patients; somnolence was experienced by 22% of pregabalin-treated patients compared to 8% of placebo-treated patients. Dizziness and somnolence generally began shortly after the initiation of pregabalin therapy and occurred more frequently at higher doses. Dizziness and somnolence were the adverse events most frequently leading to withdrawal (4% each) from controlled studies. In pregabalin-treated patients reporting these adverse events in short-term, controlled studies, dizziness persisted until the last dose in 31% and somnolence persisted until the last dose in 46% of patients.

Ophthalmological Effects

In controlled studies, a higher proportion of patients treated with pregabalin reported blurred vision (6%) than did patients treated with placebo (2%), which resolved in a majority of cases with continued dosing. Less than 1% of patients discontinued pregabalin treatment due to vision-related events (primarily blurred vision).

Prospectively planned ophthalmologic testing, including visual acuity testing, formal visual field testing and dilated funduscopic examination, was performed in over 3600 patients. In these patients, visual acuity was reduced in 7% of patients treated with pregabalin, and 5% of placebo-treated patients. Visual field changes were detected in 13% of pregabalin-treated, and 12% of placebo-treated patients. Funduscopic changes were observed in 2% of pregabalin-treated and 2% of placebo-treated patients.

Although the clinical significance of the ophthalmologic findings is unknown, patients should be informed that if changes in vision occur, they should notify their physician. If visual disturbance persists, further assessment should be considered. More frequent

assessment should be considered for patients who are already routinely monitored for ocular conditions (See **PRECAUTIONS-Information for Patients**).

Abrupt or Rapid Discontinuation

Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, and diarrhea. Pregabalin should be tapered gradually over a minimum of 1 week rather than discontinued abruptly.

Weight Gain

Pregabalin treatment caused weight gain. In pregabalin controlled clinical trials of up to 13 weeks, a gain of 7% or more over baseline weight was observed in 8% of pregabalin-treated patients and 2% of placebo-treated patients. Few patients treated with pregabalin (0.2%) withdrew from controlled trials due to weight gain. Pregabalin associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender, or age. Weight gain was not limited to patients with edema (See **Precautions-Peripheral Edema**).

Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown.

Among diabetic patients, pregabalin-treated patients gained an average of 1.6 kg (range: -16 to 16 kg), compared to an average 0.3 kg (range: -10 to 9 kg) weight gain in placebo patients. In a cohort of 333 diabetic patients who received pregabalin for at least 2 years, the average weight gain was 5.2 kg.

While the effects of pregabalin-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open label clinical trials with diabetic patients, pregabalin treatment did not appear to be associated with loss of glycemic control (as measured by HbA_{1C}).

Peripheral Edema

Pregabalin treatment caused edema, primarily described as peripheral edema. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. Peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

In controlled clinical trials the incidence of peripheral edema was 6% in the pregabalin group compared with 2% in the placebo group. In controlled clinical trials, 0.6% of pregabalin patients and no placebo patients withdrew due to peripheral edema.

Higher frequencies of weight gain and peripheral edema were observed in patients taking both LYRICA and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. The majority of patients using thiazolidinedione antidiabetic agents in the overall safety database were participants in studies of pain associated with diabetic peripheral neuropathy. In this population, peripheral edema was reported in 3% (2/60) of patients who were using thiazolidinedione antidiabetic agents only, 8% (69/859) of patients who were treated with pregabalin only, and 19% (23/120) of patients who were on both pregabalin and thiazolidinedione antidiabetic agents. Similarly, weight gain was reported in 0% (0/60) of patients on thiazolidinediones only; 4% (35/859) of patients on pregabalin only; and 7.5% (9/120) of patients on both drugs.

As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, care should be taken when co-administering LYRICA and these agents.

Because there are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status, LYRICA should be used with caution in these patients.

Creatine Kinase Elevations

Pregabalin treatment was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for pregabalin-treated patients and 28 U/L for the placebo patients. In all controlled trials across multiple patient populations, 2% of patients on pregabalin and 1% of placebo patients had a value

of creatine kinase at least three times the upper limit of normal. Three pregabalin treated subjects had events reported as rhabdomyolysis in premarketing clinical trials. The relationship between these myopathy events and pregabalin is not completely understood because the cases had documented factors that may have caused or contributed to these events. Prescribers should instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Pregabalin treatment should be discontinued if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Laboratory Changes

Decreased Platelet Count

Pregabalin treatment was associated with a decrease in platelet count. Pregabalin-treated subjects experienced a mean maximal decrease in platelet count of 20 x $10^3/\mu L$, compared to 11 x $10^3/\mu L$ in placebo patients. In the overall database of controlled trials, 2% of placebo patients and 3% of pregabalin patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and < 150 x $10^3/\mu L$. In randomized controlled trials, pregabalin was not associated with an increase in bleeding related adverse events.

ECG Changes

PR Interval Prolongation

Pregabalin treatment was associated with mild PR interval prolongation. In analyses of clinical trial ECG data, the mean PR interval increase was 3-6 msec at pregabalin doses =300 mg/day. This mean change difference was not associated with an increased risk of PR increase =25% from baseline, an increased percentage of subjects with on-treatment PR >200 msec, or an increased risk of adverse events of second or third degree AV block.

Information for Patients

Patients should be counseled that LYRICA may cause dizziness, somnolence, blurred vision and other CNS signs and symptoms. Accordingly, they should be advised not to drive, operate complex machinery, or engage in other hazardous activities until they have

gained sufficient experience on pregabalin to gauge whether or not it affects their mental, visual, and/or motor performance adversely.

Patients should be counseled that LYRICA may cause visual disturbances. Patients should be informed that if changes in vision occur, they should notify their physician (See **PRECAUTIONS**).

Patients should be advised to take LYRICA as prescribed. Abrupt or rapid discontinuation may result in insomnia, nausea, headache, or diarrhea.

Patients should be counseled that LYRICA may cause edema and weight gain.

Patients should be advised that concomitant treatment with LYRICA and a thiazolidinedione antidiabetic agent may lead to an additive effect on edema and weight gain. For patients with preexisting cardiac conditions, this may increase the risk of heart failure.

Patients should be instructed to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Patients who require concomitant treatment with central nervous system depressants such as opiates or benzodiazepines should be informed that they may experience additive CNS side effects, such as somnolence.

Patients should be told to avoid consuming alcohol while taking LYRICA, as LYRICA may potentiate the impairment of motor skills and sedation of alcohol.

Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding or intend to breast feed during therapy.

Men being treated with LYRICA who plan to father a child should be informed of the potential risk of male-mediated teratogenicity. In preclinical studies in rats, pregabalin was associated with an increased risk of male-mediated teratogenicity. The clinical significance of this finding is uncertain (see PRECAUTIONS - Carcinogenesis and Impairment of Fertility).

Diabetic patients should be instructed to pay particular attention to skin integrity while being treated with LYRICA. Some animals treated with pregabalin developed skin ulcerations, although no increased incidence of skin lesions associated with LYRICA was observed in clinical trials (see **Animal Toxicology**).

Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking LYRICA.

Drug Interactions

Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. In vitro and in vivo studies showed that LYRICA is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, there are no pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between pregabalin and commonly used antiepileptic drugs (See **CLINICAL PHARMACOLOGY**).

Pharmacodynamics

Multiple oral doses of pregabalin were co-administered with oxycodone, lorazepam, or ethanol. Although no pharmacokinetic interactions were seen, additive effects on cognitive and gross motor functioning were seen when pregabalin was co-administered with those drugs. No clinically important effects on respiration were seen (See **PRECAUTIONS, Dizziness and Somnolence and Information for Patients**).

Animal Toxicology

Dermatopathy

Skin lesions ranging from erythema to necrosis were seen in repeated-dose toxicology studies in both rats and monkeys. The etiology of these skin lesions is unknown. At the maximum recommended human dose (MRD) of 600 mg/day, there is a 2-fold safety

margin for the dermatological lesions. The more severe dermatopathies involving necrosis were associated with pregabalin exposures (as expressed by plasma AUCs) of approximately 3 to 8 times those achieved in humans given the MRD. No increase in incidence of skin lesions was observed in clinical studies.

Ocular lesions

Ocular lesions (characterized by retinal atrophy [including loss of photoreceptor cells] and/or corneal inflammation/mineralization) were observed in two lifetime carcinogenicity studies in Wistar rats. These findings were observed at plasma pregabalin exposures (AUC) =2 times those achieved in humans given the maximum recommended dose of 600 mg/day. A no-effect dose for ocular lesions was not established. Similar lesions were not observed in lifetime carcinogenicity studies in two strains of mice or in monkeys treated for 1 year. The clinical significance of this finding in rats is unknown.

Effects in Juvenile Animals

In studies in which pregabalin (50 to 500 mg/kg) was orally administered to young rats from early in the postnatal period (Postnatal Day 7) through sexual maturity, neurobehavioral abnormalities (deficits in learning and memory, altered locomotor activity, decreased auditory startle responding and habituation) and reproductive impairment (delayed sexual maturation and decreased fertility in males and females) were observed at doses = 50 mg/kg. The neurobehavioral changes (except for locomotor activity) persisted in animals tested after cessation of dosing and, thus, were considered to represent long-term effects. The low effect dose for developmental neurotoxicity and reproductive impairment in juvenile rats (50 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately equal to human exposure at the maximum recommended dose of 600 mg/day. A no-effect dose was not established.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

A dose-dependent increase in the incidence of malignant vascular tumors (hemangiosarcomas) was observed in two strains of mice (B6C3F1 and CD-1) given pregabalin (200, 1000, or 5000 mg/kg) in the diet for two years. Plasma pregabalin

exposure (AUC) in mice receiving the lowest dose that increased hemangiosarcomas was approximately equal to the human exposure at the maximum recommended dose (MRD) of 600 mg/day. A no-effect dose for induction of hemangiosarcomas in mice was not established. No evidence of carcinogenicity was seen in two studies in Wistar rats following dietary administration of pregabalin for two years at doses (50, 150, or 450 mg/kg in males and 100, 300, or 900 mg/kg in females) that were associated with plasma exposures in males and females up to approximately 14 and 24 times, respectively, human exposure at the MRD. The clinical significance of this finding in mice is unknown.

Mutagenesis

Pregabalin was not mutagenic in bacteria or in mammalian cells *in vitro*, was not clastogenic in mammalian systems in vitro and in vivo, and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes.

Impairment of Fertility

In fertility studies in which male rats were orally administered pregabalin (50 to 2500 mg/kg) prior to and during mating with untreated females, a number of adverse reproductive and developmental effects were observed. These included decreased sperm counts and sperm motility, increased sperm abnormalities, reduced fertility, increased preimplantation embryo loss, decreased litter size, decreased fetal body weights, and an increased incidence of fetal abnormalities. Effects on sperm and fertility parameters were reversible in studies of this duration (3-4 months). The no-effect dose for male reproductive toxicity in these studies (100 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately 3 times human exposure at the maximum recommended dose (MRD) of 600 mg/day.

In addition, adverse effects on reproductive organ (testes, epididymides) histopathology were observed in male rats exposed to pregabalin (500 to 1250 mg/kg) in general toxicology studies of four weeks or greater duration. The no-effect dose for male reproductive organ histopathology in rats (250 mg/kg) was associated with a plasma exposure approximately 8 times human exposure at the MRD.

In a fertility study in which female rats were given pregabalin (500, 1250, or 2500 mg/kg) orally prior to and during mating and early gestation, disrupted estrous cyclicity and an increased number of days to mating were seen at all doses, and embryolethality occurred at the highest dose. The low dose in this study produced a plasma exposure approximately 9 times that in humans receiving the MRD. A no-effect dose for female reproductive toxicity in rats was not established. The clinical significance of female fertility findings in animals is unknown.

Human Data

In a double-blind, placebo-controlled clinical trial to assess the effect of pregabalin on sperm motility, 30 healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment (one complete sperm cycle), the difference between placebo- and pregabalin-treated subjects in mean percent sperm with normal motility was <4% and neither group had a mean change from baseline of more than 2%. Effects on other male reproductive parameters in humans have not been adequately studied.

Pregnancy

Pregnancy Category C

Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity, including lethality, growth retardation, and nervous and reproductive system functional impairment, were observed in the offspring of rats and rabbits given pregabalin during pregnancy, at doses that produced plasma pregabalin exposures (AUC) ≥5 times human exposure at the maximum recommended dose (MRD) of 600 mg/day.

When pregnant rats were given pregabalin (500, 1250, or 2500 mg/kg) orally throughout the period of organogenesis, incidences of specific skull alterations attributed to abnormally advanced ossification (premature fusion of the jugal and nasal sutures) were increased at =1250 mg/kg, and incidences of skeletal variations and retarded ossification were increased at all doses. Fetal body weights were decreased at the highest dose. The low dose in this study was associated with a plasma exposure (AUC) approximately 17

times human exposure at the MRD of 600 mg/day. A no-effect dose for rat embryo-fetal developmental toxicity was not established.

When pregnant rabbits were given pregabalin (250, 500, or 1250 mg/kg) orally throughout the period of organogenesis, decreased fetal body weight and increased incidences of skeletal malformations, visceral variations, and retarded ossification were observed at the highest dose. The no-effect dose for developmental toxicity in rabbits (500 mg/kg) was associated with a plasma exposure approximately 16 times human exposure at the MRD.

In a study in which female rats were dosed with pregabalin (50, 100, 250, 1250, or 2500 mg/kg) throughout gestation and lactation, offspring growth was reduced at = 100 mg/kg and offspring survival was decreased at = 250 mg/kg. The effect on offspring survival was pronounced at doses =1250 mg/kg, with 100% mortality in high-dose litters. When offspring were tested as adults, neurobehavioral abnormalities (decreased auditory startle responding) were observed at =250 mg/kg and reproductive impairment (decreased fertility and litter size) was seen at 1250 mg/kg. The no-effect dose for pre- and postnatal developmental toxicity in rats (50 mg/kg) produced a plasma exposure approximately 2 times human exposure at the MRD.

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

Labor and Delivery: The effects of pregabalin on labor and delivery in pregnant women are unknown. In the prenatal-postnatal study in rats, pregabalin prolonged gestation and induced dystocia at exposures ≥50 times the mean human exposure ($AUC_{(0-24)}$ of 123 μg·hr/mL) at the maximum recommended clinical dose of 600 mg/day.

Use in Nursing Mothers: It is not known if pregabalin is excreted in human milk; it is, however, present in the milk of rats. Because many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for pregabalin in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and efficacy of pregabalin in pediatric patients have not been established.

Geriatric Use

In controlled clinical studies of LYRICA in neuropathic pain associated with diabetic peripheral neuropathy, 306 patients were 65 to 74 years of age, and 88 patients were 75 years of age or older.

In controlled clinical studies of LYRICA in neuropathic pain associated with postherpetic neuralgia, 282 patients were 65 to 74 years of age, and 379 patients were 75 years of age or older.

No overall differences in safety and efficacy were observed between these patients and younger patients. Even though the incidence of adverse events did not increase with age, greater sensitivity of some older individuals cannot be ruled out. LYRICA is known to be substantially excreted by the kidney, and the risk of toxic reactions to LYRICA may be greater in patients with impaired renal function.

Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for elderly patients with renal impairment, as noted in the **DOSAGE AND ADMINISTRATION** section.

ADVERSE REACTIONS

In all controlled and uncontrolled trials across various patient populations during the premarketing development of pregabalin, more than 9000 patients have received pregabalin. Approximately 4300 patients were treated for 6 months or more, over 2700 patients were treated for 1 year or longer, and over 1000 patients were treated for at least 2 years.

Adverse Events Most Commonly Leading to Discontinuation in All Controlled Clinical Studies

In controlled trials of all populations combined. 14% of patients treated with pregabalin and 7% of patients treated with placebo discontinued prematurely due to adverse events. In the pregabalin treatment group, the adverse events most frequently leading to discontinuation were dizziness (4%) and somnolence (3%). In the placebo group, 1% of patients withdrew due to dizziness and <1% withdrew due to somnolence. Other adverse events that led to discontinuation from controlled trials more frequently in the pregabalin group compared to the placebo group were ataxia, confusion, asthenia, thinking abnormal, blurred vision, incoordination, and peripheral edema (1% each)

Most Common Adverse Events in All Controlled Clinical Studies

In controlled trials of all patient populations combined, dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and "thinking abnormal" (primarily difficulty with concentration/attention) were more commonly reported by subjects treated with pregabalin than by subjects treated with placebo (≥5% and twice the rate of that seen in placebo).

Controlled Studies with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

Adverse Events Leading to Discontinuation

In clinical trials in patients with neuropathic pain associated with diabetic peripheral neuropathy, 9% of patients treated with pregabalin and 4% of patients treated with placebo discontinued prematurely due to adverse events. In the pregabalin treatment group, the most common reasons for discontinuation due to adverse events were dizziness (3 %) and somnolence (2 %). In comparison, <1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring with greater frequency in the pregabalin group than in the placebo group, were asthenia, confusion, and peripheral edema. Each of these events led to withdrawal in approximately 1% of patients.

Most Common Adverse Events

Table 1 lists all adverse events, regardless of causality, occurring in = 1% of patients with neuropathic pain associated with diabetic neuropathy in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group. A majority of pregabalin-treated patients in clinical studies had adverse events with a maximum intensity of "mild" or "moderate".

Table 1. Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body system - Preferred term	75 mg/day [N=77] %	150 mg/day [N=212] %	300 mg/day [N=321] %	600 mg/day [N=369] %	All PGB* [N=979] %	Placebo [N=459] %
Body as a whole						
Asthenia	4	2	4	7	5	2
Accidental injury	5	2	2	6	4	3
Back pain	0	2	1	2	2	0
Chest pain	4	1	1	2	2	1
Face edema	0	1	1	2	1	0
Digestive system						
Dry mouth	3	2	5	7	5	1
Constipation	0	2	4	6	4	2
Flatulence	3	0	2	3	2	1
Metabolic and nutritional disorders						
Peripheral edema	4	6	9	12	9	2
Weight gain	0	4	4	6	4	0
Edema	0	2	4	2	2	0
Hypoglycemia	1	3	2	1	2	1
Nervous system						
Dizziness	8	9	23	29	21	5
Somnolence	4	6	13	16	12	3
Neuropathy	9	2	2	5	4	3
Ataxia	6	1	2	4	3	1
Vertigo	1	2	2	4	3	1
Confusion	0	1	2	3	2	1
Euphoria	0	0	3	2	2	0
Incoordination	1	0	2	2	2	0
Thinking abnormal[1]	1	0	1	3	2	0
Tremor	1	1	1	2	1	0
Abnormal gait	1	0	1	3	1	0
Amnesia	3	1	0	2	1	0
Nervousness	0	1	1	1	1	0
Respiratory system						
Dyspnea	3	0	2	2	2	1

Table 1. Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body system - Preferred term	75 mg/day [N=77] %	150 mg/day [N=212] %	300 mg/day [N=321] %	600 mg/day [N=369] %	All PGB* [N=979] %	Placebo [N=459] %
Special senses						
Blurry vision[b]	3	1	3	6	4	2
Abnormal vision	1	0	1	1	1	0

*PGB: pregabalin

[a] Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.

[b] Investigator term; summary level term is amblyopia

Controlled Studies in Postherpetic Neuralgia

Adverse Events Leading to Discontinuation

In clinical trials in patients with postherpetic neuralgia, 14% of patients treated with pregabalin and 7% of patients treated with placebo discontinued prematurely due to adverse events. In the pregabalin treatment group, the most common reasons for discontinuation due to adverse events were dizziness (4%) and somnolence (3%). In comparison, less than 1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring in greater frequency in the pregabalin group than in the placebo group, were confusion (2%), as well as peripheral edema, asthenia, ataxia, and abnormal gait (1% each).

Most Common Adverse Events

Table 2 lists all adverse events, regardless of causality, occurring in = 1% of patients with neuropathic pain associated with postherpetic neuralgia in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group. In addition, an event is included, even if the incidence in the all pregabalin group is not greater than in the placebo group, if the incidence of the event in the 600 mg/day group is more than twice that in the placebo group. A majority of

pregabalin-treated patients in clinical studies had adverse events with a maximum intensity of "mild" or "moderate".

Table 2. Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body system - Preferred term	75 mg/d [N=84] %	150 mg/d [N=302] %	300 mg/d [N=312] %	600 mg/d [N=154] %	All PGB* [N=852] %	Placebo [N=398] %
Body as a whole						
Infection	14	8	6	3	7	4
Headache	5	9	5	8	7	5
Pain	5	4	5	5	5	4
Accidental injury	4	3	3	5	3	2
Flu syndrome	1	2	2	1	2	1
Face edema	0	2	1	3	2	1
Digestive system						
Dry mouth	7	7	6	15	8	3
Constipation	4	5	5	5	5	2
Flatulence	2	1	2	3	2	1
Vomiting	1	1	3	3	2	1
Metabolic and nutritional disorders						
Peripheral edema	0	8	16	16	12	4
Weight gain	1	2	5	7	4	0
Edema	0	1	2	6	2	1
Musculoskeletal system						
Myasthenia	1	1	1	1	1	0
Nervous system						
Dizziness	11	18	31	37	26	9
Somnolence	8	12	18	25	16	5
Ataxia	1	2	5	9	5	1
Abnormal gait	0	2	4	8	4	1
Confusion	1	2	3	7	3	0
Thinking abnormal[f]	0	2	1	6	2	2
Incoordination	2	2	1	3	2	0
Amnesia	0	1	1	4	2	0
Speech disorder	0	0	1	3	1	0
Respiratory system						
Bronchitis	0	1	1	3	1	1

Table 2. Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body system - Preferred term	75 mg/d [N=84] %	150 mg/d [N=302] %	300 mg/d [N=312] %	600 mg/d [N=154] %	All PGB* [N=852] %	Placebo [N=398] %
Special senses						
Blurry vision[b]	1	5	5	9	5	3
Diplopia	0	2	2	4	2	0
Abnormal vision	0	1	2	5	2	0
Eye Disorder	0	1	1	2	1	0
Urogenital System						
Urinary Incontinence	0	1	1	2	1	0

*PGB: pregabalin

[a] Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.

[b] Investigator term; summary level term is amblyopia

Other Adverse Events Observed During the Clinical Studies of LYRICA (pregabalin)

Following is a list of treatment-emergent adverse events reported by patients treated with LYRICA during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: **frequent** adverse events are those occurring on one or more occasions in at least 1/100 patients; **infrequent** adverse events are those occurring in 1/100 to 1/1000 patients; **rare** events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are described in the **WARNINGS** and **PRECAUTIONS** sections.

Body as a Whole – *Frequent:* Abdominal pain, Allergic reaction, Fever, *Infrequent:* Abscess, Cellulitis, Chills, Malaise, Neck rigidity, Overdose, Pelvic pain, Photosensitivity reaction, Suicide attempt, *Rare:* Anaphylactoid reaction, Ascites, Hangover effect, Shock, Suicide

Cardiovascular System –*Infrequent:* Deep thrombophlebitis, Heart failure, Hypotension, Postural hypotension, Retinal vascular disorder, Syncope

Digestive System – *Frequent*: Gastroenteritis, Increased appetite; *Infrequent:* Cholecystitis, Cholelithiasis, Colitis, Dysphagia, Esophagitis, Gastritis, Gastrointestinal hemorrhage, Melena, Mouth ulceration, Pancreatitis, Rectal hemorrhage, Tongue edema; *Rare:* Aphthous stomatitis

Hemic and Lymphatic System – *Frequent:* Ecchymosis; *Infrequent:* Anemia, Eosinophilia, Hypochromic anemia, Leukocytosis, Leukopenia, Lymphadenopathy, Thrombocytopenia; *Rare:* Polycythemia, Prothrombin decreased, Purpura, Thrombocythemia

Musculoskeletal System – *Frequent*: Arthralgia, Leg cramps, Myalgia, Myasthenia; *Infrequent:* Arthrosis

Nervous System – *Frequent:* Anxiety, Depersonalization, Hypertonia, Hypesthesia, Libido decreased, Nystagmus, Paresthesia, Stupor, Twitching; *Infrequent:* Abnormal dreams, Agitation, Apathy, Aphasia, Circumoral paresthesia, Dysarthria, Hallucinations, Hostility, Hyperalgesia, Hyperesthesia, Hyperkinesia, Hypokinesia, Hypotonia, Libido increased, Myoclonus, Neuralgia, *Rare:* Addiction, Cerebellar syndrome, Cogwheel rigidity, Coma, Delirium, Dyskinesia, Dystonia, Encephalopathy, Extrapyramidal syndrome, Guillain barre syndrome, Hypalgesia, Intracranial hypertension, Manic reaction, Paranoid reaction, Peripheral neuritis, Psychotic depression, Schizophrenic reaction, Torticollis, Trismus

Respiratory System –*Rare:* Apnea, Atelectasis, Bronchiolitis, Hiccup, Laryngismus, Lung edema, Lung fibrosis, Yawn

Skin and Appendages – *Frequent:* Pruritus, *Infrequent:* Alopecia, Dry skin, Eczema, Hirsutism, Skin ulcer, Urticaria, Vesiculobullous rash; *Rare:* Angioedema, Exfoliative dermatitis, Lichenoid dermatitis, Melanosis, Petechial rash, Purpuric rash, Pustular rash, Skin atrophy, Skin necrosis, Skin nodule, Stevens-Johnson syndrome, Subcutaneous nodule

Special senses– *Frequent:* Conjunctivitis, Diplopia, Otitis media, Tinnitus; *Infrequent:* Abnormality of accommodation, Blepharitis, Dry eyes, Eye hemorrhage, Hyperacusis, Photophobia, Retinal edema, Taste loss, Taste perversion; *Rare:* Anisocoria, Blindness, Corneal ulcer, Exophthalmos, Extraocular palsy, Iritis, Keratitis, Keratoconjunctivitis, Miosis, Mydriasis, Night blindness, Ophthalmoplegia, Optic atrophy, Papilledema, Parosmia, Ptosis

Urogenital System – *Frequent*: Anorgasmia, Impotence, Urinary frequency, Urinary incontinence, *Infrequent*: Abnormal ejaculation, Albuminuria, Amenorrhea, Dysmenorrhea, Dysuria, Hematuria, Kidney calculus, Leukorrhea, Menorrhagia, Metrorrhagia, Nephritis, Oliguria, Urinary retention, *Rare*: Acute kidney failure, Balanitis, Cervicitis, Dyspareunia, Epididymitis, Female lactation, Glomerulitis

Comparison of Gender and Race

The overall adverse event profile of pregabalin was similar between women and men There are insufficient data to support a statement regarding the distribution of adverse experience reports by race.

DRUG ABUSE AND DEPENDENCE

In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, Lyrica (450mg, single dose) received subjective ratings of "good drug effect," "high" and

"liking" to a degree that was similar to diazepam (30mg, single dose). In controlled clinical studies in over 5500 patients, 4 % of Lyrica-treated patients and 1 % of placebo-treated patients overall reported euphoria as an adverse event, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%. In clinical studies, following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache or diarrhea (See PRECAUTIONS, Abrupt Discontinuation), suggestive of physical dependence.

Pregabalin is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior).

OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans

There is limited experience with overdose of pregabalin. The highest reported accidental overdose of pregabalin during the clinical development program was 8000 mg, and there were no notable clinical consequences. In clinical studies, some patients took as much as 2400 mg/day. The types of adverse events experienced by patients exposed to higher doses (= 900 mg) were not clinically different from those of patients administered recommended doses of pregabalin.

Treatment or Management of Overdose

There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with pregabalin.

Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

DOSAGE AND ADMINISTRATION

LYRICA™ is given orally with or without food.

Neuropathic pain associated with diabetic peripheral neuropathy

The maximum recommended dose of LYRICA is 100 mg three times a day (300 mg/day) in patients with creatinine clearance of at least 60 mL/min. Dosing should begin at 50 mg three times a day (150mg/day) and may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for patients with reduced renal function (see **Patients with Renal Impairment**).

Although LYRICA was also studied at 600 mg/day, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse effects, treatment with doses above 300 mg/day are not recommended (see ADVERSE REACTIONS).

When discontinuing LYRICA, taper gradually over a minimum of 1 week.

Postherpetic neuralgia

The recommended dose of LYRICA is 75 to 150 mg two times a day, or 50 to 100 mg three times a day (150 to 300 mg/day) in patients with creatinine clearance of at least 60 mL/min. Dosing should begin at 75 mg two times a day, or 50 mg three times a day (150 mg/day) and may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for patients with reduced renal function (see **Patients with Renal Impairment**).

Patients who do not experience sufficient pain relief following 2 to 4 weeks of treatment with 300 mg/day, and who are able to tolerate LYRICA, may be treated with up to 300 mg two times a day, or 200 mg three times a day (600 mg/day). In view of the dose-dependent adverse effects and the higher rate of treatment discontinuation due to adverse events, dosing above 300 mg/day should be reserved only for those patients who have on-going pain and are tolerating 300 mg daily (see **Adverse Reactions**).

When discontinuing LYRICA, taper gradually over a minimum of 1 week.

Patients with Renal Impairment:

In view of dose-dependent adverse events and since Lyrica is eliminated primarily by renal excretion, the dose should be adjusted in patients with reduced renal function. Dosage adjustment in patients with renal impairment should be based on CLcr, as indicated in Table 3. To use this dosing table, an estimate of the patient's CLcr in mL/min is needed. CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the Cockcroft and Gault equation:

$$CLcr = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times\ 0.85 \text{ for female patients})$$

For patients undergoing hemodialysis, pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose adjustment, a supplemental dose should be given immediately following every 4-hour hemodialysis treatment (see Table 3).

Table 3: Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CLcr) (mL/min)	Total Pregabalin Daily Dose (mg/day)[a]			Dose Regimen
≥60	150	300	600	BID or TID
30-60	75	150	300	BID or TID
15-30	25-50	75	150	QD or BID
<15	25	25-50	75	QD
Supplementary dosage following hemodialysis (mg)[b]				
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg Patients on the 25-50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg				

TID = Three divided doses; BID = Two divided doses; QD = Single daily dose.

[a] Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.

[b] Supplementary dose is a single additional dose.

HOW SUPPLIED

25-mg capsules:

White, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 25" on the body; available in:

Bottles of 90 capsules: NDC0071-1012-68

Unit-Dose Blister Packages of 100: NDC0071-1012-41

50-mg capsules:

White, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 50" and an ink band on the body, available in:

Bottles of 90: NDC0071-1013-68

Unit-Dose Blister Packages of 100: NDC0071-1013-41

75-mg capsules:

White/orange hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 75" on the body; available in:

Bottles of 90:	NDC0071-1014-68
Unit-Dose Blister Packages of 100:	NDC0071-1014-41

100-mg capsules:

Orange, hard-gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 100" on the body, available in:

Bottles of 90:	NDC0071-1015-68
Unit-Dose Blister Packages of 100:	NDC0071-1015-41

150-mg capsules:

White hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 150" on the body, available in:

Bottles of 90 capsules:	NDC0071-1016-68
Unit-Dose Blister Packages of 100:	NDC0071-1016-41

200-mg capsules:

Light orange hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 200" on the body, available in:

Bottles of 90:	NDC0071-1017-68
Unit-Dose Blister Packages of 100:	NDC0071-1017-41

225-mg capsules:

White/light orange hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 225" on the body; available in:

Bottles of 90:	NDC0071-1019-68
Unit-Dose Blister Packages of 100:	NDC0071-1019-41

300-mg capsules:

White/orange hard gelatin capsule printed with black ink "Pfizer" on the cap, "PGN 300" on the body, available in:

Bottles of 90:	NDC0071-1018-68
Unit-Dose Blister Packages of 100:	NDC0071-1018-41

Storage

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

Rx Only

Distributed by:

Parke-Davis
Division of Pfizer Inc
New York, NY 10017

PATIENT INFORMATION

LYRICA (LEER-ik-ah)
PREGABALIN

Read the Patient Information that comes with LYRICA before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or treatment. If you have any questions about LYRICA, ask your doctor or pharmacist.

What is the most important information I should know about LYRICA?

1. **LYRICA may cause dizziness and sleepiness.**
   - **Do not drive a car, work with machines, or do other dangerous activities until you know how LYRICA affects how alert you are.** Ask your doctor when it is okay to do these activities.
2. **LYRICA may cause problems with your eyesight, including blurry vision.**
   - Call your doctor if you have any changes in your eyesight.

What is LYRICA?

LYRICA is a prescription medicine used in adults, 18 years and older, to treat pain from damaged nerves (neuropathic pain) that:

- happens with diabetes, or
- follows healing of shingles (a painful rash that comes after a herpes zoster infection)

Diabetes and shingles can damage your nerves. Pain from damaged nerves may feel sharp, burning, tingling, shooting, or numb. If you have diabetes, the pain can be in your arms, hands, fingers, legs, feet, or toes. If you have shingles, the pain is in the area of your rash. You may experience this kind of pain even with a very light touch. LYRICA can help relieve the pain. Some people taking LYRICA had less pain by the end of the first week of LYRICA therapy. LYRICA may not work for everyone.

LYRICA has not been studied for nerve pain in children under 18 years of age.

Who Should Not Take LYRICA?

Do not take LYRICA if you are allergic to any of its ingredients. The active ingredient is pregabalin. See the end of this leaflet for a complete list of ingredients in LYRICA.

What should I tell my doctor before taking LYRICA?

Tell your doctor about all your medical conditions, including if you:

- **have any kidney problems or get kidney dialysis**
- **have heart problems including heart failure**
- **have a bleeding problem or a low blood platelet count**
- **are pregnant or plan to become pregnant.** It is not known if LYRICA may harm your unborn baby. You and your doctor will have to decide if LYRICA is right for you while you are pregnant.
- **are breastfeeding.** It is not known if LYRICA passes into breast milk and if it can harm your baby. You and your doctor should decide whether you should take LYRICA or breastfeed, but not both.

Tell your doctor about all the medicines you take including prescription or non-prescription medicines, vitamins or herbal supplements. LYRICA and other medicines may affect each other. Especially tell your doctor if you take:

- rosiglitazone (Avandia®) or pioglitazone (Actos®) for diabetes. You may have a higher chance of weight gain or swelling if these medicines are taken with LYRICA. See "What are the possible side effects of LYRICA."
- any narcotic pain medicine (such as oxycodone), tranquilizers or medicines for anxiety (such as lorazepam). You may have a higher chance for dizziness and sleepiness if these medicines are taken with LYRICA. See "What is the most important information I should know about LYRICA?"
- any medicines that make you sleepy

Know all the medicines you take. Keep a list of them with you to show your doctor and pharmacist each time you get a new medicine.

Tell your doctor if you plan to father a child. Animal studies showed that pregabalin, the active ingredient in LYRICA, made male animals less fertile. Also, in animal studies, birth defects occurred in the offspring of male animals who were treated with pregabalin. It is not known if these effects would happen in people.

How should I take LYRICA?

- Take LYRICA exactly as prescribed. Your doctor may adjust your dose during treatment. Do not change your dose without talking to your doctor.
- Do not stop taking LYRICA suddenly without talking to your doctor. If you stop taking LYRICA suddenly, you may have headaches, nausea, diarrhea or trouble sleeping. Talk with your doctor about how to slowly stop LYRICA.
- LYRICA is usually taken 2 or 3 times a day, depending on your medical condition. Your doctor will tell you how much LYRICA to take and when to take it. Take LYRICA at the same times each day.
- LYRICA may be taken with or without food.
- If you miss a dose by a few hours, take it as soon as you remember. If it is close to your next dose, just take LYRICA at your next regular time. **Do not** take two doses at the same time.
- If you take too much LYRICA, call your doctor or poison control center or go to the nearest emergency room right away.

What Should I Avoid While Taking LYRICA?

- **Do not drive a car, work with machines, or do other dangerous activities until you know how LYRICA affects how alert you are.** See "What is the most important information I should know about LYRICA?"
- **Do not drink alcohol while taking LYRICA.** LYRICA and alcohol can affect each other and increase side effects such as sleepiness and dizziness. This can be dangerous.
- **Do not take other medicines without talking to your doctor.** Other medicines include prescription and non-prescription medicines, vitamins, and herbal supplements. LYRICA and other medicines may affect each other and increase the side effects of sleepiness and dizziness. Be especially careful about medicines that make you sleepy (such as sleeping pills, anxiety medicines, tranquilizers and some antihistamines, pain relievers and seizure medicines).

Version Date: December 30, 2004

What are the possible side effects of LYRICA?

LYRICA may cause side effects including:

- **dizziness and sleepiness.** See "What is the most important information I should know about LYRICA?"
- **eyesight problems.** See "What is the most important information I should know about LYRICA?"
- **weight gain and swelling of the hands and feet (edema).** Weight gain may affect the management of diabetes. Weight gain and swelling can also be a serious problem for people with heart problems.
- **unexplained muscle problems,** such as muscle pain, soreness, or weakness. If you develop these symptoms, especially if you also feel sick and have a fever, tell your doctor right away.

The most common side effects of LYRICA are:

- dizziness
- blurry vision
- weight gain
- sleepiness
- trouble concentrating
- swelling of hands and feet
- dry mouth

LYRICA caused skin sores in animals. Although skin sores were not seen in studies in people, if you have diabetes, you should pay extra attention to your skin while taking LYRICA and tell your doctor of any sores or skin problems.

LYRICA may cause some people to feel "high." Tell your doctor, if you have abused prescription medicines, street drugs, or alcohol in the past.

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the side effects of LYRICA. For more information, ask your doctor or pharmacist.

How should I store LYRICA?

- Store LYRICA at room temperature, 59 to 86° F (15 to 30°C) in its original package.
- Safely throw away LYRICA that is out of date or no longer needed.
- **Keep LYRICA and all medicines out of the reach of children.**.

General information about LYRICA

Medicines are sometimes prescribed for conditions other than those listed in patient information leaflets. Do not use LYRICA for a condition for which it was not prescribed. Do not give LYRICA to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about LYRICA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about LYRICA that is written for health professionals.
You can also visit the LYRICA website at www.LYRICA.com or call 1-866-4LYRICA.

What are the ingredients in LYRICA?

Active ingredient: pregabalin
Inactive ingredients: lactose monohydrate, cornstarch, talc; **Capsule shell:** gelatin and titanium dioxide; Orange capsule shell: red iron oxide; White capsule shell: sodium lauryl sulfate, colloidal silicon dioxide. Colloidal silicon dioxide is a manufacturing aid that may or may not be present in the capsule shells.
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Robert Meyer
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(12) **United States Patent**
Silverman et al.

(10) **Patent No.: US 6,197,819 B1**
(45) **Date of Patent: Mar. 6, 2001**

(54) **GAMMA AMINO BUTYRIC ACID ANALOGS AND OPTICAL ISOMERS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/420,905**

(22) Filed: **Apr. 11, 1995**

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(51) **Int. Cl.**[7] **A61K 31/195**
(52) **U.S. Cl.** **514/561**; 562/553
(58) **Field of Search** 562/553; 514/561

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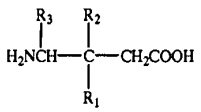
(57) **ABSTRACT**

A compound of the formula

I



wherein R_1 is a straight or branched alkyl group having from 1 to 6 carbon atoms, phenyl, or cycloalkyl having from 3 to 6 carbon atoms; R_2 is hydrogen or methyl; and R_3 is hydrogen, methyl or carboxyl; which is useful in the treatment of seizure disorders. Processes are disclosed for the preparation of the compound. Intermediates prepared during the synthesis of the compound are also disclosed.

4 Claims, No Drawings

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GAMMA AMINO BUTYRIC ACID ANALOGS AND OPTICAL ISOMERS

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation of application Ser. No. 08/064,285 filed on May 18, 1993, now abandoned; which application is a continuation-in-part of application U.S. Ser. No. 07/886,080, filed May 20, 1992, now abandoned, which is a continuation-in-part of application U.S. Ser. No. 07/618,692, filed Nov. 27, 1990, now abandoned.

GRANT REFERENCE

The research carried out in connection with this invention was supported in part by a grant from the National Institutes of Health. The U.S. Government has certain rights in this invention.

The present invention relates to novel compounds that are analogs of glutamic acid and gamma-aminobutyric acid (GABA). More specifically, the analogs are useful as anti-seizure therapy for central nervous system disorders such as epilepsy, Huntington's chorea, cerebral ischemia, Parkinson's disease, tardive dyskinesia, and spasticity. It is also possible that the present invention could be used as an antidepressant, anxiolytic, and antipsychotic activity.

BACKGROUND OF THE INVENTION

Gamma aminobutyric acid (GABA) and glutamic acid are two major neurotransmitters involved in the regulation of brain neuronal activity. GABA is the major inhibitory neurotransmitter and L-glutamic acid is an excitatory transmitter (Roberts E, et al, *GABA in Nervous System Function,* Raven Press: New York, 1976; McGeer E G, et al, *Glutamine, Glutamate, and GABA in the Central Nervous System;* Hertz L, Kvamme E, McGeer E G, Schousbal A, eds., Liss: New York, 1983;3–17). An imbalance in the concentration of these neurotransmitters can lead to convulsive states. Accordingly, it is clinically relevant to be able to control convulsive states by controlling the metabolism of this neurotransmitter. When the concentration of GABA diminishes below a threshold level in the brain, convulsions result (Karlsson A, et al, *Biochem. Pharmacol* 1974;23:3053–3061). When the GABA levels rise in the brain during convulsions, seizures terminate (Hayashi T J, *Physiol.* (London) 1959;145:570–578). The term seizure as used herein means excessive unsynchronized neuronal activity that disrupts normal neuronal function. In several seizure disorders there is concomitant with reduced brain GABA levels a diminished level of L-glutamic acid decarboxylase (GAD) activity also observed (McGeer P O, et al, In: *GABA in Nervous System Function;* Roberts E, Chase T N, Tower D B, eds., Raven Press: New York 1976:487–495; Butterworth J, et al, *Neurochem.* 1983;41:440–447; Spokes E G, *Adv. Exp. Med. Biol.* 1978;123:461–473; Wu J Y, et al, *Neurochem. Res.* 1979;4:575–586; and Iversen L L, et al, *Psychiat. Res.* 1974;11:255–256). Often, the concentrations of GAD and GABA vary in parallel because decreased GAD concentration results in lower GABA production.

Because of the importance of GABA as an inhibitory neurotransmitter, and its effect on convulsive states and other motor dysfunctions, a variety of approaches have been taken to increase the brain GABA concentration. For example, the most obvious approach was to administer GABA. When GABA is injected into the brain of a convulsing animal, the convulsions cease (Purpura D P, et al, *Neurochem.* 1959;3:238–268). However, if GABA is administered systematically, there is no anticonvulsant effect because GABA, under normal circumstances, cannot cross the blood brain barrier (Meldrum B S, et al, *Epilepsy;* Harris P, Mawdsley C, eds., Churchill Livingston: Edinburg 1974:55. In view of this limitation, there are three alternative approaches that can be taken to raise GABA levels.

The most frequent approach is to design a compound that crosses the blood brain barrier and then inactivates GABA aminotransferase. The effect is to block the degradation of GABA and thereby increase its concentration. Numerous mechanism-based inactivators of GABA aminotransferase are known (Silverman R B, *Mechanism-Based Enzyme Inactivation: Chemistry and Enzymology,* Vol. I and II, CRC: Boca Raton 1988).

Another approach is to increase GABA concentrations in the brain by making GABA lipophilic by conversion to hydrophobic GABA amides (Kaplan J P, et al, *G.J. Med. Chem.* 1980;23:702–704; Carvajal G, et al, *Biochem. Pharmacol.* 1964;13:1059–1069; Imines: Kaplan J P, Ibid.; or GABA esters: Shashoua V E, et al, *J. Med. Chem.* 1984;27:659–664; and PCT Patent Application WO85/00520, published Feb. 14, 1985) so that GABA can cross the blood brain barrier. Once inside the brain, these compounds require amidase and esterases to hydrolyze off the carrier group and release GABA.

Yet another approach is to increase 25 brain GABA levels by designing an activator of GAD. A few compounds have been described as activators of GAD. The anticonvulsant agent, maleicimid, was reported to increase the activity of GAD by 11% and as a result increase GABA concentration in the substantia nigra by up to 38% (Janssens de Varebeke P, et al, *Biochem. Pharmacol.* 1983;32:2751–2755. The anticonvulsant drug sodium valproate (Loscher W, *Biochem. Pharmacol.* 1982;31:837–842; Phillips N I, et al, *Biochem. Pharmacol.* 1982;31:2257–2261) was also reported to activate GAD and increase GABA levels.

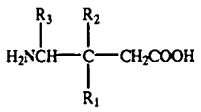
The compounds of the present invention have been found to activate GAD in vitro and have a dose dependent protective effect on-seizure in vivo.

Also, the compounds of the present invention have been found to bind a novel binding site which was identified to bind tritiated gabapentin. Gabapentin has been found to be an effective treatment for the prevention of partial seizures in patients refractory to other anticonvulsant agents. Chadwick D, Gabapentin, pp. 211–222, In: *Recent Advances in Epilepsy,* Vol. 5, Pedley T A, Meldrum B S, (eds.) Churchill Livingstone, New York (1991). The novel binding site labeled by tritiated gabapentin was described in membrane fractions from rat brain tissue and in autoradiographic studies in rat brain sections, Hill D, Ibid. This binding site has been used to evaluate the compounds of the present invention.

The novel compounds of the present invention are set forth below as Formula I. It should be noted that the compound of Formula I wherein R_1 is methyl and each of R_2 and R_3 is hydrogen is taught in Japan Patent Number 49-40460.

SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided compounds of the Formula I:

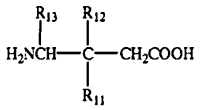


I

wherein R_1 is a straight or branched alkyl of from 1 to 6 carbons, phenyl or cycloalkyl having from 3 to 6 carbon atoms; R_2 is hydrogen or methyl; and R_3 is hydrogen, methyl, or carboxyl; with the proviso that when each of the R_2 and R_3 is hydrogen, R_1 is other than methyl. Pharmaceutically acceptable salts of the compounds of Formula I are also included within the scope of the present invention. Also included within the scope of the present invention are the individual enantiomeric isomers of the compounds of the Formula I.

The present invention also provides pharmaceutical compositions of the compounds of Formula I.

Also provided as a part of the present 10 invention is a novel method of treating seizure disorders in a patient by administering to said patient an anticonvulsant effective amount of a compound of the following Formula II:



II

wherein R_{11} is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl having from 3 to 6 carbon atoms; R_{12} is hydrogen or methyl; and R_{13} is hydrogen, methyl, or carboxyl; or an individual enantiomeric isomer thereof; or a pharmaceutically acceptable salt thereof.

Also, the present invention provides a method for increasing brain neuronal GABA and provides pharmaceutical compositions of the compounds of Formula II.

The present invention provides novel processes for the synthesis of chiral Formula I compounds.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a series of 3-alkyl-4-aminobutyric acid or 3-alkyl glutamic acid analogs which are useful as anticonvulsants. Illustrative of the alkyl moieties as represented by R_1 and R_{11} in Formulas I and II are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, isopentyl, and neopentyl as well as other alkyl groups. The cycloalkyl groups represented by R_1 and R_{11} in Formulas I and II are exemplified by cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. The analogs are further shown herein to prevent seizure while not causing the side effect of ataxia, such a side effect being found in several anti-seizure pharmaceuticals.

The more preferred compounds of the present invention are of Formula I above wherein R_3 is hydrogen, R_2 is hydrogen, and R_1 isobutyl.

That is, the preferred compound is 4-amino-3-(2-methylpropyl)butanoic acid. It has been found that this compound is unexpectedly more potent than the other analogs synthesized in accordance herewith and tested in vivo. What is further surprising, as the following data shows, is that this preferred compound is the least effective one of the analogs tested in activating GAD in vitro. Accordingly, it was very unexpected that this preferred compound had such a high potency when tested in vivo.

The most preferred compounds of the present invention are the (S)-(+)- and the (R)(-)-4-amino-3-(2-methylpropyl) butanoic acid with the (S)-(+)-enantiomer being most preferred. The (S)-(+)-enantiomer was found to be the most potent compound within the scope of the present invention for displacement of tritiated gabapentin, and both the (S)-(+)- and the (R)-(-)-enantiomers showed pronounced stereoselectivity for both displacement of tritiated gabapentin and for anticonvulsant activity in vivo.

The compounds made in accordance with the present invention may form pharmaceutically acceptable salts with both organic and inorganic acids or bases. For example, the acid addition salts of the basic compounds are prepared either by dissolving the free base in aqueous or aqueous alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution. Examples of pharmaceutically acceptable salts are hydrochlorides, hydrobromide, hydrosulfates, etc, as well as sodium, potassium, and magnesium, etc, salts.

The method for the formation of the 3-alkyl-4-aminobutanoic acids starting from 2-alkanoic esters is prepared from commercially available aldehydes and monomethyl malonate by the Knoevenagel reaction, (Kim Y C, et al, *J. Med. Chem.* 1965:8509) with the exception of ethyl 4,4-dimethyl-2-pentenoate.

More specifically, the following is a procedure which can be generally applied to the preparation of all the 3-alkylglutamic acids. Ten grams of a 3-alkyl-5,5-dicarbethoxy-2-pyrrolidinone was refluxed in 150 mL of 49% fuming HBr for 4 hours. After this time, the contents were placed in an evaporator and the volatile constituents were removed in vacuo with the aid of a hot-water bath. The gummy residue was dissolved in 25 mL of distilled water and the water was removed with the aid of the evaporator. This process was repeated once more. The residue was dissolved in 20 mL of water, and the pH of the solution was adjusted to 3.2 with concentrated NH_3 solution. At this point the chain length of the individual 3-alkylglutamic acids altered the solubility so that those whose side chains were larger precipitated with the ease from solution. Precipitation of the alkylglutamic acids with smaller substituents (methyl, ethyl, and propyl) could be encouraged by cooling on an ice bath or by diluting the aqueous solution with 100 mL of absolute ethanol. Precipitation from the water-alcohol mixture is complete in 48 hours. Care must be taken to add the ethanol slowly to prevent the precipitation of an amorphous solid which is not characteristic of the desired 3-alkylglutamic acids. Samples of the amino acids were purified for analysis by recrystallizing from a water-ethanol mixture. All melted with decomposition. Melting points of the decomposed 3-alkylglutamic acids corresponded with those of their pyroglutamic acids.

Ethyl 4,4-dimethyl-2-pentenoate was prepared from 2,2-dimethylpropanol and ethyl lithioacetate, followed by dehydration of the β-hydroxy ester with phosphoryl chloride and pyridine.

The Michael addition of nitromethane to alpha, β-unsaturated compounds mediated by 1,1,3,3-tetramethylguanidine or 1,8-diazabicyclo-[5.4.0]undec-7-ene(DBU) afforded 4-nitroesters in good yields. More

specifically, a mixture of nitromethane (5 mol), α,β-unsaturated ester (1 mol), and tetramethyl-guanidine (0.2 mol) was stirred at room temperature for 2 to 4 days. (In case of methyl acrylate, the ester has to be added at a temperature below 300.) The progress of the reaction was followed by IR (disappearance of the C=C band) and G.L.C. analysis. The reaction mixture was washed with dilute hydrochloric acid and extracted with ether. The organic extract was dried, the solvent removed at reduced pressure, and the 20 residue distilled at a pressure of 2 torr. Although the aliphatic nitro compounds are usually reduced by either high pressure catalytic hydrogenation by metal-catalyzed transfer hydrogenation, or by newly introduced hydrogenolysis methods with ammonium formate or sodium borohydride and palladium as catalysts, applicants have found that 4-nitrocarboxylic esters can be reduced almost quantitatively to the corresponding 4-aminocarboxylic esters by hydrogenation using 10% palladium on carbon as catalysts in acetic acid at room temperature and atmospheric pressure. The amino esters produced were subjected to acid hydrolysis to afford the subject inventive compounds in good yields. This procedure provides access to a variety of 3-alkyl-4-aminobutanoic acids as listed in Tables 1 and 2 as examples and thus is advantageous in comparison to methods previously used.

Examples of more specific methods of making compounds in accordance with the present invention are as follows, optionally utilizing the methods described in detail above. When the starting material is not commercially available, the synthetic sequence may be initiated with the corresponding alcohol, which is oxidized to the aldehyde by the method of Corey E J, et al, *Tetrahedron Lett.* 1975:2647–2650.

The chiral compounds of Formulas I and II are prepared as set forth in the schematic in Chart I hereof. Although the schematic in Chart I depicts the chiral synthesis of specific compound (S)-(+)-4-amino-3-(2-methylpropyl)butanoic acid, one skilled in the art can readily see that the method of synthesis can be applied to any diastereomeric compound of Formulas I and II.

In Chart I Ph is phenyl, Bn is benzyl, THF is tetrahydrofuran, LDA is lithium diisopropylamide, $BH_3.SMe_2$ is borane dimethyl sulfide complex, TsCl is tosyl chloride, and DMSO is dimethylsulfoxide.

The detailed synthetic procedure is set forth hereinbelow in Example 1. The key introductory literature for this methodology was discussed in Evans' paper, *J. Am. Chem. Soc.* 1982;104:1737–9. The metal enolate can be formed with a lithium or sodium amide base, and subsequently alkylated to give an a substituted carboxylic acid derivative. This methodology was valuable for the enantioselective synthesis of these a-substituted carboxylic acid derivatives. In this seminal paper, Evans described the preparation of propionic acid derivatives with a series of simple alkylating agents. By varying the stereochemistry of the chiral synthon (the oxazolidinone), he was able to get high stereoselectivity.

Evans has used this chiral auxiliary in other synthetic studies, but none has been related to 4-amino-3-(2-methylpropyl)butanoic acid which contains a β-substituted-γ-amino acid. The methodology as presented by Evans teaches toward α-substitution, and away from β-substitution, and has not been used in the preparation of this type of unusual amino acid. N-acyloxazolidinones have been used to form chlorotitanium enolates that have been reacted with Michael adducts such as acrylonitrile, *J. Org. Chem,* 1991;56:5750–2. They have been used in the synthesis of the rutamycin family of antibiotics, *J. Org. Chem.* 1990;55:6260–8 and in stereoselective aldol condensations, *Org. Synth.* 1990;68:83–91. Chiral i-amino acids were prepared via the oxazolidinone approach. In this sequence, a dibutylboron enolate was brominated and displaced with azide, *Tetrahedron Lett.* 1987;28:1123–6. Other syntheses of β-hydroxy-α-amino acids were also reported via this chiral auxiliary through aldol condensation (*Tetrahedron Lett.* 1987;28:39–42; *J. Am. Chem. Soc.* 1987;109:7151–7). αβ-Unsaturated N-acyloxazolidinones have also been used to induce chirality in the Diels-Alder reaction, (*J. Am. Chem. Soc.* 1988;110:1238–56. In none of these examples, or others found in the literature, is this methodology used to prepare (β-substituted carboxylic acids or 3-substituted GABA analogs.

In another embodiment, the chiral compounds of Formulas I and II can be prepared in a manner which is similar to the synthesis depicted in Chart I. In this embodiment, however, step 8 in Chart I is replaced by an alternate two step procedure which is set forth hereinbelow in Example 2 (sodium hydroxide is preferred, however, other solvents known to those of skill in the art which can hydrolyze the azide (8) to intermediate azide (8*a*) can be employed). Instead of reducing the azide (8) to the amino acid (9) in Chart I, the alternate procedure hydrolyzes the azide (8) to give an intermediate azide (8*a*) which is subsequently reduced (see Chart Ia).

There are 2 major advantages to hydrolyzing azide (8) to give the intermediate azide (8*a*) prior to reduction. The first advantage is that intermediate azide (8*a*) may be purified by extraction into aqueous base. After the aqueous extract is acidified, intermediate azide (8*a*) may be extracted into the organic phase and isolated. This allows for a purification of intermediate azide (8*a*) which does not involve chromatography. The purification of azide (8) requires chromatography which is very expensive and often impractical on a large scale.

The second advantage is that intermediate azide (8*a*) may be reduced to amino acid (9) without added acid. Reduction of azide (8) requires addition of acid, e.g., hydrochloric acid in order to obtain amino acid (9). Unfortunately, lactamization of amino acid (9) is promoted by the presence of acid. Intermediate azide (8*a*) may be reduced under near neutral conditions to give amino acid (9), thus minimizing the problem of lactam formation.

In another preferred embodiment, the chiral compounds of Formulas I and II can be prepared as set forth in the Schematic in Chart II hereof. Although the schematic in Chart II depicts the chiral synthesis of specific compound (S)-(+)-4-amino-3-(2-methyl-propyl)butanoic acid, one skilled in the art can readily see that the method of synthesis can be applied to any diastereomeric compound of Formulas I and II.

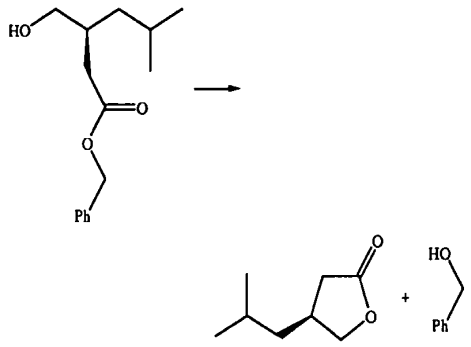
In Chart II Ph is phenyl, and Ts is tosyl.

The detailed synthetic procedure is set forth hereinbelow in Example 3. This procedure is similar to the synthesis route depicted in Chart I, however, the procedure of Chart II replaces the benzyl ester in the synthesis route of Chart I with a t-butyl ester. The desired amino acid (9) and (109) is the same end product in both Charts I and II, respectively.

There are several advantages to using the t-butyl ester rather than the benzyl ester in the synthesis of amino acid (9) or (109). A first advantage relates to the hydrolysis of the chiral auxiliary in step 4 of Chart 1. During the hydrolysis of the chiral auxiliary in this reaction some hydrolysis of the

benzyl ester often occurs. Hydrolysis of the t-butyl ester in Chart II has not been experienced.

Another advantage relates to the use of alcohol (106) in Chart II over the use of alcohol (6) in Chart I. A problem with the benzyl ester-alcohol is the tendency of the benzyl ester-alcohol to undergo lactonization as shown below. Although lactonization of the benzyl ester can be avoided under some conditions, the t-butyl ester-alcohol is far less prone to lactonization.



Still another advantage, which was previously discussed with regard to the synthetic procedure depicted by Chart Ia, is that the t-butyl synthetic route minimizes the problem of lactam formation of the amino acid end product (109). Instead of reducing azide (108) to amino acid (109) which requires the addition of acid that causes lactamization of amino acid (109), azide (108) is first hydrolyzed to intermediate azide (108*a*). Intermediate azide (108*a*) may be reduced under neutral conditions to give amino acid (109), thus minimizing the problem of lactam formation.

It should also be mentioned that several novel intermediates are produced by the processes discussed herein. Some of these intermediates which are depicted in Charts I, Ia, and II include in the racemate or R or S enantiomer form:

4-methyl-5-phenyl-2-oxazolidinone,

4-methyl-(2-methylpropyl)-2-dioxo-5-phenyl-3-oxazolidine butanoic acid, phenylmethyl ester,

4-methyl-pentanoyl chloride,

4-methyl-3-(4-methyl-1-oxopentyl)-5-phenyl-2-oxazolidinone,

2-(2-methylpropyl)-butanedioic acid, 4-(phenylmethyl) ester,

3-(azidomethyl)-5-methyl-hexanoic acid, phenylmethyl ester,

3-(hydroxymethyl)-5-methyl-hexanoic acid, phenylmethyl ester,

5-methyl-3-[[[(4-methylphenyl)sulfonyl]oxy]-methyl]-hexanoic acid, phenylmethyl ester,

3-(azidomethyl)-5-methyl-hexanoic acid,

2-(2-methylpropyl)-1,4-butanedioic acid, 4-(1,1-dimethylethyl) ester,

3-(azidomethyl)-5-methyl-, 1,1-dimethylethyl ester,

3-(hydroxymethyl)-5-methyl-hexanoic acid, 1,1-dimethyl ester,

5-methyl-3-[[[(4-methyl(phenyl)sulfonyl]oxy]-methyl-hexanoic acid, 1,1-dimethylethyl ester, or

4-methyl-(2-methylpropyl)-2-dioxo-5-phenyl-3-oxazolidinebutanoic acid, 1,1-dimethylethyl ester.

The compounds made by the aforementioned synthetic methods can be used as pharmaceutical compositions as an antidepressant, anxiolytic, antipsychotic, antiseizure, antidyskinesic, or antisymptomatic for Huntington's or Parkinson's diseases when an effective amount of a compound of the aforementioned formula together with a pharmaceutically acceptable carrier is used. That is, the present invention provides a pharmaceutical composition for the suppression of seizures resulting from epilepsy, the treatment of cerebral ischemia, Parkinson's disease, Huntington's disease and spasticity and also possibly for antidepressant, anxiolytic, and antipsychotic effects. These latter uses are expected due to functional similarities to other known compounds having these pharmacological activities. The pharmaceutical can be used in a method for treating such disorders in mammals, including human, suffering therefrom by administering to such mammals an effective amount of the compound as described in Formulas I and II above in unit dosage form.

The pharmaceutical compound made in accordance with the present invention can be prepared and administered in a wide variety of dosage forms. For example, these pharmaceutical compositions can be made in inert, pharmaceutically acceptable carriers which are either solid or liquid. Solid form preparation include powders, tablets, dispersible granules, capsules, cachets, and suppositories. Other solid and liquid form preparations could be made in accordance with known methods of the art. The quantity of active compound in a unit dose of preparation may be varied or adjusted from 1 mg to about 300 mg/kg (milligram per kilogram) daily, based on an average 70 kg patient. A daily dose range of about 1 mg to about 50 mg/kg is preferred. The dosages, however, may be varied depending upon the requirement with a patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for particular situations is within the skill of the art.

Illustrative examples of compounds made in accordance with the present invention were tested to demonstrate the ability of the compounds to activate GAD in vitro and to prevent seizure in vivo without the side effect of ataxia.

In Vitro GAD Activation

Assays were carried out in 10 mL vials sealed with serum caps through which a center well (Kontes Catalog No. 882320-000) was inserted. The center well was charged with 200 μL of freshly prepared 8% KOH solution. Various concentrations of L-glutamic acid (0.5, 0.25, 0.166, 0.125, 0.10 mM) containing [^{14}C]L-glutamate (10 μCi/mmol) in 50 mM potassium phosphate buffer, pH 7.2 were shaken at 37° C. in separate vials with purified L-glutamic acid decarboxylase (18.75 μg; spec. act 10.85 μmol/min mg) in a total volume of 2.00 mL. After being shaken for 60 minutes, the enzyme reactions were quenched by the addition of 200 μL of 6 M sulfuric acid to the contents of each of the vials. The vials were shaken for an additional 60 minutes at 37° C. The center wells were removed and placed in scintillation vials with 10 mL of scintillation fluid for radioactivity determination. The same assays were repeated except in the presence of various concentrations of the activators (2.5, 1.0, 0.5, 0.25, 0.1, 0.05 mM). The Vmax values were determined from plots of 1/cpm versus 1/[glutamate] at various concentrations of activators. The data were expressed as the ratio of the Vmax in the presence of the activators to the Vmax in the absence of the activators times 100%.

The results of the experiment are shown in Table 1. The tests show that there was significant activation by the various compounds tested to differing degrees. The known activator sodium valproate and gabapentin were tested.

In vivo tests were performed to demonstrate the seizure preventing capabilities of the novel compounds. Threshold

maximum electroshock is an animal model test for generalized seizures that is similar to that of Piredda S G, et al, *Pharmacol. and Exptl. Therap.* 1985;232(3):741–45. The methods for this test are described as follows.

Male CF-1 mice (22–30 g) were allowed free access to food and water prior to testing. For screening, groups of five mice were given a compound intravenously at doses of 30, 100, and 300 mg/kg and tested at 0.5, 2.0, and 4.0 hours after dosing. Drugs were either dissolved in 0.9% saline or suspended in 0.2% methylcellulose. Animals were shocked with corneal electrodes (see below) and observed for tonic hindlimb extensor seizures. Absence of hindlimb extension was taken as an anticonvulsant effect.

The electroshock apparatus delivered a 60 Hz sine wave with a current amplitude of 14 mA (peak-to-peak) for 0.2 seconds. The current strength of 14 mA used in this procedure produced tonic extensor seizures in approximately 95% of untreated mice, but was only slightly above threshold for tonic extension.

Summaries of the numbers of animals protected from seizures when tested 120 minutes after administration of each compound set forth in the left-hand column are given in Table 2 for varying dose levels set forth in the second column of the table.

Due to the interesting phenomena related to the (R,S)-i-butyl GABA (the compound having significantly higher potency and effectiveness without causing ataxia), threshold maximal electroshock tests where conducted varying the time of testing from 1 hour to 8 hours, the dose being 10 mg/kg in mice, injected intravenously. Table 3 shows the results of these tests indicating a maximum protection after 2 hours of testing.

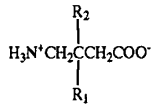
In view of the above results, a dose response curve was made for the 2 hour testing time period in mice, the drug being given intravenously at 10 mg/kg. The results of this test is shown in Table 4 with a calculated ED_{50} equaling 2.07 mg/kg.

A third pharmacological test was performed as described in Krall R L, et al, *Epilepsia.* 1978;19:409. In this procedure, drugs were tested for attenuation of threshold clonic seizures in mice caused by subcutaneous administration of pentylenetetrazol (85 mg/kg) which is a generally accepted model for absence type seizures. Results from the third test for the compound when administered either intravenously or orally is shown in Table 5. The test was conducted at three dose levels, showing effective protection at 30 mg/kg and 100 mg/kg with no ataxia.

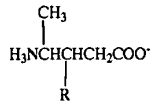
The above is a significant finding because the compound having the least ability to activate GAD in vitro surprisingly had an approximately 10-fold increase in potency over the other compounds tested. Even more unexpected is the absence of ataxic side effect coupled to this increase in potency.

TABLE 1

Activation of GAD by GABA analogs at various Concentrations expressed in %



R_1, R_2	2.5 mM	1.0 mM	0.5 mM	0.25 mM	0.1 mM	0.05 mM
(R, S)-CH_3, H	239	168	142	128	118	107
(R)-CH_3H	327	202	185	135	128	109
(S)-CH_3H	170	118	—	103	—	—
CH_3, CH_3	174	125	—	109	—	
(R, S)-CH_5, H	172	128	—	108	—	—
(R, S)-n-C_3H_7, H	156	112	—	105	—	
(R, S)-i-C_3H_7, H	140	108	—	104	—	—
(R, S)-n-C_4H_9, H	178	117	—	105	—	—
(R, S)-i-C_4H_9, H	143	113	—	109	—	—
(R, S)-s-C_4H_9, H	169	119	—	105	—	—
(R, S)-t-C_4H_9, H	295	174	147	121	117	108
(R, S)-neo-C_5H_{11}, H	279	181	—	130	—	—
(R, S)-i-C_5H_{11}, H	142	118	—	109	—	—
(R, S)-C_6H_{11}, H	125	100	—	100	—	—
(R, S)-C_6H_5, H	218	129	—	110	—	—

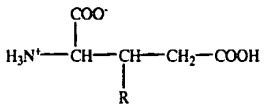


R	2.5 mM	1.0 mM	0.5 mM	0.25 mM	0.1 mM	0.05 mM
H(R, S)	140	111	—	104	—	—
H(R)	173	125	—	108	—	—
H(S)	100	100	—	100	—	—
CH_3	143	121	—	109	—	—
C_6H_5	207	151	—	112	—	—
Sodium Valproate	207	138	124	119	115	105

TABLE 1-continued

GABAPENTIN	178	145	—	105	—	—

Activation of GAD by glutamate analogs expressed in %



R	2.5 mM	1.0 mM	0.25 mM
CH_3	212	144	113
C_2H_5	170	128	113
n-C_3H_7	153	125	108
i-C_3H_7	144	114	105
n-C_4H_9	133	117	105
i-C_4H_9	129	112	106
C_6H_5	172	135	112
Sodium Valproate	207	138	119

TABLE 2

Prevention of tonic extensor seizures in mice following intravenous administration of 3-substituted GABA derivatives

R	Dose (mg/kg)	Time After Dose (min)	Effect # Protected/ # Tested	Ataxia # Ataxia/ # Tested
(R,S)—CH_3	10	120	0/5	0/5
	30	120	4/5	0/5
	100	120	3/5	0/5
CH_3	1	120	1/10	0/10
	3	120	2/10	0/10
	10	120	4/10	0/10
	30	120	3/10	0/10
	100	120	3/10(5/10)	1/10
CH_3	10	120	1/10	1/10
	30	120	2/10	0/10
	100	120	5/10	0/10
t-C_4H_9	10	120	2/10	0/10
	30	120	2/10	0/10
	100	120	5/10	0/10
C_2H_5	3	120	1/5	0/5
	10	120	1/5	0/5
	30	120	2/5	0/5
	100	120	5/5	0/5
$(CH_3)_2$	30	120	4/5	0/5
	100	120	4/5	0/5
n-C_4H_9	10	120	1/10	0/10
	30	120	3/10	0/10
	100	120	4/10	0/10
s-C_4H_9	3	120	2/10	0/10
	10	120	3/10	0/10
	30	120	2/10	0/10
i-C_4H_9	0.3	120	1/10	0/10
	0.8	120	3/10	0/10
	2.0	120	5/10	0/10
	5.5	120	7/10	0/10
	14.4	120	9/10	0/10
n-C_3H_7	3	120	2/10	0/10
	10	120	2/10	3/10
	100	120	3/10	0/10
i-C_3H_7	10	120	5/10	1/10
	30	120	5/10	0/10
	100	120	6/10	0/10

TABLE 2-continued

Prevention of tonic extensor seizures in mice following intravenous administration of 3-substituted GABA derivatives

R	Dose (mg/kg)	Time After Dose (min)	Effect # Protected/ # Tested	Ataxia # Ataxia/ # Tested
C_6H_5	100	120	0/10	0/10
neo-C_5H_{11}	10	120	2/10	0/10
	30	120	4/10	0/10
	100	120	4/10	0/10

- High-intensity corneal electroshock consisted of 50 mA, base-to-peak sinusoidal current for 0.2 seconds. All other data was from low-intensity electroshock, 17 mA base-to-peak sinusoidal current for 0.2 seconds.

TABLE 3

Threshold maximal electroshock with isobutyl GABA

Time of Testing	# Protected
1 hr.	2/10
2 hr.	8/10
4 hr.	4/10
8 hr.	2/10

TABLE 4

Threshold maximal electroshock with isobutyl GABA

Dose m/k	# Protected
0.3	1/10
0.8	3/10
2.0	5/10
5.5	7/10
14.4	9/10

TABLE 5

Maximal electroshock data				
R	Dose (mg/kg)	Time After Dose (min)	Effect # Protected/ # Tested	Ataxia # Ataxia/ # Tested
i-C_4H_9	10	120	1/5	0/5
i-C_4H_9	30	120	4/5	0/5
i-C_4H_9	100	120	4/5	0/5

As noted hereinabove, the S-(+)enantiomer of 4-amino-3-(2-methylpropyl)butanoic acid (3-isobutyl GABA or IBG) which is structurally related to the known anticonvulsant, gabapentin, potently displaces tritiated gabapentin from a novel high-affinity site in rat brain membrane fractions. Also the S-(+)enantiomer of 3-isobutyl GABA is responsible for virtually all blockade of maximal electroshock seizures in mice and rats. The R(−) enantiomer of 3-isobutyl GABA is much less effective in the blockade of maximal electroshock seizures and in displacement of tritiated gabapentin from the novel high-affinity binding site. Table 6 below sets forth data comparing gabapentin, racemic 3-isobutyl GABA ((±)-IBG), S-(+)-3-isobutyl GABA ((S)-IBG) and R-(−)-3-isobutyl GABA ((R)-IBG) in these assays.

TABLE 6

	3-Isobutyl GABA (ED_{50})			
Test System	Gabapentin	(±)-IBG	(S)-IBG	(R)-IBG
Gabapentin Receptor Binding (IC_{50})	0.14 μM	0.10 μM	0.044 μM	0.86 μM
IV Mouse Low-Intensity Electroshock	4.3 mg/Kg	4.8 mg/Kg	4.0 mg/Kg	>100 mg/Kg
IV Mouse Maximal Electroshock	75 mg/Kg	10 mg/Kg	18 mg/Kg	>100 mg/Kg
PO Mouse Maximal Electroshock	200 mg/Kg	47 mg/Kg	12 mg/Kg	
IV Mouse Ataxia	>100 mg/(IP) Kg	>100 mg/Kg	>300 mg/Kg	>100 mg/Kg

Time course of anticonvulsant activity (all compounds) peaks 2.0 hours after dose and mostly gone 8 hours after dose.

The data set forth in Table 6 was obtained as follows. For anticonvulsant testing, male CF-1 strain mice (20–25 g) and male Sprague-Dawley rats (75–115 g) were obtained from Charles River Laboratories and were maintained with free access to food and water before testing. Maximal electroshock was delivered with corneal electrodes by conventional methods (Krall, supra, 1975) except that low-intensity electroshock with mice consisted of 17 mA of current rather than the conventional 50 mA (zero to peak). Briefly, mice were given test substance and were tested for prevention of seizures by application of electrical current to the corneas by 2 metal electrodes covered with gauze and saturated with 0.9% sodium chloride. Electroshock stimulation was delivered by a constant-current device that produced 60 Hz sinusoidal electrical current for 0.2 seconds. For rats, maximal electroshock stimulation consisted of 120 mA of current. Ataxia in mice was assessed by the inverted screen procedure in which mice were individually placed on a 4.0-inch square of wire mesh that was subsequently inverted (Coughenour, supra, 1978). Any mouse that fell from the wire mesh during a 60 second test period was rated as ataxic. ED_{50} values were determined by probit analysis of results with at least 5 dose groups of 10 mice or 8 rats each.

All drugs were freely soluble in aqueous media. For in vivo studies, drug solutions were made in 0.9% sodium chloride and given in a volume of 1 mL/100 g body weight. Intravenous administration was given by bolus injection into the retro-orbital sinus in mice. Oral administrations were by intragastric gavage.

For binding studies, partially purified synaptic plasma membranes were prepared from rat neocortex using sucrose density gradients. The cerebral cortex of 10 rats was dissected from the rest of the brain and homogenized in 10 volumes (weight/volume) of ice-cold 0.32 M sucrose in 5 mM tris-acetate (pH 7.4) using a glass homogenizer fitted with a teflon pestle (10–15 strokes at 200 rpm). The homogenate was centrifuged at 100 g for 10 minutes and the supernatant collected and kept on ice. The pellet (PI) was rehomogenized in 20 mL of tris-sucrose and the homogenate recentrifuged. The combined supernatants were centrifuged at 21,500 g for 20 minutes. The pellet (P2) was resuspended in 1.2 M tris-sucrose and 15 mL of this mixture was added to ultracentrifuge tubes. On to this, 10 mL of 0.9 M sucrose was layered followed by a final layer of 5 mM tris-acetate, pH 8.0. Tubes were centrifuged at 100,000 g for 90 minutes. The synaptic plasma membranes located at the 0.9/1.2 M sucrose interface were collected, resuspended in 50 mL of 5 mM tris-acetate, pH 7.4, and centrifuged at 48,000 g. The final pellet was resuspended in 50 mL of tris-acetate, pH 7.4, aliquoted, and then frozen until use.

The assay tissue (0.1 to 0.3 mg protein) was incubated with 20 mM [^{3}H]-gabapentin in 10 mM HEPES buffer (pH 7.4 at 20° C., sodium free) in the presence of varying concentrations of test compound for 30 minutes at room temperature, before filtering onto GFB filters under vacuum. Filters were washed 3 times with 5 mL of ice cold 100 mM NaCl solution and dpm bound to filters was determined using liquid scintillation counting. Nonspecific binding was defined by that observed in the presence of 100 mM gabapentin.

In view of the above demonstrated activity of the compounds characterizing the present invention and in particular the 4-amino-3-(2-methylpropyl)butanoic acid (isobutyl GABA) the compounds made in accordance with the present invention are of value as pharmacological agents, particularly for the treatment of seizures in mammals, including humans.

EXAMPLE 1

(S)-(+)-4-amino-3-(2-methylpropyl)butanoic acid

The following "steps", refer to Chart I.

Step 1

To a solution of 4-methylvaleric acid (50.0 g, 0.43 mol) in 100 mL of anhydrous chloroform was added thionyl chloride (60 mL, 0.82 mol). The reaction mixture was refluxed for 2 hours and then cooled to room temperature. Excess chloroform and thionyl chloride was removed by distillation. The residue oil was then fractionally distilled to give 45.3 g (78%) of the acid chloride (2), bp=143–144° C.

Acid chloride (2) was also be prepared by an alternative method which eliminated use of chloroform which has waste disposal and operator exposure difficulties. The alternate method also minimized the formation of 4-methylvaleric anhydride.

To a solution of thionyl chloride (98.5 kg, 828 mol) and N,N-dimethylformamide (2 kg, 27 mol) was added 4-methylvaleric acid (74 kg, 637 mol) while maintaining a

reaction temperature of 25–30° C. Hexanes (30 L) were added and the solution was maintained at 30–350C. for 1 hour and 15 minutes. The solution was then heated to 70–75° C. for 1 hour and 10 minutes. The solution was subjected to atmospheric distillation until a solution temperature of 95° C. was reached. After cooling, hexanes (30 L) were added and the solution was subjected to atmospheric distillation until a solution temperature of 97° C. was reached. Distillation of the residual oil produced 79 kg (92%) of acid chloride (2), bp=-77° C., 60–65 mm Hg.

Step 2

To a solution of (4R,5S)-(+)-4-methyl-5-phenyl-2-oxazolidinone (5.27 g, 29.74 mol) in 70 mL of anhydrous tetrahydrofuran at -78° C. under argon atmosphere was added a 1.6 M solution of n-butyllithium (19 mL, 30.40 mmol) in hexanes slowly. The mixture was allowed to stir at -78® C. for 15 minutes then the acid chloride (4.5 g, 33.43 mmol) was added to quench the reaction. The reaction was stirred at -78° C. for 10 minutes then 0° C. for 30 minutes. A saturated solution of sodium bicarbonate (50 mL) was added and the mixture was stirred at 0° C. for 30 minutes. The organic layer was collected and the aqueous layer was extracted with ethyl acetate (3x). The organic extracts were combined and dried with anhydrous magnesium sulfate. It was then filtered and concentrated to give a colorless oil. The oil was then chromatographed with 8% ethyl acetate in hexanes on silica gel to give 7.56 g (82%) of the acyloxazolidinone (3) as a white solid.

Anal. Calcd for $C_{16}H_{21}NO_3$:

C, 69.79; H, 7.69; N, 5.09.

Found: C, 69.56; H, 7.63; N. 5.06.

Acyloxazolidinone (3) was also prepared by an alternate method which was conducted at -5° C. to 0° C. rather than -78° C. which is difficult and expensive to achieve on a manufacturing scale. The alternate method also gave a crystalline solid from the reaction mixture rather than an oil which must be chromatographed.

To a solution of 4-methyl-5-phenyl-2-oxazolidinone (64 g, 0.36 mol) in anhydrous tetrahydrofuran (270 g) at -5° C. was added a 15% solution of n-butyllithium in hexane (160 g, 0.37 mol) over a temperature range of -5° C. to 0° C. Acid chloride (2) (48.6 g, 0.36 mol) was added at -10° C. to 0° C. The reaction was quenched with a solution of water (90 mL) and sodium bicarbonate (4 g). Ethyl acetate (200 g) was added and the layers were separated. The organic layer was extracted with water (2x50 mL) and the aqueous phases were back extracted with ethyl acetate (100 g). The organic extracts were combined and approximately 150 mL of solvent was removed by distillation. Atmospheric distillation was continued and heptane (2x200 g) was added until a vapor temperature of 95° C. was reached. The solution was cooled to 5° C. The product was collected by filtration, washed with cold heptane, and dried to give 79 g (80%) of acyloxazolidinone (3).

Step 3

To a solution of diisopropylamine (4.8 mL, 34.25 mmol) in 30 mL of anhydrous tetrahydrofuran at 0° C. under argon atmosphere was added a 1.6 M solution of n-butyllithium (21 mL, 33.60 mmol) in hexanes slowly. The solution was stirred at 0° C. for 30 minutes then cooled to -78° C. A solution of the acyloxazolidinone (3) (7.56 g, 27.46 mmol) in 30 mL of anhydrous tetrahydrofuran was added and the pale yellow solution was stirred at -78° C. for 30 minutes. Benzyl α-bromoacetate was added and the resulting solution was stirred at -25° C. for 2 hours. The reaction mixture was quenched with a half-saturated ammonium chloride solution and extracted by ethyl acetate (2x). The combined organic layers were dried with anhydrous magnesium sulfate and then filtered and concentrated to give a colorless oil. The oil was then chromatographed with 8% ethyl acetate in hexanes on silica gel to give 6.16 g (53%) of the acyloxazolidinone (4) as a white solid.

Anal. Calcd for $C_{25}H_{29}NO_5$:

C, 70.90; H. 6.90; N, 3.31.

Found: C, 70.47; H, 6.87; N, 3.45.

Acyloxazolidinone (4) was also prepared by an alternate method that was advantageous in that the reaction was conducted a higher temperature (-35° C. to -25° C. rather than -78° C.) and an expensive and difficult chromatographic separation was avoided.

Acyloxazolidinone (3) (85 kg, 308 mol) was dissolved in anhydrous tetrahydrofuan (201 kg) and cooled to -30° C. Lithium diisopropyl amine (340 mol) in methyl-t-butyl ether/hexane was added while maintaining a reaction temperature of -35° C. to -25° C. Benzyl bromoacetate (85 kg, 371 mol) was then added while maintaining a reaction temperature of -35° C. to -25° C. Water (60 kg) and methyl-t-butyl ether (93 kg) were added and the mixture was allowed to warm to 18° C. The layers were separated and the organic layer was extracted with a solution of water (40 L) and sodium chloride (7 kg). The layers were separated and the organic layer was concentrated to 200 liters by distillation. Isopropyl alcohol (200 L) was added and the solution was again concentrated to 200 liters by distillation. Isopropyl alcohol (425 L) and water (160 L) were added and the mixture was heated to 50° C. The solution was cooled to 18° C. The product was collected by filtration, washed with isopropyl alcohol/water and dried under reduced pressure to give 58.7 kg (49% yield) of acyloxazolidinone (4) as a solid.

Step 4

To a pre-cooled (0° C.) solution of the acyloxazolidinone (4) (24.3 g, 57.38 mmol) in 600 mL of tetrahydrofuran was added a solution of 30% hydrogen peroxide (23.7 mL) in 320 mL of 0.2 M lithium hydroxide solution via a dropping funnel in 20 minutes. The reaction mixture was allowed to stir at 0° C. for 4 hours. A solution of sodium meta-bisulphite (62.2 g, 0.33 mol) in 320 mL of water was then added slowly to quench the reaction. The mixture was stirred at 0° C. for 20 minutes. Excess tetrahydrofuran was removed on a rotavap. The aqueous residue was extracted with ethyl acetate (3x350 mL). The combined organic extracts were dried with anhydrous magnesium sulfate and then filtered. The oily residue after concentration was chromatographed by 40% ethyl acetate in hexane on silica gel to give 13.34 g (88%) of the acid (5) as a clear oil. The column was then eluted with 50% ethyl acetate in hexane to give the oxazolidinone chiral auxiliary.

^{1}H NMR (300 MHz, $CDCl_3$) of acid (5): δ 9.80 (br s, 1H), 7.36 (m, 5H), 5.14 (narrow ABq, 2H, J_{AB}=11.4 Hz), 2.80 (m, 1H), 2.63 (ABX, 2H, J_{AB}=16.75 Hz, J_{AB} =9.13 Hz, J_{BX}=5.16 Hz, U_{AB}=73.20 Hz), 1.66 (m, 2H), 1.33 (m, 1H), 0.93 (d, 3H, J=7.32 Hz), 0.91 (d, 3H, J=6.45 Hz).

In an alternate method, after concentration of the reaction to an oily residue, hexane or heptane may be added in order to precipitate the oxazolidinone chiral auxiliary. Filtration then yields the chiral auxiliary in 80% recovery. The hexane or heptane filtrate containing acid (5) is then extracted with either an ethanol water solution or with warm water to remove any remaining chiral auxiliary. This alternative method avoids a costly and difficult chromatographic separation of the chiral auxiliary from the acid (5).

Step 5

To a solution of the acid (5) (13.34 g, 50.47 mmol) in 460 mL anhydrous tetrahydrofuran at 0° C. under argon was

added borane dimethyl sulfide complex (10 M, 11.2 mL, 112.0 mmol) slowly. The reaction mixture was stirred at 0° C. for 30 minutes then room temperature for 4 hours. The reaction was cooled to 0° C. and 250 mL of methanol was added slowly. The mixture was stirred at 0° C. for 30 minutes and excess solvent was removed under vacuum. The resulting oil was chromatographed by 15% ethyl acetate in hexanes on silica gel to give 10.59 g (84%) of the alcohol (6) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (m, 5H), 5.14 (s, 2H), 3.57 (ABX, 2H, J_{AB}=10.99 Hz, J_{AX}=4.34 Hz, J_{BX}=6.85 Hz, ν_{AB}=51.71 Hz), 2.42 (ABX, 2H, J_{AB}=15.26 Hz, J_{AX}=7.60 Hz, J_{BX}=5.56 Hz, ν_{AB}=18.81 Hz), 2.15 (m, 1H), 1.87 (br s, 1H), 1.63 (m, 1H), 0.93 (m, 2H), 0.88 (d, 3H, J=6.15 Hz), 0.87 (d, 3H, J=6.45 Hz).

Step 6

To a solution of the alcohol (6) (10.22 g, 40.82 mmol) in 50 mL of anhydrous pyridine at 0° C. was added tosyl chloride (8.60 g, 45.11 mmol). The reaction mixture was stirred at 0° C. for 15 minutes then stood overnight in a refrigerator at 4° C. The reaction mixture was diluted with 160 mL of ethyl acetate and 100 mL of water. The mixture was cooled to 0° C. in an ice-water bath and then concentrated hydrochloric acid was added slowly to neutralize excess pyridine (until pH 2). The organic layer was collected and the aqueous layer was extracted with ethyl acetate (3×100 mL). The combined organics were dried with anhydrous magnesium sulfate and then filtered. The resulting pale yellow oil after concentration was chromatographed by 10% ethyl acetate in hexanes on silica gel to give 14.44 g (87%) of the tosylate (7) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, 2H, J=8.27 Hz), 7.34 (m, 7H), 5.07 (s, 2H), 4.00 (ABX, 2H, J_{AB}=9.77 Hz, J_{AX}=4.07 Hz, J_{BX}=5.69 Hz, ν_{AB}=27.58 Hz), 2.44 (s, 1H), 2.44-2.20 (m, 3H), 1.46 (m, 1H), 1.28-1.02 (m, 2H), 0.81 (d, 6H, J=6.58 Hz).

The tosylate (7) was also prepared from acid (5) in an alternate method. This method was advantageous over the previous procedure above since it minimized the amount of β-isobutyl-γ-lactone produced as a by-product in the reaction above.

A solution of acid (5) (22.3 kg, 84.4 mol) in methyl-t-butyl ether (198 kg) was cooled to −6° C. Borane-methyl sulfide complex (15.6 kg, 177 mol) was added while maintaining a reaction temperature of 5° C. or less. The mixture was then warmed to 20° C. and stirred for two hours. The mixture was cooled to 0 C. and methanol (24 L) was added while maintaining a reaction temperature of 5° C. or less. Water (132 L) was added at a temperature of 15° C. or less. The phases were separated and the aqueous phase was extracted with methyl-t-butyl ether (27 kg). The organic were combined and extracted with water (72 L). The solution was concentrated to an oil by distillation and ethyl acetate (23 kg) was added. The solution was again concentrated to an oil by distillation to give alcohol (6). Pyridine (53 kg) was added. The solution was cooled to 1° C. and para-toluenesulfonyl chloride (23 kg, 121 mol) was added while maintaining a reaction temperature of −5° C. to 5° C. The mixture was stirred at 2° C. for 8 hours then warmed to 20° C. Water (12 L) was added while maintaining a reaction temperature of 23° C. or less. The mixture was cooled to 1° C. and aqueous hydrochloric acid (52 kg concentrated acid in 63 L water) was added. Methyl-t-butyl ether (296 kg) was added and the mixture was warmed to 18° C. The phases were separated and the aqueous phase was extracted with methyl-t-butyl ether (74 kg). The organic phases were combined and extracted with aqueous hydrochloric acid (0.6 kg concentrated hydrochloric acid in 20 liters water), aqueous sodium bicarbonate (2.7 kg sodium bicarbonate in 50 liters water), and water (30 L). The organic solution was concentrated to an oil by distillation. Methyl-t-butyl ether (19 kg) was added and the mixture was again concentrated to an oil. The resulting product was dissolved in methyl-t-butyl ether (37.9 kg) and stored as a solution. Weight of tosylate (7) contained in methyl-t-butyl ether solution 30.1 kg (88% yield).

Step 7

A mixture of the tosylate (7) (14.44 g, 35.70 mmol) and sodium azide (5.50 g, 84.59 mmol) in 180 mL of anhydrous dimethylsulfoxide was heated at 65° C. overnight. The reaction mixture was cooled to room temperature and 900 mL of water was added. The mixture was extracted (4×) with a total of 2 L of hexanes. The combined organic extracts were dried with anhydrous magnesium sulfate and then filtered. The filtrate was concentrated and the resulting oil was then chromatographed by 8% ethyl acetate in hexanes on silica gel to give 8.55 g (87%) of the azide (8) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (m, 5H) 5.14 (s, 2H), 3.33 (ABX, 2H, J_{AB}=12.27 Hz, J_{AX}=4.95 Hz, J_{BX}=6.10 Hz, ν_{AB}=22.87 Hz), 2.39 (m, 2H), 2.19 (m, 1H), 1.62 (m, 1H), 1.20 (m, 2H), 0.88 (d, 6H, J=6.44 Hz).

Step 8

To a solution of the azide (8) (8.55 g, 31.05 mmol) in 500 mL of tetrahydrofuran was added 62 mL of a 1N aqueous hydrochloric acid solution and 1 g of 10% palladium on carbon catalyst. The mixture was shaken overnight at room temperature on a Parr apparatus. The catalyst was removed by filtration over a pad of celite. The filtrate was concentrated and 50 mL of a 1N aqueous hydrochloric acid solution was added. The aqueous solution was washed with ether (3×50 mL). The aqueous layer was collected and then chromatographed on a Dowex 50W×8 (H^+form) column eluted with a 0.5N ammonium hydroxide solution. Fractions containing the amino acid (Ninhydrin positive) were collected and then lyophilized to give 3.2 g (65%) of the amino acid (9) as a white solid. mp=175–176° C.; $[\alpha]D^{23}$=10.520 (1.06, H_2O).

EXAMPLE 2

(S)-(+)-4-amino-3-(2-methylpropyl)butanoic acid

This compound was prepared in the same manner as Example 1, except that amino acid (9) is prepared from azide (8) by a 2 step process utilizing an intermediate azide (8*a*) which is subsequently reduced (the 1 step reduction approach identified as step 8 is described above). The synthetic procedure of Example 2 is depicted in Chart Ia.

Step 1: Preparation of Intermediate Azide (8*a*)

Azide (8) (10.7 g, 0.040 mol) in ethanol (100 mL) and water (20 mL) was treated with 50% aqueous sodium hydroxide (9.8 g). The mixture was stirred at 30° C. for 45 minutes. Ethanol was removed under reduced pressure until 30 g of liquid remained, water (100 mL) was added and the mixture was extracted with methyl-t-butyl ether (4×100 mL). The methyl-t-butyl ether extracts were extracted with 1 M sodium hydroxide and the aqueous phases were combined and acidified to pH 1.6 with concentrated hydrochloric acid. The aqueous mixture was then extracted with methyl-t-butyl ether (2×100 mL) and the organic extracts were combined and concentrated under reduced pressure. The resulting oil was dissolved in heptane (50 mL) and extracted with saturated aqueous sodium bicarbonate (2×40 mL). The

aqueous extracts were extracted with heptane (50 mL), combined and acidified to pH 1.6 with concentrated hydrochloric acid. The aqueous mixture was extracted with heptane (2x50 mL). The heptane extracts were extracted with water (40 mL), combined, and concentrated under reduced pressure to give 5.4 g (75%) of intermediate azide (8*a*) as an oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 10.8 (br s, 1H), 3.36 (m, 2H), 2.38 (m, 2H), 2.18 (m, 1H), 1.64 (m, 1H), 1.25 (m, 2H), 0.91 (d, 6H, J=6.56 Hz).

Step 2: Synthesis of Amino Acid (9) from Intermediate Azide (8*a*)

Intermediate azide (8*a*) (12.7 g, 68.6 mol) was dissolved in methyl-t-butyl ether (80 kg). The mixture was subjected to catalytic hydrogenation in the presence of 5% palladium on carbon (2.0 kg of 50% water wet) at 49 to 55 psi of hydrogen until intermediate azide (8*a*) has been consumed. The mixture was filtered and the solid was washed with methyl-t-butyl ether (30 kg). The solid was dissolved in a solution of hot isopropanol (75 kg) and water (60 kg) and the solution was filtered. The isopropanol water solution was cooled to -3° C. and the product was filtered and washed with cold isopropanol (16 kg). The solid was dried under reduced pressure to give 6.4 kg (59%) of amino acid (9).

This reduction may be conducted in a variety of solvents. Successful reductions have been carried out in heptane, ethanol/water, isopropanol, isopropanol/water, methanol/water, and tetrahydrofuran/water as well as methyl-t-butyl ether.

EXAMPLE 3

(S)-(+)-4-amino-3-(2-methylpropyl)butanoic acid

The following "steps", refer to Chart II. All reactions were carried out under an atmosphere of nitrogen.

Step 1

To a solution of 4-methylvaleric acid (50.0 g, 0.43 mol) in 100 ml of anhydrous chloroform was added thionyl chloride (60 mL, 0.82 mol). The reaction mixture was refluxed for 2 hours and then cooled to room temperature. Excess chloroform and thionyl chloride was removed by distillation. The residue oil was then fractionally distilled to give 45.3 g (78%) of the acid chloride (102), bp=143–144° C.

Acid chloride (102) was also prepared by an alternative method which eliminated use of chloroform which has waste disposal and operator exposure difficulties. The alternate method also minimized the formation of 4-methylvaleric anhydride.

To a solution of thionyl chloride (98.5 kg, 828 mol) and N,N-dimethylformamide (2 kg, 27 mol) was added 4-methylvaleric acid (74 kg, 637 mol) while maintaining a reaction temperature of 25–30° C. Hexanes (30 L) were added and the solution was maintained at 30° C. to 35° C. for 1 hour and 15 minutes. The solution was then heated to 70° C. to 75° C. for 1 hour and 10 minutes. The solution was subjected to atmospheric distillation until a solution temperature of 95° C. was reached. After cooling, hexanes (30 L) were added and the solution was subjected to atmospheric distillation until a solution temperature of 97° C. was reached. Distillation of the residual oil produced 79 kg (92%) of acid chloride (102), bp=-77° C., 60–65 mm Hg.

Step 2

To a solution of (4R,5S)-(+)-4-methyl-5-phenyl-2-oxazolidinone (5.27 g, 29.74 mmol) in 70 mL of anhydrous tetrahydrofuran at -78° C. under argon atmosphere was added a 1.6 M solution of n-butyllithium (19 mL, 30.40 mmol) in hexanes slowly. The mixture was allowed to stir at -78° C. for 15 minutes then the acid chloride (4.5 g, 33.43 mmol) was added to quench the reaction. The reaction was stirred at -78° C. for 10 minutes then 0° C. for 30 minutes. A saturated solution of sodium bicarbonate (50 mL) was added and the mixture was stirred at 0° C. for 30 minutes. The organic layer was collected and the aqueous layer was extracted with ethyl acetate (3x). The organic extracts were combined and dried with anhydrous magnesium sulfate. It was then filtered and concentrated to give a colorless oil. The oil was then chromatographed with 8% ethyl acetate in hexanes on silica gel to give 7.56 g (82%) of the acyloxazolidinone (103) as a white solid.

Anal. Calcd for $C_{16}H_{21}NO_3$:

C, 69.79; H, 7.69; N, 5.09.

Found: C, 69.56; H, 7.63; N, 5.06.

Acyloxazolidinone (103) was also prepared by an alternate method which was conducted at -5° C. to 0° C. rather than -78° C. which is difficult and expensive to achieve on a manufacturing scale. The alternate method also gave a crystalline solid from the reaction mixture rather than an oil which must be chromatographed.

To a solution of 4-methyl-5-phenyl-2-oxazolidinone (64 g, 0.36 mol) in anhydrous tetrahydrofuran (270 g) at -5° C. was added a 15% solution of n-butyllithium in hexane (160 g, 0.37 mol) over a temperature range of -5° C. to 0° C. Acid chloride (102) (48.6 g, 0.36 mol) was added at -10° C. to 0C. The reaction was quenched with a solution of water (90 mL) and sodium bicarbonate (4 g). Ethyl acetate (200 g) was added and the layers were separated. The organic layer was extracted with water (2x50 mL) and the aqueous phases were back extracted with ethyl acetate (100 g). The organic extracts were combined and approximately 150 mL of solvent was removed by distillation. Atmospheric distillation was continued and heptane (2x200 g) was added until a vapor temperature of 95° C. was reached.

The solution was cooled to 5° C. The product was collected by filtration, washed with cold heptane, and dried to give 79 g (80%) of acyloxazolidinone (103).

Step 3

To a solution of diisopropylamine (7.6 g, 0.075 mol) in anhydrous tetrahydrofuran (10 mL) at 0° C. under nitrogen was added a 1.6 M U-butyllithium in hexane (47 mL, 0.075 mol) while maintaining a temperature of -5° C. to 0° C. The resulting solution was added to a solution of acyloxazolidinone (103) (18.6 g, 0.068 mol) in tetrahydrofuran (160 mL) at -55° C. to -45° C. The solution was stirred at -55° C. to -45° C. for 30 minutes. The solution was then added to a solution of t-butyl bromoacetate (14.6 g, 0.075 mol) in tetrahydrofuran at -55° C. to -45° C. The solution was cooled to -65° C. and allowed to warm to 10° C. over a period of 2 hours. The reaction mixture was quenched with the addition of saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was recrystallized from heptanes, filtered, and dried under reduced pressure to give 18 g (68%) of acyloxazolidinone (104).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.4–7.2 (m, 5H), 5.65 (d, 1H, J=7.09 Hz), 4.74 (m, 1H), 4.26 (m, 1H), 2.69 (m, 1H), 2.44 (m, 1H), 1.65–1.45 (m, 2H), 1.39 (S, 9H), 0.93 (m, 6H), 0.89 (d, 3H, J=7.87 Hz).

Alternatively, the order of addition of the reagents may be reversed. t-Butyl bromoacetate may be added to the solution containing diisopropylamine, n-butyllithium and acyloxazo-

lidinone (103). The final product isolation may also be conducted by doing a distillation and replacing the solvents present (hexane and tetrahydrofuran) with isopropyl alcohol.

Acyloxazolidinone (104) then crystallizes from the isopropyl alcohol solution. The following experimental procedure illustrates this alternative.

To a solution of diisopropylamine (23.1 g, 0.229 mol).in anhydrous tetrahydrofuran (30 mL) at 0° C. under nitrogen was added a 2.5 M n-butyllithium in hexane (92 mL, 0.229 mol) while maintaining a temperature of −5° C. to 0° C. The resulting solution was added to a solution of acyloxazolidinone (103) (60.0 g, 0.218 mol) in tetrahydrofuran (400 mL) at −45° C. to 40° C. The solution was stirred at −45° C. to −40° C. for 30 minutes. t-Butyl bromoacetate (44.6 g, 0.229 mol) was then added to the reaction solution at −45° C. to −40° C. The solution was allowed to warm to 10° C. over a period of 2 to 3 hours. The reaction mixture was quenched with the addition of saturated aqueous ammonium chloride. The organic layer was separated from the water layer. The solvent was removed under reduced pressure and replaced with isopropyl alcohol. The product crystallized from isopropyl alcohol and was filtered and dried under reduced pressure to give 53.8 g (63%) of acyloxazolidinone (104).

Step 4

To a precooled (5° C.) solution of acyloxazolidinone (104) (60.0 g, 0.15 mol) in tetrahydrofuran (266 g) was added a solution of 30% hydrogen peroxide (71 g), 9.4 g lithium hydroxide monohydrate (0.22 mol) and water (120 mL) over a period of 35 minutes so as to maintain a reaction temperature of 5° C. The mixture was stirred at 3–5° C. for 2.5 hours. The reaction was quenched by addition of a solution of sodium sulfite (50 g), sodium bisulfite (27 g), and water (310 mL) at a temperature of less than 29° C. Heptane (100 mL) and methyl-t-butyl ether (100 mL) were added and the layers were separated. The aqueous layer was extracted with methyl-t-butyl ether (100 mL) and the organic layers were combined. The solvent was replaced with heptane by distillation and the resulting heptane solution (400 mL) was cooled to 5° C. The resulting solids were filtered and the filtrate was extracted with warm water (2×150 mL, 1×200 mL, 1×300 mL). The solution was concentrated by evaporation to give 34.5 g (97%) acid (105) as an oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 11.5 (br, s, 1H), 2.85 (m, 1H), 2.67-2.29 (m, 2H), 1.60 (m, 1H), 1.44 (s, 9H), 1.32 (m, 2H), 0.92 (m, 6H).

Step 5

Acid (105) (72.4 g, 0.314 mol) was dissolved in tetrahydrofuran (360 mL) and cooled to 0° C. A 2.0 M solution of borane dimethylsulfide complex in tetrahydrofuran (178 mL, 0.356 mol) was added at 0° C. The solution was allowed to warm to 48° C. then cooled to 25° C. After 2 hours and 45 minutes, the reaction was quenched with the addition of methanol (300 mL) and the solvent was removed under reduced pressure. Additional methanol (300 mL) was added and the solution was concentrated under reduced pressure to give 66 g (97%) of alcohol (106) as an oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.62 (m, 1H), 3.45 (m, 1H), 2.44 (br s, 1H), 2.36-2.21 (m, 2H), 2.05 (m, 1H), 1.64 (m, 1H), 1.45 (s, 9H), 1.24-1.04 (m, 2H), 0.91 (m, 6H).

Step 6

Alcohol (107) (51.9 g, 0.24 mol) was dissolved in pyridine (130 mL) and cooled to 5° C. p-Toluene sulfonyl chloride (57.2 g, 0.30 mol) was added and the mixture was stirred at 22° C. for 21 hours. The reaction was quenched with the addition of water (95 mL) and 18% aqueous hydrochloric acid (300 mL) at less than 300° C. Methyl-t-butyl ether (350 mL) was added and the layers were separated. The aqueous layer was extracted with methyl-t-butyl ether (350 mL). The organic layers were combined, washed with 1% aqueous hydrochloric acid (2×100 mL), saturated aqueous sodium bicarbonate (1×150 mL), and water (1×100 mL). The organic solution was treated with decolorizing charcoal, filtered, and evaporated to give 77 g (86%) of the tosylate (107) as an oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.78 (d, 2H, J=8.25 Hz), 7.34 (d, 2H, J=8.25 Hz), 3,96 (m, 2H), 2.45 (s, 3H), 2.32-2.12 (m, 3H), 1.6-1.4 (m, 1H), 1.40 (s, 9H), 1.2-1.1 (m, 2H), 0.83 (m, 6H).

Step 7

Tosylate (107) (65 g, 0.175 mol) was dissolved in dimethyl sulfoxide (40 mL). The dimethyl sulfoxide solution along with additional dimethyl sulfoxide (10 mL) was than added to a solution of sodium azide (11 g, 0.26 mol) in dimethyl sulfoxide (450 g) at 63° C. The mixture was then stirred at 65° C. for 6 hours. Water (140 mL) and heptane (250 mL) were added to the reaction and the layers were separated. The aqueous layer was extracted with heptane (250 mL) and the organic layers were combined. The solvent was removed under reduced pressure to give 42 g (95%) of the azide (108) as an oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ d3.32 (m, 2H), 2.22 (m, 2H), 2.15 (m, 1H), 1.63 (m, 1H), 1.46 (s, 9H), 1.19 (m, 2H), 0.89 (m, 6H).

Step 8

Azide (108) (36.3 g, 0.15 mol) was placed in 88% aqueous formic acid (365 mL). The mixture was stirred at 30° C. for 4.5 hours. Decolorizing charcoal was added and the mixture was filtered and concentrated under reduced pressure to give an oil. Heptane (250 mL) was added and the mixture was vacuum distilled to give an oil. Water (125 mL) and heptane (250 mL) were added and mixed vigorously. The layers were separated and the water layer was washed with heptane (250 mL). The heptane layers were combined and concentrated under reduced pressure to give 24.6 g (88%) of intermediate azide (108*a*) as an oil.

Alternatively, aqueous hydrochloric acid may be used rather than aqueous formic acid in order to conduct the hydrolysis.

Step 9

Intermediate azide (108*a*) (12.7 g, 68.6 mol) was dissolved in methyl-t-butyl ether (80 kg). The mixture was subjected to catalytic hydrogenation in the presence of 5% palladium on carbon (2.0 kg of 50% water wet) at 49–55 psi of hydrogen until intermediate azide (108*a*) has been consumed. The mixture was filtered and the solid was washed with methyl-t-butyl ether (30 kg). The solid was dissolved in a solution of hot isopropanol (75 kg) and water (60 kg) and the solution was filtered. The isopropanol water solution was cooled to −3° C. and the product was filtered and washed with cold isopropanol (16 kg). The solid was dried under reduced pressure to give 6.4 kg (59%) of amino acid (109).

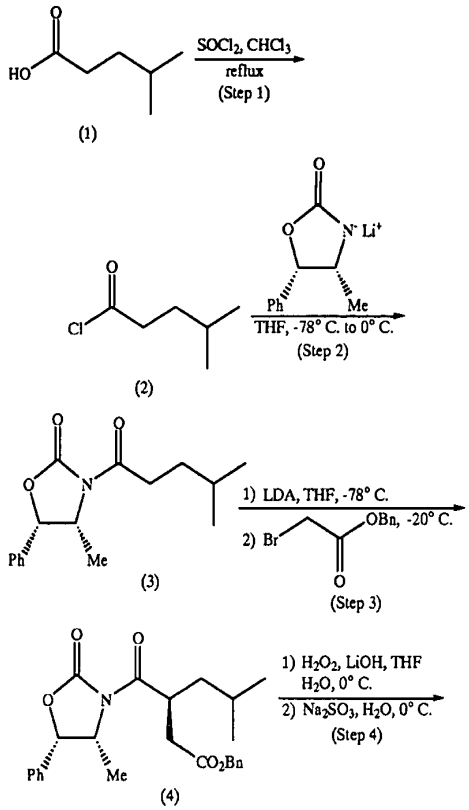
This reduction may be conducted in a variety of solvents. Successful reductions have been carried out in heptane, ethanol/water, isopropanol, isopropanoll water, methanol/water, and tetrahydrofuran/water as well as methyl-t-butyl ether.

The invention has been described in an illustrative manner, and it is to be understood that the terminology which has been used is intended to be in the nature of words of description rather than of limitation.

Obviously many modifications and variations of the present invention are possible in light of the above teachings. It is, therefore, to be understood that within the scope of the appended claims wherein reference numerals are

merely for convenience and are not to be in any way limiting, the invention may be practiced otherwise than as specifically described.

CHART I



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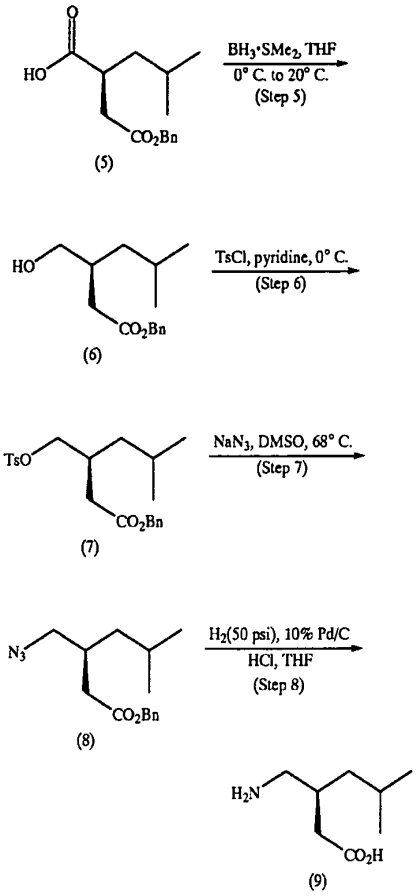

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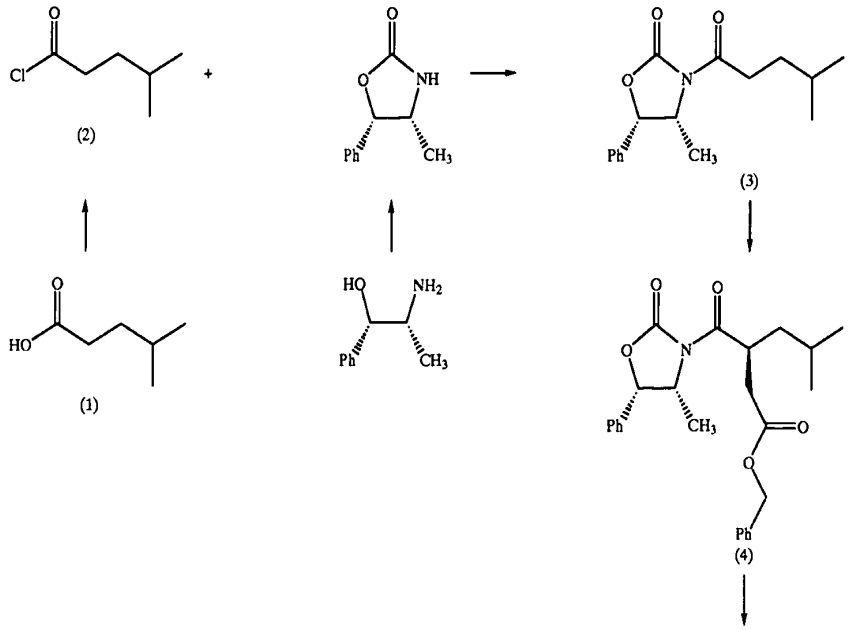

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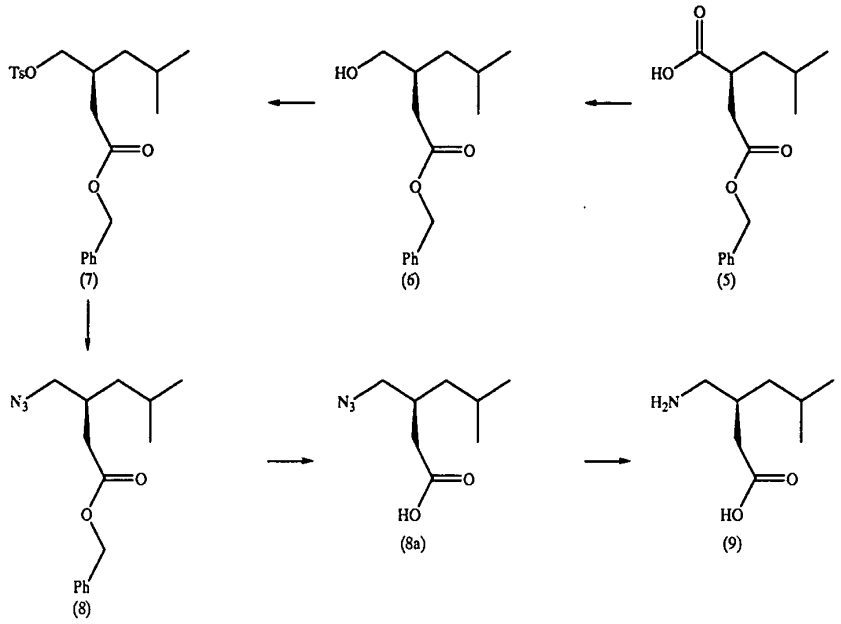
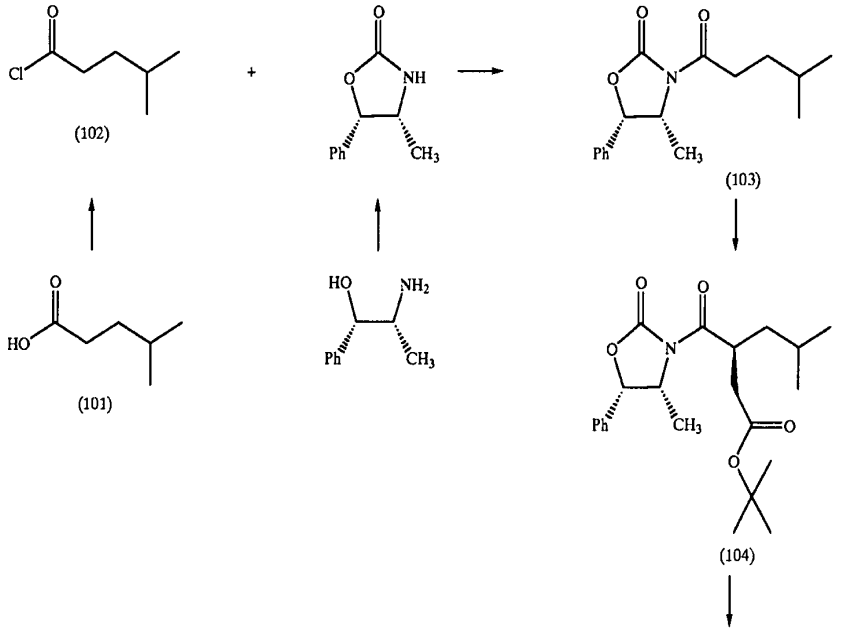
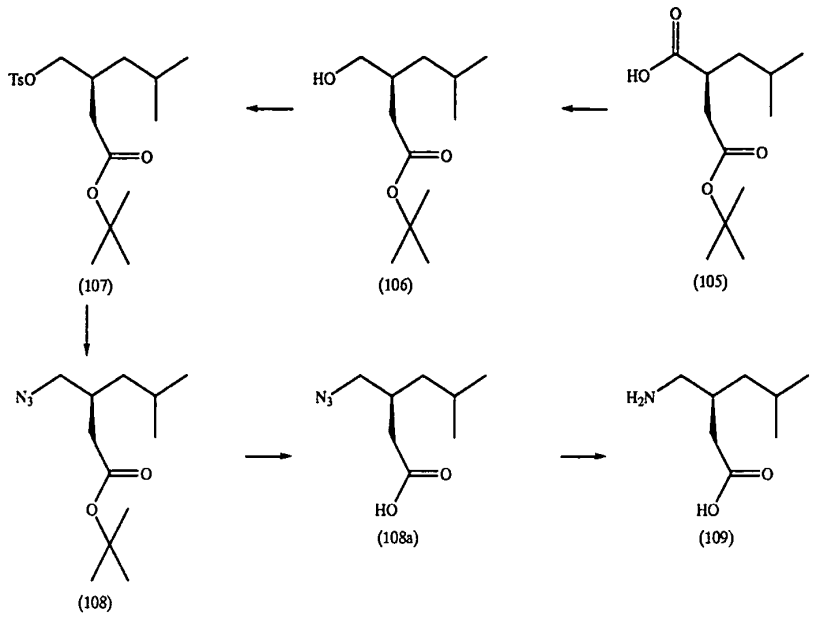


CHART II



-continued



What is claimed is:

1. A compound of the formula S-(+)-4-amino-3-(2-methylpropyl) butanoic acid as a single optical isomer.

2. 4-amino-3-(2-methylpropyl) butanoic acid, or a pharmaceutically acceptable salt thereof.

3. A pharmaceutically acceptable salt of S-(+)-(4)-amino-3-(2-methylpropyl) butanoic acid, said salt being present as a single optical isomer.

4. A pharmaceutical composition comprising a compound any one of claims 1 or 3, together with a pharmaceutically acceptable carrier.

* * * * *

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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 10, "STAT", below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE 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.

PATENT NUMBER	FEE CODE	FEE AMT	SUR CHARGE	APPLICATION NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT	ATTY DKT NUM
6,197,819	1551	$910.00	$0.00	08/420,905	03/06/01	04/11/95	04	NO	PAID	4362-C1-01-CA

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Date	IND/NDA No.	Serial No.	Activity	Submission Details
IND 53,763 - Analgesia				
24-Jul-97	53,763	0	Submission to FDA	Initial IND
05-Aug-97	53,763		Letter from FDA	IND Number Assigned 25July1997
14-Aug-97	53,763	1	Submission to FDA	Meeting (8/12/97) Minutes regarding study protocol 1008-013
02-Oct-97	53,763	2	Submission to FDA	Protocol amendment for 1008-013 based on FDA meeting on 12Aug1997
07-Oct-97	53,763	3	Submission to FDA	3 research reports submitted
10-Oct-97	53,763	4	Submission to FDA	Notice of study initiation for study 1008-013
07-Nov-97	53,763	5	Submission to FDA	Investigators Brochure
24-Nov-97	53,763	6	Submission to FDA	Request for End-of-Phase meeting and study protocol 1008-014 review
19-Dec-97	53,763	7	Submission to FDA	Comparator dissolution data and profiles for over-encapsulated comparators for study 1008-013
06-Jan-98	53,763	8	Submission to FDA	Meeting (18Dec1997) minutes regarding the proposed clinical development plan for neuropathic and chronic pain
29-Jan-98	53,763	9	Submission to FDA	1 research report submitted
06-Feb-98	53,763	10	Submission to FDA	CMC submission - revised impurity specifications
16-Feb-98	53,763	11	Submission to FDA	New study protocols 1008-014 and -015
04-Mar-98	53,763	12	Submission to FDA	Protocol amendment to include new investigators and study centers for protocols 1008-014 and -015
06-Mar-98	53,763	13	Submission to FDA	Annual Report covering periods 01Jan1997 to 01Jan1998
16-Mar-98	53,763	14	Submission to FDA	Protocol amendment to include new investigators and study centers for protocols 1008-014 and -015
30-Mar-98	53,763	15	Submission to FDA	Protocol amendment to include new investigators and study centers for protocols 1008-014 and -015
14-Apr-98	53,763	16	Submission to FDA	Protocol amendment to include new investigators and study centers for protocols 1008-014 and -015
01-May-98	53,763	17	Submission to FDA	Protocol amendment to include new investigators and study centers for protocols 1008-014 and -015
14-May-98	53,763	18	Submission to FDA	General correspondance relative to a protocol amendment for protocol 1008-014
21-May-98	53,763	19	Submission to FDA	Protocol amendment to include new investigators and study centers for protocols 1008-013, -014, and -015
02-Jun-98	53,763	20	Submission to FDA	Response to FDA inquiry (14May1998) for additional rat toxicology data
03-Jun-98	53,763	21	Submission to FDA	2 research reports submitted
16-Jun-98	53,763	22	Submission to FDA	Protocol amendment to include new investigators and study centers for protocols 1008-014 and -015
23-Jun-98	53,763	23	Submission to FDA	New protocols 1008-032 and -033
24-Jun-98	53,763	24	Submission to FDA	New protocols 1008-029 and -030
09-Jul-98	53,763	25	Submission to FDA	Protocol amendment to include new investigators and study centers for protocols 1008-013, -014, and -015

Date	IND/NDA No.	Serial No.	Activity	Submission Details
13-Jul-98	53,763	26	Submission to FDA	New protocol 1008-027
20-Jul-98	53,763	27	Submission to FDA	Protocol amendment to include new investigators and study centers for protocols 1008-029, -030, -032, and -033
30-Jul-98	53,763	28	Submission to FDA	Protocol amendment to include new investigators and study centers for protocols 1008-029, -030, -032, and -033
30-Jul-98	53,763	29	Submission to FDA	3 research reports submitted
11-Aug-98	53,763	30	Submission to FDA	Protocol amendment to include new investigators and study centers for protocols 1008-014, -015, -029, -030, -032, and -033
26-Aug-98	53,763	31	Submission to FDA	Protocol amendment to include new investigators and study centers for protocols 1008-029, -030, -032, and -033
02-Sep-98	53,763	32	Submission to FDA	1 research report submitted
09-Sep-98	53,763	33	Submission to FDA	Initial Medwatch safety report from study -027
16-Sep-98	53,763	34	Submission to FDA	1 research report submitted
17-Sep-98	53,763	35	Submission to FDA	1 research report submitted
24-Sep-98	53,763	36	Submission to FDA	1 research report submitted
30-Sep-98	53,763	37	Submission to FDA	3 research reports submitted
09-Oct-98	53,763	38	Submission to FDA	Protocol amendment to include new investigators and study centers for protocols 1008-014, -015, -029, -030, -032, and -033
13-Oct-98	53,763	39	Submission to FDA	New protocol 1008-031
15-Oct-98	53,763	40	Submission to FDA	Correspondance to update pain IND from safety data reported under protocol 1008-027 (epilepsy)
23-Oct-98	53,763	41	Submission to FDA	Protocol amendment to include new investigators and study centers for protocols 1008-014, -015, -029, -030, -032, and -033
29-Oct-98	53,763	42	Submission to FDA	Protocol amendment to include new investigators and study centers for protocols 1008-031 and -033
13-Nov-98	53,763	43	Submission to FDA	Protocol amendment to include new investigators and study centers for protocols 1008-014, -015, -030, -031, -032, and -033
24-Nov-98	53,763	44	Submission to FDA	Initial Medwatch safety report for study 1008-009
02-Dec-98	53,763	45	Submission to FDA	Protocol amendment to include new investigators and study centers for protocols 1008-029, -030, -031, -032, and -033
03-Dec-98	53,763	46	Submission to FDA	Correspondance to update pain IND from safety data reported under protocol 1008-009 (epilepsy)
14-Dec-98	53,763	47	Submission to FDA	Initial Medwatch safety report for protocol -015
22-Dec-98	53,763	48	Submission to FDA	Updated Investigational Brochure
06-Jan-99	53,763	49	Submission to FDA	Protocol amendment to include new investigators and study centers for protocols 1008-014, -015, -029, -030, -032, and -033
15-Jan-99	53,763	50	Submission to FDA	5 research reports submitted

Date	IND/NDA No.	Serial No.	Activity	Submission Details
28-Jan-99	53,763	51	Submission to FDA	Protocol amendments to include either new study centers and/or sub-investigators for protocols 1008-014, -015, and -029
17-Feb-99	53,763	52	Submission to FDA	Protocol amendments to include either new study centers and/or sub-investigators for protocols 1008-014, -015, -029, -030, -031, -032, and -033
02-Mar-99	53,763	53	Submission to FDA	Updated Investigational Brochure
08-Mar-99	53,763	54	Submission to FDA	Annual Report covering periods 09Jan1998 to 01Nov1998
15-Mar-99	53,763	55	Submission to FDA	Protocol amendments to include either new study centers and/or sub-investigators for protocols 1008-014, -015, -029, -030, -031, 1008-032, and -033
29-Mar-99	53,763	56	Submission to FDA	Request for an End-of-Phase 2 meeting with the Division to reach consensus on the Phase 3 clinical development plan to identify any additional preclinical and/or clinical information necessary to support NDA approval of pregabalin
01-Apr-99	53,763	57	Submission to FDA	Protocol amendments to include either new principle and/or sub-investigators for protocols 1008-014, -015, -030, -032, and -033
07-Apr-99	53,763	58	Submission to FDA	3 research reports submitted
14-Apr-99	53,763	59	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-015
21-Apr-99	53,763	60	Submission to FDA	Submission to request an End-of-Phase 2 meeting to discuss the development of pregabalin (CI-1008) administered TID either alone or in conjunction with other analgesics for the management of chronic pain
21-Apr-99	53,763	61	Submission to FDA	Protocol amendments to include either new study centers and/or sub-investigators for protocols 1008-014, -015, -029, -, and -033
29-Apr-99	53,763	62	Submission to FDA	Initial Medwatch safety report for protocol 1008-015
11-May-99	53,763	63	Submission to FDA	Updated Investigator's Brochure
12-May-99	53,763	64	Submission to FDA	Protocol amendments to include either new sub-investigators and/or change's of address for protocols 1008-030, -031, -032, and -033
14-May-99	53,763	65	Submission to FDA	End-of Phase 2 meeting agenda and objectives for meeting scheduled 17June1999
19-May-99	53,763	66	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-015
20-May-99	53,763	67	Submission to FDA	Preliminary results from a clinical trial in painful diabetic peripheral neuropathy (1008-014)
26-May-99	53,763	68	Submission to FDA	Initial Medwatch safety report for protocol 1008-033
02-Jun-99	53,763	69	Submission to FDA	2 research reports submitted
03-Jun-99	53,763	70	Submission to FDA	Updated Investigator's Brochure
04-Jun-99	53,763	71	Submission to FDA	Initial Medwatch safety report, protocol 1008-018
07-Jun-99	53,763	72	Submission to FDA	Protocol amendments to include new sub-investigators for protocols 1008-014, -015, -029, -030, -031, -032, and -033
08-Jun-99	53,763	73	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-015
08-Jun-99	53,763	74	Submission to FDA	Reference made to our 29March1999 request for an End-of-Phase 2 meeting, list of meeting objectives for four upcoming FDA meetings

Date	IND/NDA No.	Serial No.	Activity	Submission Details
11-Jun-99	53,763	75	Submission to FDA	Protocol amendment to include new study center for protocol 1008-104
15-Jun-99	53,763	76	Submission to FDA	Initial Medwatch safety report, protocol 1008-033
16-Jun-99	53,763	77	Submission to FDA	Updated Investigator's Brochure
29-Jun-99	53,763	78	Submission to FDA	Initial Medwatch safety report for protocol 1008-015
06-Jul-99	53,763	79	Submission to FDA	Protocol amendments to include either new study centers and/or sub-investigators for protocols 1008-031, -033, and -104
09-Jul-99	53,763	80	Submission to FDA	Submission including copy of the 14May1998 (SN 018) which provided a critical assessment of the effects of Pregabalin on the male reproductive system, as well as further evaluations done in man to identify any effects of pregabalin on spermatogenesis
13-Jul-99	53,763	81	Submission to FDA	End-of-Phase 2 Meeting Minutes for EOP2 Meeting held on 17June1999 to reach consensus with FDA on the Phase 3 clinical development plan and to identify clinical/preclinical information to support NDA submission approval of pregabalin
15-Jul-99	53,763	82	Submission to FDA	2 research reports submitted
16-Jul-99	53,763	83	Submission to FDA	Request of a pre-NDA meeting to discuss the CMC development of Pregabalin. Meeting objectives are to reach consensus with FDA on the CMC development of Pregabalin (CI-1008) for above indications, and to identify CMC information for marketing approval
22-Jul-99	53,763	84	Submission to FDA	Initial Medwatch safety report for protocol 1008-011
27-Jul-99	53,763	85	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-015
27-Jul-99	53,763	86	Submission to FDA	Initial Medwatch safety report for protocol 1008-061
29-Jul-99	53,763	87	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-033
04-Aug-99	53,763	88	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-033
05-Aug-99	53,763	89	Submission to FDA	Appendices A-C of Protocol 1008-072
06-Aug-99	53,763	90	Submission to FDA	Updated Investigator's Brochure
11-Aug-99	53,763	91	Submission to FDA	9 research reports submitted
11-Aug-99	53,763	92	Submission to FDA	Updated Investigator's Brochure
13-Aug-99	53,763	93	Submission to FDA	Updates for a pre-NDA meeting request. Original information forwarded 16July1999
17-Aug-99	53,763	94	Submission to FDA	Protocol amendment to include new study centers for protocol 1008-033
31-Aug-99	53,763	95	Submission to FDA	New Protocol 1008-105 and new study center
10-Sep-99	53,763	96	Submission to FDA	Initial Medwatch safety report for protocol 1008-012
15-Sep-99	53,763	97	Submission to FDA	Protocol amendments to include new study centers, investigators, and/or sub-investigators for protocols 1008-029, -030, -033, and -104
16-Sep-99	53,763	98	Submission to FDA	Two-year mouse toxicology study update
24-Sep-99	53,763	99	Submission to FDA	Request regarding a continuation of the 14Sept1999 meeting to discuss deferred topics

Date	IND/NDA No.	Serial No.	Activity	Submission Details
24-Sep-99	53,763	100	Submission to FDA	Meeting (14Sept1999) minutes, overheads, and amended questions regarding CMC content for the NDA
29-Sep-99	53,763	101	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-015
04-Oct-99	53,763	102	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-015
06-Oct-99	53,763	103	Submission to FDA	Copy of a letter to Investigators for FDA review and proposed wording to include in the Investigator' s Brochure
07-Oct-99	53,763	104	Submission to FDA	Initial Medwatch safety report for protocol 1008-012
08-Oct-99	53,763	105	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-012
14-Oct-99	53,763	106	Submission to FDA	Protocol amendments to include either new study centers, change of address, and/or sub-investigators for protocols 1008-029, -033, -104, and -105
29-Oct-99	53,763	107	Submission to FDA	Protocol amendments to include new study centers for protocols -033 and -105
03-Nov-99	53,763	108	Submission to FDA	Protocol amendments to include new study centers for protocols 1008-033 and -105
05-Nov-99	53,763	109	Submission to FDA	Meeting Request for End-of-Phase 2 meeting
16-Nov-99	53,763	110	Submission to FDA	Updated Investigator Brochure and Informed Consent
17-Nov-99	53,763	111	Submission to FDA	1 research report submitted
22-Nov-99	53,763	112	Submission to FDA	Protocol amendments to include either new study centers, change of address, and/or sub-investigators for protocols 1008-030, -033, and -105
02-Dec-99	53,763	113	Submission to FDA	Protocol amendments to include new study centers for protocols 1008-033 and -105
06-Dec-99	53,763	114	Submission to FDA	Protocol amendments to include new protocols and study centers for protocols 1008-127, -131, and -134
08-Dec-99	53,763	115	Submission to FDA	Protocol amendments to include either new study centers and/or sub-investigators for protocols 1008-031, -033, -105, -0127, and -134
09-Dec-99	53,763	116	Submission to FDA	Initial Medwatch safety report for protocol 1008-061
10-Dec-99	53,763	117	Submission to FDA	Clinical Amendment to Protocol 1008-072 and Meeting (Aug 18, 1999) minutes
13-Dec-99	53,763	118	Submission to FDA	Additional evidence and pre-meeting materials to support a 300-600 mg/day dosing recommendation
15-Dec-99	53,763	119	Submission to FDA	Protocol amendments to include new study centers for protocols 1008-033, -105, -127, -131, and -134
17-Dec-99	53,763	120	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-012
21-Dec-99	53,763	121	Submission to FDA	Updated Investigator's Brochure
21-Dec-99	53,763	122	Submission to FDA	Notice of clinical study start for 1008-72
23-Dec-99	53,763	123	Submission to FDA	Pre-NDA Meeting (14Sept1999) minutes regarding CMC expiry dating
23-Dec-99	53,763	124	Submission to FDA	Initial Medwatch safety report for protocol 1008-105
23-Dec-99	53,763	125	Submission to FDA	Initial Medwatch safety report for protocol 1008-061
28-Dec-99	53,763	126	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-061

Date	IND/NDA No.	Serial No.	Activity	Submission Details
06-Jan-00	53,763	127	Submission to FDA	Protocol amendments to include either new study centers and/or change of adress for protocols 1008-033 and -105
06-Jan-00	53,763	128	Submission to FDA	Protocol amendments to include new study centers for protocols 1008-127, -131, and -134
07-Jan-00	53,763	129	Submission to FDA	Updated Investigator's Brochure
11-Jan-00	53,763	130	Submission to FDA	Resubmission with updates for a Type A Pre-NDA meeting, origianl information forwarded 23Dec1999
20-Jan-00	53,763	131	Submission to FDA	Protocol amendments to include new study centers for protocols 1008-033, -105, -127, -131, and -134
21-Jan-00	53,763	132	Submission to FDA	10 research reports submitted
21-Jan-00	53,763	133	Submission to FDA	Initial Medwatch safety report for protocol 1008-045
25-Jan-00	53,763	134	Submission to FDA	Protocol amendments to include new study centers for protocols 1008-072, -105, -127, -131, and -134
25-Jan-00	53,763	135	Submission to FDA	Updated Investigator's Brochure
31-Jan-00	53,763	136	Submission to FDA	Protocol amendments to include either amendments, new study centers and/or sub-investigators for protocols 1008-104, -127, -131, and -134
03-Feb-00	53,763	137	Submission to FDA	Protocol amendments to include new study centers for protocols 1008-127, -131, and -134
10-Feb-00	53,763	138	Submission to FDA	Protocol amendments to include new study centers for protocols 1008-033, -105, -127, -131, and -134
14-Feb-00	53,763	139	Submission to FDA	Pre-NDA Meeting (07Feb2000) minutes regarding CMC information
15-Feb-00	53,763	140	Submission to FDA	Request for a Pre-NDA Teleconference Meeting, agenda and attachments provided
16-Feb-00	53,763	141	Submission to FDA	End-of-Phase 2 Meeting (20Dec1999) Minutes
17-Feb-00	53,763	142	Submission to FDA	Initial Medwatch safety report for protocol 1008-035
23-Feb-00	53,763	143	Submission to FDA	Initial Medwatch safety report for protocol 1008-012
25-Feb-00	53,763	144	Submission to FDA	5 research reports submitted
29-Feb-00	53,763	145	Submission to FDA	Protocol amendments to include new study centers for protocols 1008-127, -131, and -134
01-Mar-00	53,763	146	Submission to FDA	Type C meeting Request: Comment on Analysis Plan for Visual Field Monitoring and Visual Adverse Events
06-Mar-00	53,763	147	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-012
07-Mar-00	53,763	148	Submission to FDA	Updated Investigator's Brochure
08-Mar-00	53,763	149	Submission to FDA	Annual Report covering periods 09Nov1998 to 08Nov1999
10-Mar-00	53,763	150	Submission to FDA	3 research reports submitted
17-Mar-00	53,763	151	Submission to FDA	Type B Meeting Request for a pre-NDA meeting
21-Mar-00	53,763	152	Submission to FDA	1 research report submitted
24-Mar-00	53,763	153	Submission to FDA	1 research report submitted

Date	IND/NDA No.	Serial No.	Activity	Submission Details
29-Mar-00	53,763	154	Submission to FDA	Protocol amendments to include either new study centers and/or sub-investigators for protocols 1008-031, -033, -127, and -134
07-Apr-00	53,763	155	Submission to FDA	Protocol amendments to include either new study centers and/or sub-investigators for protocols 1008-033, -127, -131, and -134
10-Apr-00	53,763	156	Submission to FDA	1 research report submitted
10-Apr-00	53,763	157	Submission to FDA	Initial Medwatch safety report for protocol 1008-080
12-Apr-00	53,763	158	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-012
20-Apr-00	53,763	159	Submission to FDA	Protocol amendments to include either new subinvestigators and/or new study centers for protocols1008-014, -015, -030, -031, -033, and -104
24-Apr-00	53,763	160	Submission to FDA	Updated Investigator's Brochure
26-Apr-00	53,763	161	Submission to FDA	1 research report submitted
27-Apr-00	53,763	162	Submission to FDA	1 research report submitted
03-May-00	53,763	163	Submission to FDA	1 research report submitted
03-May-00	53,763	164	Submission to FDA	Follow-up Medwatch Safety report for protocol 1008-080
05-May-00	53,763	165	Submission to FDA	Type B Meeting: Pre-NDA Meeting Package regarding Neuropathic Pain/Add-on Epilepsy
11-May-00	53,763	166	Submission to FDA	Follow-up Medwatch safety report for for protocol 1008-080
17-May-00	53,763	167	Submission to FDA	Protocol amendments to include either new sub-investigators and/or change of address for protocols 1008-015, -029, -031, -032, and -033
24-May-00	53,763	168	Submission to FDA	Protocol amendments to include either new study centers, change of address, and/or sub-investigators for protocols 1008-015, -030, -031, -033, -104, and -105
01-Jun-00	53,763	169	Submission to FDA	1 research report submitted
02-Jun-00	53,763	170	Submission to FDA	Transfer of sponsor obligations to Kendle International Inc.
06-Jun-00	53,763	171	Submission to FDA	Correspondance to inform FDA of contact information following the Pfizer merger
08-Jun-00	53,763	172	Submission to FDA	2 research reports submitted
16-Jun-00	53,763	173	Submission to FDA	2 research reports submitted
20-Jun-00	53,763	174	Submission to FDA	Updated Investigator's Brochure
22-Jun-00	53,763	175	Submission to FDA	Response to FDA inquiry for additional information for Type C Meeting request
28-Jun-00	53,763	176	Submission to FDA	Protocol amendments to include new sub-investigators for protocols 1008-029, -032, -033, -104, -105, -127, -131, and -134
30-Jun-00	53,763	177	Submission to FDA	Protocol amendments to include new sub-investigators for protocols 1008-029, -035, -131, and -134
06-Jul-00	53,763	178	Submission to FDA	Follow-up Medwatch Safety reports for protocols 1008-015 and -033
13-Jul-00	53,763	179	Submission to FDA	Updated CMC information
20-Jul-00	53,763	180	Submission to FDA	Protocol amendments to include either new study centers and/or sub-investigators for protocols 1008-015, -033, -105, -127, and -134
25-Jul-00	53,763	181	Submission to FDA	Meeting minutes from the pre-NDA meeting on 07June2000

Date	IND/NDA No.	Serial No.	Activity	Submission Details
01-Aug-00	53,763	182	Submission to FDA	Protocol amendments to include new sub-investigators for protocols 1008-015, -033, -104, -105, and -134
01-Aug-00	53,763	183	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-012
03-Aug-00	53,763	184	Submission to FDA	Follow-up Medwatch Safety report for protocol 1008-033
09-Aug-00	53,763	185	Submission to FDA	Follow-up Medwatch Safety report for protocol 1008-015
11-Aug-00	53,763	186	Submission to FDA	Protocol amendments to include either new study centers and/or sub-investigators for protocols 1008-033, -072, -104, -105, -127, and -134
16-Aug-00	53,763	187	Submission to FDA	Follow-up Medwatch Safety report for protocol 1008-045
21-Aug-00	53,763	188	Submission to FDA	2 research reports submitted
23-Aug-00	53,763	189	Submission to FDA	2 research reports submitted
23-Aug-00	53,763	190	Submission to FDA	Reference is made to IND for pregablin and to a CMC meeting request in which we included a request for a Type A Pre-NDA
25-Aug-00	53,763	191	Submission to FDA	Forwarded a copy of protocol 1008-098, per agency request
30-Aug-00	53,763	192	Submission to FDA	Protocol amendments to include new sub-investigators for protocols 1008-030, -033, and -104
31-Aug-00	53,763	193	Submission to FDA	Background document - overview of the pregabalin ERS by NDA Item
01-Sep-00	53,763	194	Submission to FDA	Type C meeting minutes from 03Aug2000 meeting regarding visual fields analysis
06-Sep-00	53,763	195	Submission to FDA	Response to FDA inquiry (07June and 12July2003) for patient safety data from protocol 1008-012
19-Sep-00	53,763	196	Submission to FDA	Protocol amendments to include new sub-investigators for protocol 1008-033
22-Sep-00	53,763	197	Submission to FDA	Request to withdraw follow-up pre-NDA CMC meeting without prejudice, for business reasons
02-Oct-00	53,763	198	Submission to FDA	Decision to delay the submission of pregablin until completion of our BID program for neuropathic pain
03-Oct-00	53,763	199	Submission to FDA	Protocol amendments to include either new co-principals, change of address, and/or sub-investigators for protocols 1008-015, -104, -032, -105, -131, and -134
20-Oct-00	53,763	200	Submission to FDA	Protocol amendments to include new study centers for protocols 1008-060, -132, -173, -174, and -183
25-Oct-00	53,763	201	Submission to FDA	Protocol amendments to include new study centers for protocols 1008-132, -173, and -174
30-Oct-00	53,763	202	Submission to FDA	Protocol amendments to include either new study centers for protocols 1008-132, -160, -173, and -174
07-Nov-00	53,763	203	Submission to FDA	Protocol amendment submitted for protocol 1008-160
10-Nov-00	53,763	204	Submission to FDA	Provided protocol to FDA due to missing pages from earlier submission
10-Nov-00	53,763	205	Submission to FDA	7 research reports submitted
13-Nov-00	53,763	206	Submission to FDA	Protocol amendments to include new study centers for protocols 1008-060, -132, -173, -174, and -183

Date	IND/NDA No.	Serial No.	Activity	Submission Details
20-Nov-00	53,763	207	Submission to FDA	Protocol amendments to include new study centers for protocols 1008-132, -160, -173, and -174
29-Nov-00	53,763	208	Submission to FDA	Protocol amendments to include either new study centers and/or sub-investigators for protocols 1008-031, -132, -134, -160, -173, and -174
01-Dec-00	53,763	209	Submission to FDA	Protocol amendments to include new study centers for protocols 1008-132, -160, -173, and -174
07-Dec-00	53,763	210	Submission to FDA	Protocol amendments to include either new study centers, change of address, and/or change of principal investigator for protocols 1008-033, -105, -132, and -134
15-Dec-00	53,763	211	Submission to FDA	Protocol amendments to include either new study centers and/or sub-investigators for protocols 1008-015, -033, -060, -132, -160, -174, and -183
21-Dec-00	53,763	212	Submission to FDA	Initial Medwatch safety report for protocol 1008-060
28-Dec-00	53,763	213	Submission to FDA	Updated Investigator's Brochure
28-Dec-00	53,763	214	Submission to FDA	Initial Medwatch safety report for protocol 1008-074
29-Dec-00	53,763		Letter from FDA	Minutes of the Executive Carcinogenicity Committee meeting on 12Dec2000
04-Jan-01	53,763	215	Submission to FDA	Protocol amendments to include new study centers for protocols 1008-060, -132, -160, -173, -174, and -183
05-Jan-01	53,763	216	Submission to FDA	7 research reports submitted
09-Jan-01	53,763	217	Submission to FDA	Updated Investigator's Brochure
16-Jan-01	53,763	218	Submission to FDA	Protocol amendments to include either new study centers, new principal investogator, and/or sub-investigators for protocols 1008-015, -033, -105, -132, -134, -160, -173, and -174
18-Jan-01	53,763	219	Submission to FDA	Information regarding the 2-year carcinogenicity studies of pregabalin in rats and mice, and to provide an assessment of the carcinogenic potential of pregabalin
19-Jan-01	53,763	220	Submission to FDA	Amendment to allow edition and rationale for Physician Withdrawal Checklist and Creatinine Clearance Exclusion criteria
19-Jan-01	53,763	221	Submission to FDA	Protocol amendments to include either new study centers and/or sub-investigators for protocols 1008-072, -160, -173, -174, and -183
22-Jan-01	53,763	222	Submission to FDA	Meeting minutes from 17Jan2001 regarding protocols 1008-060, -132, and -173
24-Jan-01	53,763	223	Submission to FDA	Protocol amendments to include new study centers for protocols 1008-173 and -183
25-Jan-01	53,763	224	Submission to FDA	Amendment to correct a typographical error in previous submission
25-Jan-01	53,763	225	Submission to FDA	Follow-up Medwatch Safety report for protocol 1008-033
29-Jan-01	53,763	226	Submission to FDA	Expert opinions regarding the carcinogenic potential of pregabalin based upon all available data and providing an overview of regulatory status outside the United States
06-Feb-01	53,763	227	Submission to FDA	3 research reports submitted
07-Feb-01	53,763	228	Submission to FDA	Clinical proposal regarding FDA risk/benefit concerns

Date	IND/NDA No.	Serial No.	Activity	Submission Details
08-Feb-01	53,763	229	Submission to FDA	Response to request for additional references from 02Feb2001 meeting
09-Feb-01	53,763	230	Submission to FDA	4 research reports submitted
14-Feb-01	53,763	231	Submission to FDA	5 research reports submitted
16-Feb-01	53,763	232	Submission to FDA	Correspondance informing FDA of our discontinuation of Pain and fibromylagia studies in the USA as part of the partial clinical hold imposed by FDA because none of the patients in the study met the refractory requirements for continuance
27-Feb-01	53,763		Letter from FDA	Letter placing a partial hold on clinical studies until additional information is known regarding the tumorigenic mechanism of hemangiosarcoma in mice, and the relevance of this finding to humans
28-Feb-01	53,763	233	Submission to FDA	3 research reports submitted
09-Mar-01	53,763	234	Submission to FDA	Annual report covering periods 09Nov1999 to 08Nov2000
09-Mar-01	53,763	235	Submission to FDA	3 research reports submitted
14-Mar-01	53,763	236	Submission to FDA	Updated Investigator's Brochure
22-Mar-01	53,763	237	Submission to FDA	Initial Medwatch safety report for protocol 1008-134
28-Mar-01	53,763	238	Submission to FDA	Protocol amendments to include new investigators for protocols 1008-014, -015, -031, -032, and -033
28-Mar-01	53,763	239	Submission to FDA	Updated Investigator's Brochure
30-Mar-01	53,763	240	Submission to FDA	Meeting minutes from meetings on 26Jan2001, 29Jan2001, 02Feb2001, 08Feb2001, and 13Feb2001 regarding mouse carcinogenicity
02-Apr-01	53,763	241	Submission to FDA	Initial Medwatch safety report for protocol 1008-074
23-Apr-01	53,763	242	Submission to FDA	2 research reports submitted
27-Apr-01	53,763	243	Submission to FDA	8 research reports submitted
27-Apr-01	53,763	244	Submission to FDA	Protocol amendment to include new investigators for protocols 1008-014, -015, -033, -104, -127, and -131
01-May-01	53,763	245	Submission to FDA	5 research reports submitted
09-May-01	53,763	246	Submission to FDA	Request for Agency review and agreement regarding open-label treatment in refractory neuropathic pain patients for protocol 1008-197
10-May-01	53,763	247	Submission to FDA	Protocol amendments to include new sub-investigators for protocols 1008-132, -160, -173, and -174
18-May-01	53,763	248	Submission to FDA	Request for joint meeting with DAAODP and DACCADP to reconcile the apparent discrepancies in advice between the two Divisions
30-May-01	53,763	249	Submission to FDA	Initial Medwatch safety report for protocol 1008-084
01-Jun-01	53,763	250	Submission to FDA	Letter to inform agency of company procedural change relative to updating the Investigator Brochure
07-Jun-01	53,763	251	Submission to FDA	Protocol amendments to include new sub-investigators for protocols 1008-060, -131, -132, -134, -160, -173, -174, and -183

Date	IND/NDA No.	Serial No.	Activity	Submission Details
14-Jun-01	53,763	252	Submission to FDA	Request for a Type C meeting to discuss new data relevant to possible mechanisms of hemangiosarcoma development in mice, to outline experimental approaches planned to test mechanistic hypotheses
26-Jun-01	53,763	253	Submission to FDA	Initial Medwatch safety report for protocol 1008-074
27-Jun-01	53,763		Letter from FDA	Response to request for a type C meeting regarding mouse hemangiosarcoma
02-Jul-01	53,763	254	Submission to FDA	Protocol amendments to include change of site names and/or change of address for protocols 1008-015, 029, 030, 032, and -033
10-Jul-01	53,763	255	Submission to FDA	1 research report submitted
11-Jul-01	53,763	256	Submission to FDA	2 research reports submitted
19-Jul-01	53,763	257	Submission to FDA	Initial Medwatch safety report for protocol 1008-100
31-Jul-01	53,763	258	Submission to FDA	The ERS plan for the Chemistry, Manufacturing, and Controls section was not included in previous correspondence and is included with this submission
06-Aug-01	53,763	259	Submission to FDA	Protocol amendment to include new sub-investigators to protocols 1008-033, -132, and -173
06-Aug-01	53,763		Letter from FDA	Letter pertaining to revised ophthalmological analysis plan
13-Aug-01	53,763	260	Submission to FDA	Letter to inform FDA of IND ownership and appointment of Pfizer to act as an authorized agent for purposes of all correspondence and interactions
17-Aug-01	53,763		Letter from FDA	Controlled Substance and abuse liability proposal
23-Aug-01	53,763	261	Submission to FDA	Meeting minutes and slide presentation from Toxicology/FDA Scientific meeting of July 12, 2001
06-Sep-01	53,763	262	Submission to FDA	Update on the regulatory status of clinical trials for pregabalin around the world
07-Sep-01	53,763	263	Submission to FDA	Protocol amendments to include new sub-investigators for protocols 1008-033 and -134
12-Sep-01	53,763		Letter from FDA	Acceptance of Amendment submissions regarding electronic submission for the NDA
19-Sep-01	53,763	264	Submission to FDA	Additional relevant publication on VEGF induction of angiosarcoma from the American Journal of Pathology, Vol. 156, No. 4, April 2000
19-Sep-01	53,763	265	Submission to FDA	Protocol amendment to include new sub-investigators for protocol 1008-173
19-Oct-01	53,763	266	Submission to FDA	Deferral and partial waiver request for collection of pediatric data
25-Oct-01	53,763	267	Submission to FDA	Follow-up Medwatch Safety report for protocol 1008-033
01-Nov-01	53,763	268	Submission to FDA	Minutes regarding teleconference meeting with the DACCADP and DNDP on 19Oct2001
09-Nov-01	53,763	269	Submission to FDA	1 research report submitted
16-Nov-01	53,763	270	Submission to FDA	New Protocol and study site centers for protocol 1008-197
18-Dec-01	53,763	271	Submission to FDA	Protocol amendments to include either new study centers and/or sub-investigators for protocols 1008-160, -174, -183, and -197
07-Jan-02	53,763	272	Submission to FDA	Protocol amendments to include either new study centers and/or sub-investigators for protocols 1008-014, -105, and -197

Date	IND/NDA No.	Serial No.	Activity	Submission Details
18-Jan-02	53,763	273	Submission to FDA	Protocol amendment to include a new study center for protocol 1008-197
29-Jan-02	53,763	274	Submission to FDA	Protocol amendments to include either new investigators and/or sub-investigators for protocols 1008-033, -131, -134, and -197
13-Feb-02	53,763	275	Submission to FDA	Protocol amendment to include new investigator for protocol 1008-197
22-Feb-02	53,763	276	Submission to FDA	Initial Medwatch safety report for protocol 1008-040
04-Mar-02	53,763	277	Submission to FDA	Protocol amendment to include new investigators for protocol 1008-197
08-Mar-02	53,763	278	Submission to FDA	Annual report covering periods 09Nov2000 to 08Nov2001
27-Mar-02	53,763	279	Submission to FDA	Initial Medwatch safety report for protocol 1008-149
01-Apr-02	53,763	280	Submission to FDA	Protocol amendments to include either new investigators and/or sub-investigators for protocols 1008-060 and -197
01-Apr-02	53,763	281	Submission to FDA	3 research reports submitted
09-Apr-02	53,763	282	Submission to FDA	2 research reports submitted
29-Apr-02	53,763	283	Submission to FDA	Follow-up Medwatch Safety report for protocol 1008-149
02-May-02	53,763	284	Submission to FDA	Protocol amendments to include new sub-investigators for protocols 1008-030, -033, -105, and -197
03-May-02	53,763	285	Submission to FDA	14 research reports submitted
06-May-02	53,763	286	Submission to FDA	Initial Medwatch safety report for protocol 1008-196
15-May-02	53,763	287	Submission to FDA	1 research report submitted
15-May-02	53,763	288	Submission to FDA	21 research reports submitted
15-May-02	53,763	289	Submission to FDA	Request for a pre-NDA meeting with the Division to reach consensus on the data for an NDA
20-May-02	53,763	290	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-196
21-May-02	53,763	291	Submission to FDA	19 research reports submitted
29-May-02	53,763	292	Submission to FDA	Initial Medwatch safety report for protocol 1008-155
03-Jun-02	53,763	293	Submission to FDA	3 research reports submitted
03-Jun-02	53,763	294	Submission to FDA	Information regarding reports of anaphylaxis or symptoms that might be anaphylaxis in our pregabalin database as requested per FDA
03-Jun-02	53,763	295	Submission to FDA	Protocol amendments to include either new principal investigators and/or sub-investigators for protocols 1008-131, -132, and -197
12-Jun-02	53,763	296	Submission to FDA	Request for a pre-NDA meeting including objectives and background information
18-Jun-02	53,763		Letter from FDA	Type B Meeting Request for pre-NDA Meeting with FDA
18-Jun-02	53,763	297	Submission to FDA	Initial Medwatch report for protocol 1008-035
10-Jul-02	53,763	298	Submission to FDA	Follow-up Medwatch Safety report for protocol 1008-155
22-Jul-02	53,763	299	Submission to FDA	Protocol amendment to include new sub-investigators for protocol 1008-105
02-Aug-02	53,763	300	Submission to FDA	Pfizer notification to FDA regarding the transfer of the sponsor obligations and activities for studies 1008-014, -015, -027, -029, -030, -031, -032, -033, -104, -105, -127, -131, -132, -134, -160, -173, -174, and -183
02-Aug-02	53,763	301	Submission to FDA	Protocol amendment to include new sub-investigator to protocol 1008-197

Date	IND/NDA No.	Serial No.	Activity	Submission Details
08-Aug-02	53,763	302	Submission to FDA	Proposal Trade Name Lyrica for pregabalin
16-Aug-02	53,763	303	Submission to FDA	NDA Table of Contents
30-Aug-02	53,763	304	Submission to FDA	Protocol amendments to include either new principal, co-investigator, and/or sub-investigators for protocols 1008-131, -134, and -174
06-Sep-02	53,763	305	Submission to FDA	1 research report submitted
06-Sep-02	53,763	306	Submission to FDA	Protocol amendment to include new sub-investigators for protocol 1008-197
13-Sep-02	53,763	307	Submission to FDA	1 research report submitted
20-Sep-02	53,763	308	Submission to FDA	Protocol amendment to include either new sub-investigators, principal; investigators, and/or change of address for protocols 1008-033, -104, -132, -134, -173, and -197
23-Sep-02	53,763	309	Submission to FDA	Initial Medwatch safety report for protocol 1008-155
30-Sep-02	53,763		Letter from FDA	Reference to FDA amendments dated 12June2002 regarding a preNDA meeting package including questions regarding ophthalmologic safety assessment data
30-Sep-02	53,763	310	Submission to FDA	Pregabalin Pfizer Pre-NDA Meeting Minutes from 17July2002 FDA Meeting
02-Oct-02	53,763	311	Submission to FDA	Initial Medwatch safety report for protocol 1008-155
04-Oct-02	53,763	312	Submission to FDA	Protocol amendments for protocols 1008-014, -029, -030, -031, -032, -033, -105, -127, -131, and -197
11-Oct-02	53,763	313	Submission to FDA	12 research reports submitted
07-Nov-02	53,763	314	Submission to FDA	Updated Investigator's Brochure
15-Nov-02	53,763	315	Submission to FDA	Protocol amendment to change co-principal investigator for protocol 1008-134
18-Nov-02	53,763	316	Submission to FDA	Initial Medwatch report for protocol 1008-012
19-Nov-02	53,763	317	Submission to FDA	Protocol amendments to include either new study centers and/or sub-investigators for protocols 1008-014, -029, -030, -031, -131, and -132
25-Nov-02	53,763	318	Submission to FDA	Response to FDA inquiry (17Sept2002) that Pfizer provide a list of ongoing and planned mechanistic studies of Pregabalin related to the finding of hemangiosarcomas in mice
26-Nov-02	53,763	319	Submission to FDA	Initial Medwatch safety report for protocol 1008-125
13-Dec-02	53,763	320	Submission to FDA	Medwatch safety report for protocol 1008-012
18-Dec-02	53,763	321	Submission to FDA	Protocol amendments to include either new study centers and/or sub-investigators for protocols 1008-015, -033, -105, and -174
17-Jan-03	53,763	322	Submission to FDA	Initial Medwatch safety report for protocol 1008-196
28-Jan-03	53,763	323	Submission to FDA	Protocol amendments to include either new study centers, change of address, facilities, principal investigator, and/or sub-investigators for protocols 1008-033, -105, and -134
31-Jan-03	53,763	324	Submission to FDA	1 research report submitted
31-Jan-03	53,763	325	Submission to FDA	Results of the CD-1 Mouse Carcinogenicity Bioassay and submission of 14 research reports
07-Feb-03	53,763	326	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-198

Date	IND/NDA No.	Serial No.	Activity	Submission Details
21-Feb-03	53,763	327	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-155
21-Feb-03	53,763	328	Submission to FDA	Protocol amendments to include either new study centers, prinicpal investigators, labs, and/or sub-investigators for protocols 1008-015, -031, -032, -033, -132, -160, and -197
25-Feb-03	53,763	329	Submission to FDA	Initial Medwatch safety report for protocol 1008-198
27-Feb-03	53,763	330	Submission to FDA	Annual Report covering the period 11/09/2001 to 10/12/2002
10-Mar-03	53,763	331	Submission to FDA	2 research reports submitted
13-Mar-03	53,763	332	Submission to FDA	Protocol amendments to include either new study centers, IRB address, and/or sub-investigators for protocols 1008-029, -174, and -197
19-Mar-03	53,763	333	Submission to FDA	Request for a CAC Meeting
15-Apr-03	53,763	334	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-134
18-Apr-03	53,763	335	Submission to FDA	Request for a Type A 'critical path' meeting to discuss plans regarding submission of the NDA
28-Apr-03	53,763	336	Submission to FDA	Follow-up Medwatch safety rport for protocol 1008-198
02-May-03	53,763	337	Submission to FDA	Follow-up Medwatch safety rport for protocol 1008-198
13-May-03	53,763	338	Submission to FDA	Protocol amendments to include either new study centers, change of address and/or sub-investigators for protocol 1008-197
20-May-03	53,763		Letter from FDA	FDA acknowledgment of our request for a Type A meeting to discuss clinical plans for the NDA. Meeting accepted
22-May-03	53,763	339	Submission to FDA	Final questions and attendee list for Type A meeting scheduled 26June2003
10-Jun-03	53,763	340	Submission to FDA	Protocol amendment to include sub-investigator for protocol 1008-060
23-Jun-03	53,763	341	Submission to FDA	Response to the FDA inquiry for Information in reference to the Type A Meeting request
25-Jun-03	53,763	342	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-198
17-Jul-03	53,763	343	Submission to FDA	Proposed Pregabalin NDA Strategy for 2003
23-Jul-03	53,763		Letter from FDA	FDA Meeting Minutes from 26June2003 meeting
13-Aug-03	53,763	344	Submission to FDA	New Protocol A0081035 and Phase 4 Post-Approval Commitment
14-Aug-03	53,763	345	Submission to FDA	Letter to inform agency regarding regulatory status of clinical trials for pregabalin in France
21-Aug-03	53,763	346	Submission to FDA	Study reports regarding mouse hemangiosarcoma submitted to DACCADP and DNDP per 11Aug2003 teleconference. First of three consecutive submissions
22-Aug-03	53,763	347	Submission to FDA	Study reports regarding mouse hemangiosarcoma submitted to DACCADP and DNDP per 11Aug2003 teleconference. Second of three consecutive submissions
25-Aug-03	53,763	348	Submission to FDA	Study reports regarding mouse hemangiosarcoma submitted to DACCADP and DNDP per 11Aug2003 teleconference. Third of three consecutive submissions
26-Aug-03	53,763	349	Submission to FDA	Request that the Lyrica name be submitted for review by DMETS in advance of our 30Oct2003 NDA Submission
29-Aug-03	53,763	350	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-125

Date	IND/NDA No.	Serial No.	Activity	Submission Details
16-Sep-03	53,763	351	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-065
22-Sep-03	53,763	352	Submission to FDA	Commitment to conduct pediatric studies and plans to address pediatrics in the NDA
23-Sep-03	53,763	353	Submission to FDA	Protocol revisions regarding study centers for protocol 1008-197
03-Oct-03	53,763	354	Submission to FDA	Pfizer commitment to submit the following study reports: 740-03614,745-03407, 745-03659,745-03740,745-03762,745-03763,745-03766, 745-03770,745-03771,745-03828,745-03832,745-03834, 745-03835,745-03855,745-03856
28-Oct-03	53,763	355	Submission to FDA	Protocol revisions for protocol 1008-197
29-Oct-03	53,763	356	Submission to FDA	Follow-up Medwatch safety report for protocol 1008-202
30-Oct-03	**21-446**		**Submission to FDA**	**Original NDA Application**
07-Nov-03	21-446		Submission to FDA	Ophthalmic visual field images to update the NDA database
20-Nov-03	21-446		Submission to FDA	Ophthalmic visual field images to update the NDA database
25-Nov-03	21-446		Letter from FDA	This application has been administratively split by the Agency according to indication. Two applications have been submitted to HFD-170
05-Dec-03	53,763	357	Submission to FDA	Regarding the interactions between Pfizer and AFSSAPS specific to conducting clinical studies in France, enclosed are the two submissions sent to the French Agency in response to their questions
09-Dec-03	21-446		Submission to FDA	Response to FDA inquiry (01Dec2003) for additional pivotal study data
10-Dec-03	21-446		Submission to FDA	Response to FDA inquiry (08Dec2003), providing Carcinogenicity Section 4.2.3.4 of Module 4 (Volumes M4 I5 Vol. 25 - M4 I5 Vol. 65)
23-Dec-03	21-446	-	Submission to FDA	Response to FDA inquiry (18Dec2003), providing specific GAD and Epilepsy study data
30-Dec-03	53,763	358	Submission to FDA	Initial Medwatch safety report for protocol 1008-165
08-Jan-04	21-446		Submission to FDA	Response to FDA inquiry, providing a revised diardiar dataset and a separate dataset with specified patient information
09-Jan-04	21-446		Letter from FDA	We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review
12-Jan-04	21-446		Submission to FDA	Response to FDA inquiry, providing additional SAS Codes, submission of a population PK report, and additional files in the POPPK folder
16-Jan-04	21-446		Submission to FDA	Response to FDA inquiry (09Jan2004) providing replacement file sp1994.pdf to the EDR
23-Jan-04	53,763	359	Submission to FDA	Protocol amendment for protocol 1008-197
30-Jan-04	21-446		Submission to FDA	Response to FDA inquiry (07, 09, 23, 22Jan2004) for previously dated requests
05-Feb-04	21-446		Submission to FDA	Response to FDA inquiry (21, 28, 29Jan2004) for previously dated requests
06-Feb-04	21-446		Submission to FDA	DSI Response for FDA inquiry (21, 28, 29Jan2004) for Information
12-Feb-04	21-446		Submission to FDA	Response to FDA inquiry (03Feb2004) of Information from the Biopharmaceutics Reviewer

Date	IND/NDA No.	Serial No.	Activity	Submission Details
13-Feb-04	21-446		Submission to FDA	Response to FDA inquiry (21Jan2004), resubmission of time exposure tables
16-Feb-04	21-446		Submission to FDA	Response to FDA inquiry (09Jan2004) regarding the Day 74 Letter
17-Feb-04	21-446		Submission to FDA	Response to CMC Reviewer (11Feb2004) Information
20-Feb-04	21-446		Submission to FDA	Response to Medical Officers (17Feb204) in the Division of DACCADP
20-Feb-04	53,763	360	Submission to FDA	Follow-up IND Safety Report for protocol 1008-165
23-Feb-04	21-446		Submission to FDA	4 Month Safety Update
25-Feb-04	21-446		Submission to FDA	Response to FDA inquiry (21Jan2004), resubmitting electronic files to Clinical Pharmacology/Biopharmaceutics
25-Feb-04	21-446		Submission to FDA	Response to FDA inquiry (28Jan2004), provided electronic files to the FDA Safety Group
25-Feb-04	21-446		Submission to FDA	Response to FDA inquiry (29Jan2004), resubmitting electronic files to Clinical Pharmacology/Biopharmaceutics
25-Feb-04	53,763	361	Submission to FDA	Annual Report for periods covering 13 October 2002 through 12 October 2003
26-Feb-04	21-446		Submission to FDA	Response to FDA inquiry (17Feb2004) for information from the Medical Officers in DACCADP
27-Feb-04	21-446		Submission to FDA	Resubmission of Electronic Files: Response to FDA inquiry (17Feb2004) of Information for the Day 74 Letter
03-Mar-04	21-446		Submission to FDA	Response to FDA inquiry (27Feb2004) for Information from the Biopharmaceutics Reviewer
05-Mar-04	53,763	362	Submission to FDA	Pfizer has addressed the partial clinical hold issues identified in the Agency's partial clinical hold letter dated 27Feb2001
17-Mar-04	21-446		Submission to FDA	Revised Label with 4-Month Safety Data
19-Mar-04	21-446		Submission to FDA	Response to FDA inquiry (04March2004) for Information from the DNDP Safety Group
19-Mar-04	21-446		Submission to FDA	Response to the CSS FDA inquiry (04March2004) from the DACCADP
31-Mar-04	21-446		Submission to FDA	Response to FDA inquiry (16March2004) for Information from the DNDP Safety Group
31-Mar-04	21-446		Letter from FDA	We have received the following comments from the Controlled Substance Staff (CSS, HFD-009) in response to our consult request
06-Apr-04	21-446		Submission to FDA	Response to FDA inquiry (24March2004) for Information from the DACCADP Medical Officer
07-Apr-04	53,763		Letter from FDA	We refer to your amendment dated 05 March 2004 (SN-362) citing reasons for placing your IND on partial clinical hold. FDA concluded that studies in the neuropathic patient population may be resumed.
08-Apr-04	21-446		Submission to FDA	Response to FDA inquiry (01April2004) for Information from the DACCADP Medical Officer
09-Apr-04	21-446		Submission to FDA	Meeting Request for 13 April 2004 Meeting with the DACCADP and the CSS

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12-Apr-04	21-446		Submission to FDA	Response to FDA inquiry (24March2004) for Information from the DNDP Safety Group
16-Apr-04	21-446		Letter from FDA	On 08April2004, receipt of 06April2004 major amendment to NDA, extension of user fee goal date to 30July2004
19-Apr-04	21-446		Submission to FDA	Response to FDA inquiry (07April2004) for Information from the Safety Teams in the DACCADP and the DNDP
20-Apr-04	21-446		Submission to FDA	Response to the Chemistry Reviewer FDA inquiry (09April2004) for information for the empty capsule shells of each pregabalin strength
21-Apr-04	21-446		Submission to FDA	Response to FDA inquiry (13April2004) for Information from the Chemistry Reviewer
22-Apr-04	21-446		Submission to FDA	Response to FDA inquiry (14April2004) for Information from the Chemistry Reviewer
28-Apr-04	21-446		Submission to FDA	Response to FDA inquiry (20April2004) for information from the Division's Safety Group
03-May-04	21-446		Submission to FDA	Meeting Request with the Agency Specific to the Visual Data in the Pregabalin Development Program
04-May-04	21-446		Submission to FDA	Response to FDA inquiry (22April2004) for information from the Division's Pharmacology/Toxicology Group
05-May-04	53,763	363	Submission to FDA	Updated Investigator's Brochure
10-May-04	21-446		Letter from FDA	Rejection of a Type A meeting request, deemed unnecessary
14-May-04	21-446		Submission to FDA	Response to CMC following 23April2004 teleconference
14-May-04	53,763	364	Submission to FDA	Protocol amendment for protocol 1008-197
17-May-04	21-446		Letter from FDA	Meeting Minutes (13April2004) regarding preliminary assessment by the Controlled Substance Staff and product scheduling
17-May-04	21-446		Submission to FDA	Response to FDA inquiry (12May2004) for information from the Division's Safety Group
18-May-04	21-446		Submission to FDA	Response to FDA inquiry (05, 10May2004) for chemistry information from the Field Investigator
19-May-04	21-446		Submission to FDA	Follow-up Response to FDA inquiry (04March2004) for information from the DNDP Safety Group
20-May-04	21-446		Submission to FDA	Response to FDA inquiry (06May2004) for toxicology information
25-May-04	21-446		Submission to FDA	Response to FDA inquiry (13, 14May2004) for information from the CMC Reviewer
26-May-04	21-446		Submission to FDA	Response to FDA inquiry (10May2004) for information from the Statistical Reviewer
27-May-04	21-446		Submission to FDA	Response to FDA inquiry (13April2004) Regarding Visual Fields
02-Jun-04	21-446		Submission to FDA	Follow-up to 13 April 2004 Discussion
03-Jun-04	21-446		Submission to FDA	Follow-up to 26 April 2004 Discussion

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04-Jun-04	21-446		Submission to FDA	Response to FDA inquiry (07May2004) for information from the Division's Safety Group
07-Jun-04	21-446		Submission to FDA	Response to FDA inquiry (10May2004) for information from the Statistical Reviewer
09-Jun-04	21-446		Submission to FDA	Response to FDA inquiry (18May2004) for information from the Division's Safety Group
11-Jun-04	53,763	365	Submission to FDA	New study protocols A0081036 and A0081060
14-Jun-04	21-446		Submission to FDA	Proposed Changes to the 07June2004 FDA Proposed Package Insert from the DACCADP
18-Jun-04	21-446		Submission to FDA	Response to FDA inquiry following the 16June2004 teleconference
21-Jun-04	21-446		Submission to FDA	Response to FDA inquiry (14June2004) for information from the Clinical Pharmacologist regarding Study 1008-196
22-Jun-04	21-446		Submission to FDA	Response to FDA inquiry (15June2004) for Information from the Division's Safety Group
24-Jun-04	21-446		Submission to FDA	Response to FDA inquiry (16June2004) for Information from the Safety Group Division
25-Jun-04	21-446		Submission to FDA	Response to FDA inquiry (17June2004) for Information from the Division's Clinical Group
28-Jun-04	21-446		Submission to FDA	Response to FDA inquiry (23June2004) for Information from the Division's CMC Group
29-Jun-04	21-446		Submission to FDA	NDA Transfer Notification (Pfizer Inc. to CP Pharmaceuticals International)
01-Jul-04	21-446		Submission to FDA	Proposed Labeling for Dicussion at the 30June2004 teleconference
02-Jul-04	21-446		Submission to FDA	Response to FDA inquiry following the 30June2004 teleconference
06-Jul-04	21-446		Submission to FDA	Response to FDA inquiry (23June2004) for Information from the Division's Safety Group
07-Jul-04	21-446		Submission to FDA	Response to FDA inquiry (24June2004) for Information from the Division's Safety Group
09-Jul-04	21-446		Submission to FDA	Revised carton and container labeling
13-Jul-04	21-446		Submission to FDA	CPPI NDA Transfer Notification Letter and Right of IND Reference Statements
15-Jul-04	21-446		Submission to FDA	Response to FDA inquiry (11May2004) for Information from the Division's Safety Group
16-Jul-04	21-446		Submission to FDA	Formal Dispute Resolution Request - Abuse Liability Assessment of Pregabalin by the Controlled Substance Staff
20-Jul-04	21-446		Submission to FDA	Response to FDA inquiry (14July2004) for information from DACCADP
22-Jul-04	21-446		Submission to FDA	Response to FDA inquiry (08 and 09July2004) for information from DACCADP
23-Jul-04	21-446		Letter from FDA	FDA acknowledges receipt on 16 July 2004 of our request for formal dispute resolution concerning the abuse liability assessment
26-Jul-04	21-446		Submission to FDA	Response to FDA inquiry (20July2004) for Information from the Safety Group

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27-Jul-04	21-446		Submission to FDA	Response to FDA inquiry (08July2004) for Information from DACCADP
29-Jul-04	21-446		Letter from FDA	We have completed our review of this application, before this application is approved, however, you must submit draft labeling revision as follows
03-Aug-04	21-446		Submission to FDA	Response to FDA inquiry (27July2004) for Information from the DACCADP
05-Aug-04	21-446		Submission to FDA	Response to 29 July 2004 Appprovable Letter - Intent to File an Amendment and Meeting Request
12-Aug-04	21-446		Submission to FDA	Response to FDA inquiry (14July2004) for information from DACCADP
18-Aug-04	21-446		Submission to FDA	Response to FDA inquiry (04, 13August2004) for information from a medical reviewer
19-Aug-04	21-446		Submission to FDA	Briefing Package for 18 August 2004 meeting regarding visual function
20-Aug-04	21-446		Submission to FDA	Proposed Labeling
23-Aug-04	21-446		Submission to FDA	Response to FDA inquiry (09August2004) for information from the Division's Safety Group
24-Aug-04	21-446		Submission to FDA	Final Safety Update Plan
24-Aug-04	21-446		Letter from FDA	Meeting minutes regarding request (04Aug2004) for formal dispute resolution
25-Aug-04	21-446		Submission to FDA	Response to FDA inquiry (08June2004 and 25May2004) for information and amendment clarification
31-Aug-04	21-446		Letter from FDA	Type B official Meeting Minutes from 18Apr2004 meeting regarding ophthalmology
31-Aug-04	53,763	366	Submission to FDA	New Protocol A0081004
03-Sep-04	21-446		Submission to FDA	Response to 31Aug2004 Approvable Letter for NDA 21-723) (NeP), Intent to File an Amendment
07-Sep-04	21-446		Submission to FDA	Response to 31Aug2004 Approvable Letter for NDA 21-724 (AOE), Intent to File an Amendment
07-Sep-04	53,763	367	Submission to FDA	Initial safety report (spontaneous consumer report)
08-Sep-04	21-446		Submission to FDA	Response to 31Aug2004 Non-Approvable Letter on NDA 21-725 (GAD), Intent to File an Amendment
13-Sep-04	21-446		Submission to FDA	Request for End of Review Conference on NDA 21-723 (NeP)
15-Sep-04	53,763	368	Submission to FDA	Revised FDA 1572 Forms for protocols 1008-197 - 0139, 0152 and new investigators for protocols A008103619 and A0081060
13-Oct-04	53,763	369	Submission to FDA	New informed consent form submitted for protocol A0081004
13-Oct-04	53,763	370	Submission to FDA	New protocol A0081004 submitted
13-Oct-04	53,763	371	Submission to FDA	Amendment for protocol A0081004 submitted
26-Oct-04	21-446		Submission to FDA	Response to key issues from 01Oct2004 meeting
01-Nov-04	21-446		Submission to FDA	NDA Resubmission and Final Safety Update
02-Nov-04	53,763	372	Submission to FDA	General Correspondence regarding the approval of investigator IND
08-Nov-04	53,763	373	Submission to FDA	Protocol amendment to include new study centers for protocols A0081036 and A0081060

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16-Nov-04	21-446		Letter from FDA	All applications for new active ingredients, dose forms, indications, routes of administration and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients
18-Nov-04	53,763	374	Submission to FDA	Protocol amendment to include new study centers for protocol A0081004
24-Nov-04	53,763	375	Submission to FDA	Protocol amendment to include new study centers and Form 1572 revisions for protocols A0081036 and A0081060
07-Dec-04	53,763	376	Submission to FDA	Initial spontaneous, health care professionals safety report
14-Dec-04	53,763	377	Submission to FDA	Protocol amendment to include new study centers for protocols A0081004, A0081036, and A0081060
22-Dec-04	53,763	378	Submission to FDA	New protocol A0081007 submitted
30-Dec-04	21-446		Submission to FDA	This letter seeks to formalize the previous communications, supply FDA with requested material and provide the Agency with an update of our position regarding the abuse potential for pregabalin
30-Dec-04	21-446		Submission to FDA	This letter seeks to formalize previous communications and to supply the Division with Lyrica package insert and patient package insert
30-Dec-04	21-446		Letter from FDA	We have completed review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text