CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-446

Chemistry Review(s)

NDA 21-446

LYRICA (pregabalin) Capsules, 25, 50, 75, 100 mg

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant:

Pfizer Global Research and Development
2800 Plymouth Road
Ann Arbor, MI

Indication: Neuropathic Pain

Presentation: [redacted]

EER Status: Acceptable 22_JUN_2004

Consults: DMETS – Tradename: LYRICA - acceptable 15-MAR-2004
Statistics – none
EA – no consult - waiver requested – granted

Phase IV Commitments: The first 3 lots of drug substance manufactured at the Ringaskiddy IRE facility using [redacted]

The original NDA was received 30-OCT-2003

The **drug substance** is manufactured by:

Pfizer Ireland, Inc.
Ringaskiddy, IRE

Manufacturing and controls information was reviewed and were found acceptable – acceptable. Of note was the issue of the potential carcinogenic impurity [redacted] which could be formed during [redacted] the drug substance from [redacted] Data were provided from the analyses of — batches for [redacted] and none was detected. This is considered adequate. No controls for this potential impurity are considered needed. A [redacted] was proposed so a phase 4 commitment was made to test the first 3 lots of drug substance manufactured at the Ringaskiddy IRE facility using [redacted] Comparability protocols providing for alternate starting materials and manufacturing processes were found acceptable following the establishment of added

controls. The alternate manufacturing protocols provide, in part, for a new method for producing [ ]

Structural characterization of the drug substance was satisfactory. Specifications were found acceptable. A re-test period of [ ] was requested, and is supported by [ ] submitted stability data on only pilot scale batches from the R&D site – [ ] re-test was granted. The stability testing protocol is considered adequate.

Conclusion
Drug substance is satisfactory.

The **drug product** is capsules of 25, 50, 75, 100 mg.

Manufacturer:

Parke Davis, Div Warner Lambert Co.
Vega Baja, PR

The manufacturing method is a standard blend and capsule filling process. Adequate in-process controls are in place. The proposed regulatory specifications are acceptable. The submitted stability data is adequate to support the 36 month expiry in all presentations. Note that the expiry for other strengths for different indications have not been finalized. The stability testing protocol is considered adequate. The established name pregabalin is USAN.

Labeling is acceptable.

The overall Compliance recommendation is acceptable as of 22-JUN-2004.

All associated DMFs are acceptable

Overall Conclusion
From a CMC perspective the application is recommended for approval.

Eric P Duffy, PhD
Director, DNDC II/ONDC

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/s/

Eric Duffy
7/29/04 03:41:45 PM
CHEMIST

CMC Team Leader Memo to File
NDA 21446 Lyrica (Pregabalin) capsules
Ravi S. Harapanhalli, Ph.D.
CMC Team Leader, HFD-170
Division of Anesthetics, Critical Care, and Addiction Drug Products
June 04, 2004

Overall CMC recommendation:

The NDA is recommended for approval pending an acceptable cGMP recommendation from the Office of Compliance.

CMC Reviews:

Sharon Kelly reviewed this NDA from CMC perspective. In the course of the extended review cycle of nine months (initially 6 months cycle that was extended by three months to July 28, 2004), two reviews were written based on the original NDA and the subsequent amendments resulting from information request (IR) letters sent to the firm. Her reviews were signed off into the Division Filing System (DFS) on May 24, 2004 and June 03, 2004 respectively.

Secondary review:

While critical issues pertaining to the approvability of the NDA were resolved, the following issues were discussed with Pfizer on June 4, 2004 in a teleconference and agreement was reached on all the issues except the one on — expiration dating for the 150, 200, 225, and 300-mg strengths. Pfizer stated that they would like to discuss this issue further.

List of CMC reminders and comments resolved in the teleconference dated June 04, 2004:

1. We remind you of your commitment in the Amendment dated 13-MAY-2004 to test the first three Ringaskiddy lots of pregabalin for [ ] If the observed levels are more than [ ]PM, submit the data in a prior-approval supplement and propose a specification of NMT [ ]PPM for this impurity.

Pfizer agreed for the proposed filing mechanism.

2. The batch reference for [ ] was omitted for the manufacturing example in the NDA submission, Section 3.2.S.2.2.2 page 34. Adequately document the batch reference for the regulatory starting material in all future manufacturing campaigns.

Pfizer agreed to revise their batch records to include batch reference to the regulatory starting material.

3. The data in support of a [ ] retest interval for the drug substance were based on only three batches from Holland; MI. Statistical analysis revealed that at end of proposed retest interval, the tolerance limits were outside the acceptable range of [ ] Therefore, a retest interval of [ ] is granted at this time. Accrual of additional stability data may qualify for a future extension of the retest interval.

Pfizer agreed to accept a retest interval of [ ] for the drug substance with the understanding that this may be extended based on the accrual of satisfactory real time data.

4. Provide a revision to the drug substance specifications with the acceptance criteria for the bulk density of NLT [ ] which is reflective of the batch experience by the proposed [ ] process. This may be submitted in the next annual report.

Pfizer agreed to establish a limit of NLT [ ] for the bulk density of the drug substance and to report it in the next annual report

5. A [ ] shelf life is granted only for the currently proposed configuration of the drug product, i.e. 60 cc HDPE bottles containing [ ] capsules for the strengths 25-, 50-, 75-, and 100 mg.

Pfizer agreed with this recommended shelf life

6. For the strengths 150-, 200-, 225-, and 300 mg capsules, a shelf life of [ ] is grantable at this time. Based on the accrual of additional real time stability data on the appropriate container/closer configurations, the shelf life may be extended in the next annual report.

Pfizer stated that they would like to discuss this issue further and that they would like to present their calculations to support a shelf life of [ ] for these strengths.

7. Revise the post-approval stability protocol to include semi-annual testing in the [ ] of testing.

Pfizer agreed to revise their post-approval stability protocol to include semi-annual testing in the first and second year of testing.

8. Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, your continued cooperation is expected to resolve any problems that may be identified.

Pfizer agreed to cooperate with the Agency on the issue of method validation activities.

This reviewer concurs with the views of the reviewing chemist that there is no need for the validation of the analytical methods in the FDA laboratories as the analytical methods are conventional in nature and are clearly described and are adequately validated by the firm. Also they do not qualify for any of the criteria described in the interim ONDC policy on method validations.

Outstanding approvability issue:
Satisfactory cGMP recommendation from the Office of Compliance for this NDA is awaited.

Final recommendation from CMC perspective: The NDA is recommended for approval pending an acceptable cGMP recommendation from the Office of Compliance. The pending sites needing OC recommendation are the Pfizer Ireland sites. The sites have been inspected and the final report is pending for these sites.

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ON ORIGINAL

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/s/

Ravi Harapanhalli
6/4/04 03:27:26 PM
CHEMIST
AP pending OC recommendation

NDA 21-446

Lyrica (Pregabalin Capsules)

Pfizer Global Research & Development

CMC Review # 4
Sharon L. Kelly
Anesthetic, Critical Care and Addiction
HFD 170

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-446

2. REVIEW #: 4

3. REVIEW DATE: December 20, 2004

4. REVIEWER: Sharon Kelly

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	30-OCT-2003
Amendment	17-FEB-2004
Amendment	21-APR-2004
Amendment	13-MAY-2004
Amendment	18-MAY-2004
Amendment	25-MAY-2004
Amendment	24-JUN-2004
Amendment	28-JUN-2004
Amendment	25-AUG-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s)	Document Date
Amendment	25-AUG-2004
Amendment, NDA 21-446	01-NOV-2004
Amendment, NDA 21-723	01-NOV-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Pfizer Global Research and Development
Address:	2800 Plymouth Road Ann Arbor, Michigan 48105
Representative:	Jonathon M. Parker, R.Ph., M.S.
Telephone:	734 - 622 - 5377

8. DRUG PRODUCT NAME/CODE/TYPE: LYRICA (pregabalin) Capsules

a) Proprietary Name: LYRICA
b) Non-Proprietary Name (USAN): Pregabalin
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1 New Molecular Entity
- Submission Priority: P Priority Review

9. LEGAL BASIS FOR SUBMISSION: 21 USC Sec. 505 (b)(1)

10. PHARMACOL. CATEGORY: Diabetic Neuropathy Agents

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 25, 50, 75, 100, 150, 200, 225, 300 mg

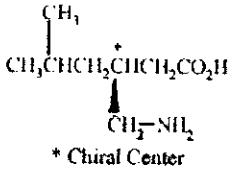
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _XX_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(S)-3-(aminomethyl)-5-methylhexanoic acid $C_8H_{17}NO_2$ Mol.Wt. 159.23



* Chiral Center

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
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	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	IV			4	N/A		

	III			4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		
IND		
IND		
NDA	21-723	Pregabalin Capsules Neuropathic pain associated with Post-herpetic Neuralgia
NDA	21-724	Pregabalin Capsules Epilepsy
NDA		Pregabalin Capsules Generalized Anxiety Disorder

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	— retest schedule for drug substance *	10-MAY-2004	Karl K. Lin, Ph.D.
Biometrics	Extrapolation of no more than — — ; beyond amount of actual stability data for drug product: — shelf life. Yearly interval stability testing of annual batches insufficient. +	10-MAY-2004	Roswitha Kelly, MS

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

EES	Pending, May 19, 2004		
Pharm/Tox	Lactam degradation product adequately qualified	07-APR-2004	Jerry Cott, Ph.D.
Biopharm	preNDA Meeting: Human Pharmacokinetics and Bio - availability - Dissolution Profile	07-JUN-2000	Meeting Minutes Finalized 23-JAN-2001
Methods Validation	Pending Approval **		
ODS / DMETS	Labeling revisions. Proprietary name Lyrica™ acceptable	03-FEB-2004	Kimberly Culley, RPh
EA	FONSI Recommended	25-FEB-2004	Florian Zielinski, Ph.D.
Microbiology	N/A		

* As reviewed here, additional data supports a retest interval of [redacted] for the drug substance.

+ Based on review of the amendment, a shelf life of [redacted] is grantable to the drug product (all strengths and configurations).

** The test procedures are conventional in nature and do not meet any of the requirements of the interim policy on methods validation. There are no issues with any of the analytical procedures and therefore the methods validation will not be initiated with the Division of Parmaceutical Analysis.

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-446

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA application can be Approved from a chemistry review perspective.

A [C .] shelf life is grantable for the drug substance when stored at the recommended conditions. Data from additional batches is needed to support the Sponsor's proposal of a [C .] test period.

A [C .] shelf life is grantable for the drug product when stored at the recommended conditions for the currently proposed commercial configuration ie 60 cc bottles containing 90 capsules for the 25 mg, 50 mg, 75 mg, and 100 mg capsule strengths; 120 cc bottles containing 90 capsules for the 150 mg, 200 mg, 225 mg, and 300 mg capsule strengths. For the addition of new product configurations or dosage strengths, the expiry dating period will have to be supported by additional real time stability data that is ongoing.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

It is proposed that pregabalin capsules should be indicated for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN [C .] The indication for this NDA and for the purposes of this chemistry review is neuropathic pain associated with DPN.

In order to support TID dosing of pregabalin, the Sponsor is revising their bottle count for commercial pregabalin capsules from [redacted] count to 90-count for all strengths (25-, 50-, 75-100-, 150-, 200-, 225- and 300-mg strengths). This change will require use of a larger bottle with the 150-, 200-, and 225-mg capsule strengths. In addition, 45-cc bottles containing 2-count for the stability program will contain 30 or 45 count (physician sample kits). The Changes are addressed in this Chemistry Review #4.

There is no aseptic processing or sterilization needed for pregabalin manufacture. The excipient, lactose monohydrate, and the bovine gelatin used in capsule shells, are in full compliance with the Guidance "The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-regulated Products for Human Use".

The drug substance IUPAC designation is (S)-3-(aminomethyl)-5-methylhexanoic acid. The synthetic route for pregabalin employs classical resolution ([ ] of the racemic amino acid to produce the desired (S)-enantiomer. If there is inadequate removal of the (R)-enantiomer, the amount can be reduced by applying the [ ] procedure or by recrystallization from IPA/water. [ ]

[ ]

The drug product manufacturing process attributes (critical parameters) have been adequately examined and have been shown not to influence batch reproducibility, product performance and/or quality. The manufacturing process consists of [ ] The excipients are lactose monohydrate, corn starch, and talc.

B. Description of How the Drug Product is Intended to be Used

Pregabalin is an analogue of the mammalian neurotransmitter gamma-aminobutyric acid (GABA). It interacts with an auxiliary subunit (α_2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [^{3}H]-gabapentin. Binding to the α_2-δ site is required for analgesic, anticonvulsant and anxiolytic activity in animal models. In addition, pregabalin reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P. The significance of these effects for the clinical pharmacology of pregabalin is not known.

For drug product development, the stability studies included the following configurations:

Bottle Size (cc)	Closure Type	Closure Size (mm)	Product Count	Product Strength
45	CR	24	2	All
120	CR	38	100	25, 50, 75, 100, 150, 200, 300
230	CR	45	100	150, 300
325	CR	38	500	25, 50, 75, 100
710	CT	43	500	150, 200, 225, 300

CR = Child resistant
CT = Continuous thread

The marketed drug product will use a 60 cc and 120 cc bottle size (NDA 21-446 Amendment 01-NOV-2004).

The Sponsor proposes an expiration dating period of three years for all strengths of pregabalin capsules packaged in HDPE bottles and PVC blister packs when stored at 25°C. Based on the statistical analysis of real time stability data (updated data in NDA 21-723 Amendment 01-NOV-2004), the Agency grants a three year expiration period for the dosage strengths 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg capsules.

C. Basis for Approvability or Not-Approval Recommendation

This NDA application can be Approved from a CMC perspective.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Sharon Kelly, Ph.D. / Dec. 20, 2004
Ravi Harapanhalli, Ph.D. /
Lisa Malandro, Project Manager /

C. CC Block

5 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Sharon Kelly
12/21/04 03:03:32 PM
CHEMIST

Ravi Harapanhalli
12/21/04 03:12:33 PM
CHEMIST
AP recommended with no comments

NDA 21-446

Lyrica (Pregabalin Capsules)

Pfizer Global Research & Development

CMC Review # 2
Sharon L. Kelly
Anesthetic, Critical Care and Addiction
HFD 170

Table of Contents

There is no CMC review #3 missing from this section

Per the reviewer, there was an error in numbering the reviews

Chemistry Review Data Sheet

1. NDA 21-446

2. REVIEW #: 2

3. REVIEW DATE: June 3, 2004

4. REVIEWER: Sharon Kelly

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	30-OCT-2003
Amendment	17-FEB-2004
Amendment	21-APR-2004
Amendment	13-MAY-2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s)	Document Date
Amendment	18-May-2004
Amendment	25-May-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Pfizer Global Research and Development
Address:	2800 Plymouth Road Ann Arbor, Michigan 48105
Representative:	Jonathon M. Parker, R.Ph., M.S.
Telephone:	734 - 622 - 5377

8. DRUG PRODUCT NAME/CODE/TYPE: LYRICA (pregabalin) Capsules

a) Proprietary Name: LYRICA
b) Non-Proprietary Name (USAN): Pregabalin
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1 New Molecular Entity
- Submission Priority: P Priority Review

9. LEGAL BASIS FOR SUBMISSION: 21 USC Sec. 505 (b)(1)

10. PHARMACOL. CATEGORY: Diabetic Neuropathy Agents

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 25, 50, 75, 100, 150, 200, 225, 300 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _XX_Rx ___OTC

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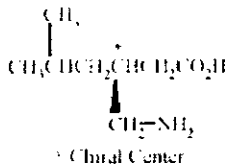
(S)-3-(aminomethyl)-5-methylhexanoic acid $C_8H_{17}NO_2$ Mol.Wt. 159.23



* Chiral Center

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	III			4	N/A		
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	III			4	N/A		
	IV			4	N/A		

	III			4	N/A		

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[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		
IND		
IND		
NDA	21-723	Pregabalin Capsules Neuropathic pain associated with Post-herpetic Neuralgia
NDA	21-724	Pregabalin Capsules Epilepsy
NDA		Pregabalin Capsules Generalized Anxiety Disorder

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	— retest schedule for drug substance	10-MAY-2004	Karl K. Lin, Ph.D.
Biometrics	Extrapolation of no more than — — beyond amount of actual stability data for drug product: — shelf life. Yearly interval stability testing of annual batches insufficient.	10-MAY-2004	Roswitha Kelly, MS

EES	Pending, June 02, 2004		
Pharm/Tox	Lactam degradation product adequately qualified	07-APR-2004	Jerry Cott, Ph.D.
Biopharm	preNDA Meeting: Human Pharmacokinetics and Bio - availability - Dissolution Profile	07-JUN-2000	Meeting Minutes Finalized 23-JAN-2001
Methods Validation	Pending Approval		
ODS / DMETS	Labeling revisions. Proprietary name Lyrica™ acceptable	03-FEB-2004	Kimberly Culley, RPh
EA	FONSI Recommended	25-FEB-2004	Florian Zielinski, Ph.D.
Microbiology	N/A		

The Chemistry Review for NDA 21-446

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA application can be Approved from a chemistry review perspective, pending an Acceptable EES report. The two Comparability Protocols included in this application are acceptable based upon the recommended revisions and the commitments agreed to by the Sponsor.

A — re-test period is grantable for the drug substance when stored at the recommended conditions. Data from additional batches is needed to support the Sponsor's proposal of a — re-test period.

A — shelf life is grantable for the drug product when stored at the recommended conditions only for the currently proposed configuration ie 60 cc bottles containing — capsules for the 25 mg, 50 mg, 75 mg, and 100 mg capsule strengths [ ] For other product configurations and strengths, the expiration period of — may be granted, which may be extended based on the on-going stability studies.

The EES report is pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

It is proposed that pregabalin capsules should be indicated for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN) [

] The indication for this NDA and for the purposes of this chemistry review is neuropathic pain associated with DPN.

Chemistry Assessment Section

Pregabalin was developed as opaque hard gelatin shell capsules in dosage strengths of 25, 50, 75, 100, 150, 200, 225, and 300 mg. The marketed dosage strengths will be 25, 50, 75 mg and 100 mg capsules. To avoid any possible patient or pharmacist confusion, the capsules are colored, and imprinted with black ink to indicate the strength and product code, as follows:

Strength (mg)	Capsule Size	Capsule Color (Body/Cap)
25	4	White/white
50	3	White (with black ink band)/white
75	4	White/orange
100	3	Orange/orange
150	2	White/white
200	1	Light orange/light orange
225	1	White/light orange
300	0	White/orange

The issue of medical error pertaining to capsule size and color was discussed in the Agency's review divisions and the consensus is that the above combinations are acceptable.

The drug product is packaged into either HDPE bottles or PVC blisters. The marketed configuration will be the 60 cc HDPE bottle. However, during development, HDPE bottle configurations were in the range [ ] The configurations include [ ] seals and both child-resistant and nonchild-resistant closures, and identical liner material. The blister system is made of a [ ] PVC blister with [ ] foil backing.

There is no aseptic processing or sterilization needed for pregabalin manufacture. The excipient, lactose monohydrate, and the bovine gelatin used in capsule shells, are in full compliance with the Guidance "The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-regulated Products for Human Use".

The Sponsor proposes a — retest period for pregabalin drug substance when packaged in [ ] The drug substance , although not light sensitive, will be protected from light during storage according to the usual precautions. The stability data is evaluated in the Chemistry Assessment, drug substance section of this review. Statistical analysis of the data supports only a — retest period for the drug substance.

The physicochemical and biological properties have been adequately characterized and are shown not to influence batch reproducibility, product performance and/or drug product quality. The impurity levels are sufficiently characterized and controlled by [ ] characteristics of the drug substance. The drug substance synthesis employs [ ] procedures that are adequately documented.

Pregabalin is crystalline [ ] It is not solvated. It is [ ] and soluble in water. At room temperature the saturation solubility of Pregabalin in aqueous media is [ ] The compound is

classified as highly soluble and highly permeable under the Biopharmaceutical Classification System (BCS). Data demonstrates that the drug product is almost completely dissolved within [ ] and is independent of API particle size. The manufacture and performance of the drug product has been demonstrated over a wide range of drug substance particle size, due, in part, to the evolution of process and — parameters at three manufacturing sites.
The drug substance IUPAC designation is (S)-3-(aminomethyl)-5-methylhexanoic acid. The synthetic route for pregabalin employs classical resolution [ ] of the racemic amino acid to produce the desired (S)-enantiomer. If there is inadequate removal of the (R)-enantiomer, the amount can be reduced by applying the [ ] by recrystallization from IPA/water. [

]

The synthetic scheme employs — a Class II solvent according to ICH Q3C. For anticipated doses of [ ] of pregabalin, the — is controlled at a sufficient level [ ] (ICH Q3C recommends ≤ 720 ppm). The scheme also employs isopropyl alcohol, which is not listed in ICH Q3C, but controls are established at [ ] This solvent most closely resembles Class III solvents, and according to ICH Q3C, they should be limited by GMP or other quality-based requirements. Available data indicate amounts of — per day or less (corresponding to [ ] would be acceptable without justification.

The drug product manufacturing process attributes (critical parameters) have been adequately examined and have been shown not to influence batch reproducibility, product performance and/or quality. The manufacturing process consists of [ ] The excipients are lactose monohydrate, corn starch, and talc.

Pregabalin capsule composition has remained unchanged throughout development and commercial introduction. Changes in capsule shell color and size were made to accommodate blinding and market image aesthetics. Three different powder blends, designated as A, B, and C have been used in clinical studies. The bioequivalence of clinical formulations was demonstrated *in vitro* and a biowaiver was granted as documented in the preNDA meeting minutes of 07-JUN-2000.

The proposed commercial capsule products are filled with 1 of 2 powder blend formulations. The Series A powder blend contains 25% Pregabalin by weight and is used to produce 25- and 50-mg capsule strengths; Series C powder blend contains 75% Pregabalin by weight and is used to produce 75-, 100-, 150-, 200-, 225-, and 300-mg capsule strengths. Note the 150- and higher capsule strengths are not being proposed for marketing at this time for NDA 21-446.

B. Description of How the Drug Product is Intended to be Used

Pregabalin is an analogue of the mammalian neurotransmitter gamma-aminobutyric acid (GABA). It interacts with an auxiliary subunit (α_2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [^{3}H]-gabapentin. Binding to the α_2-δ site is

required for analgesic, anticonvulsant and anxiolytic activity in animal models. In addition, pregabalin reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P. The significance of these effects for the clinical pharmacology of pregabalin is not known.

The Agency agrees to 25, 50, 75 or 100 mg capsule strengths to be given in three divided doses, to a maximum recommended dose of 300 mg/day.

For drug product development, the stability studies included the following configurations:

Bottle Size (cc)	Closure Type	Closure Size (mm)	Product Count	Product Strength
45	CR	24	2	All
120	CR	38	100	25, 50, 75, 100, 150, 200, 300
230	CR	45	100	150, 300
325	CR	38	500	25, 50, 75, 100
710	CT	43	500	150, 200, 225, 300

CR - Child resistant
CT - Continuous thread

The marketed drug product will use a 60 cc bottle size.

The Sponsor proposes an expiration dating period of three years for all strengths of pregabalin capsules packaged in HDPE bottles and PVC blister packs when stored at 25°C. Based on the statistical analysis of real time stability data, the Agency grants a three year expiration period for the recommended market dosage strengths 25, 50, 75 and 100 mg capsules when packaged in the currently proposed count, 60 cc HDPE bottle configuration. However, for all other strengths (150, 200, 225, and 300 mg) and configurations a shelf life of [redacted] is grantable at this time. Based on the accrual of additional real time stability data on the appropriate container/closer configurations, the Sponsor may extend the shelf life in the next annual report.

C. Basis for Approvability or Not-Approval Recommendation

This NDA application can be Approved from a CMC perspective, pending an Acceptable EES report. Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated.

Nevertheless, the Sponsor is expected to provide continued cooperation to resolve any problems that may be identified.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Sharon Kelly, Ph.D. / June 02, 2004
Ravi Harapanhalli, Ph.D. /
Lisa Malandro, Project Manager /

C. CC Block

11 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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

/s/

Sharon Kelly
6/3/04 01:22:01 PM
CHEMIST

Ravi Harapanhalli
6/3/04 02:26:12 PM
CHEMIST
AE pending satisfactory EERs

NDA 21-446

Lyrica (Pregabalin Capsules)

Pfizer Global Research & Development

Sharon L. Kelly
Anesthetic, Critical Care and Addiction
HFD 170

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-446

2. REVIEW #: 1

3. REVIEW DATE: December 18, 2003

4. REVIEWER: Sharon Kelly

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	30-OCT-2003
Amendment	17-FEB-2004
Amendment	03-MAR-2004
Amendment	21-APR-2004
Amendment	13-MAY-2004
Submission(s) Not Reviewed*	**Document Date**
Amendment	18-May-2004

*To be Reviewed in CMC Review #2

7. NAME & ADDRESS OF APPLICANT:

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

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

Representative: Jonathon M. Parker, R.Ph., M.S.

Telephone: 734 - 622 - 5377

8. DRUG PRODUCT NAME/CODE/TYPE: LYRICA (pregabalin) Capsules

a) Proprietary Name: LYRICA
b) Non-Proprietary Name (USAN): Pregabalin
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1 New Molecular Entity
- Submission Priority: P Priority Review

9. LEGAL BASIS FOR SUBMISSION: 21 USC Sec. 505 (b)(1)

10. PHARMACOL. CATEGORY: Diabetic Neuropathy Agents

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 25, 50, 75, 100, 150, 200, 225, 300 mg

13. ROUTE OF ADMINISTRATION: Oral

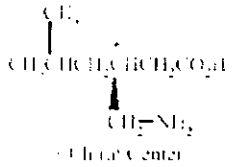
14. Rx/OTC DISPENSED: _XX_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(S)-3-(aminomethyl)-5-methylhexanoic acid $C_8H_{17}NO_2$ Mol.Wt. 159.23



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

	III			4	N/A		
/	IV	/	/	4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 - Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 - Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		
IND		
IND		
NDA	21-723	Pregabalin Capsules Neuropathic pain associated with Post-herpetic Neuralgia
NDA	21-724	Pregabalin Capsules Epilepsy
NDA	/	Pregabalin Capsules Generalized Anxiety Disorder

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER

Biometrics	— retest schedule for drug substance	10-MAY-2004	Karl K. Lin, Ph.D.
Biometrics	Extrapolation of no more than — — beyond amount of actual stability data for drug product: — shelf life. — — stability testing of annual batches insufficient.	10-MAY-2004	Roswitha Kelly, MS
EES	Pending, May 19, 2004		
Pharm/Tox	Lactam degradation product adequately qualified	07-APR-2004	Jerry Cott, Ph.D.
Biopharm	preNDA Meeting: Human Pharmacokinetics and Bio - availability - Dissolution Profile	07-JUN-2000	Meeting Minutes Finalized 23-JAN-2001
Methods Validation	Pending Approval		
ODS / DMETS	Labeling revisions. Proprietary name Lyrica™ acceptable	03-FEB-2004	Kimberly Culley, RPh
EA	FONSI Recommended	25-FEB-2004	Florian Zielinski, Ph.D.
Microbiology	N/A		

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-446

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA application can be Approved from a chemistry review perspective, pending an Acceptable EES report. In addition, there are two Comparability Protocols included in this application that are acceptable if further commitments are agreed to by the Sponsor. The Sponsor has not yet responded to an Information Request letter. However, in the 13-May-2004 Amendment, a major deficiency was addressed. The Sponsor demonstrated that a drug substance Specification for [ ] *was not necessary.*

A — shelf life is grantable for the drug substance when stored at the recommended conditions. Data from additional batches is needed to support the Sponsor's proposal of — test period.

A — shelf life is grantable for the drug product when stored at the recommended conditions only for the currently proposed configuration ie 60 cc bottles containing — capsules for the 25 mg, 50 mg, 75 mg, and 100 mg capsule strengths [ ]. *For the addition of new product configurations or dosage strengths, the expiry dating period will have to be supported by additional real time stability data that is ongoing.*

The EES report is pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

It is proposed that pregabalin capsules should be indicated for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN) [

]

[ ] The indication for this NDA and for the purposes of this chemistry review is neuropathic pain associated with DPN.

Pregabalin was developed as opaque hard gelatin shell capsules in dosage strengths of 25, 50, 75, 100, 150, 200, 225, and 300 mg. The marketed dosage strengths will be 25, 50, 75 mg and 100 mg capsules. To avoid any possible patient or pharmacist confusion, the capsules are colored, and imprinted with black ink to indicate the strength and product code, as follows:

Strength (mg)	Capsule Size	Capsule Color (Body/Cap)
25	4	White/white
50	3	White (with black ink band)/white
75	4	White/orange
100	3	Orange/orange
150	2	White/white
200	1	Light orange/light orange
225	1	White/light orange
300	0	White/orange

The drug product is packaged into either HDPE bottles or PVC blisters. The marketed configuration will be the 60 cc HDPE bottle. However, during development, HDPE bottle configurations were in the range [ ] The configurations include [ ] seals and both child-resistant and nonchild-resistant closures, and identical liner material. The blister system is made of a — PVC blister with a — foil backing.

There is no aseptic processing or sterilization needed for pregabalin manufacture. The excipient, lactose monohydrate, and the bovine gelatin used in capsule shells, are in full compliance with the Guidance "The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-regulated Products for Human Use".

The Sponsor proposes a — retest period for pregabalin drug substance when packaged in [ ] when stored at room temperature, or — The drug substance , although not light sensitive, will be protected from light during storage according to the usual precautions. The stability data is evaluated in the Chemistry Assessment, drug substance section of this review. Statistical analysis of the data supports only a — retest period for the drug substance.

The physicochemical and biological properties have been adequately characterized and are shown not to influence batch reproducibility, product performance and/or drug product quality. The impurity levels are sufficiently characterized and controlled by [ ] characteristics of the drug substance. The drug substance synthesis employs [ ] procedures that are adequately documented.

Chemistry Assessment Section

Pregabalin is crystalline [ ] It is [ ] soluble in water. At room temperature the saturation solubility of Pregabalin in aqueous media is [ ] The compound is classified as highly soluble and highly permeable under the Biopharmaceutical Classification System (BCS). Data demonstrates that the drug product is almost completely dissolved within [ ] and is independent of API particle size. The manufacture and performance of the drug product has been demonstrated over a wide range of drug substance particle size, due, in part, to the evolution of process and — parameters at three manufacturing sites.

The drug substance IUPAC designation is (S)-3-(aminomethyl)-5-methylhexanoic acid. The synthetic route for pregabalin employs classical resolution [ ] of the racemic amino acid to produce the desired (S)-enantiomer. If there is inadequate removal of the (R)-enantiomer, the amount can be reduced by applying the [ ] by recrystallization from IPA/water. The racemate stage is a control point in the synthetic scheme. [ ]

The synthetic scheme employs — a Class II solvent according to ICH Q3C. For anticipated doses of [ ] of pregabalin, the — is controlled at a sufficient level [ ] (ICH Q3C recommends ≤ 720 ppm). The scheme also employs isopropyl alcohol, which is not listed in ICH Q3C, but controls are established at [ ] This solvent most closely resembles Class III solvents, and according to ICH Q3C, they should be limited by GMP or other quality-based requirements. Available data indicate amounts of 50 mg per day or less (corresponding to [ ] would be acceptable without justification.

The drug product manufacturing process attributes (critical parameters) have been adequately examined and have been shown not to influence batch reproducibility, product performance and/or quality. The manufacturing process consists of [ ] The excipients are lactose monohydrate, corn starch, and talc.

Pregabalin capsule composition has remained unchanged throughout development and commercial introduction. Changes in capsule shell color and size were made to accommodate blinding and market image aesthetics. Consequently, three different powder blends, designated as A, B, and C have been used in clinical studies. The bioequivalence of clinical formulations was demonstrated *in vitro* and a biowaiver was granted as documented in the preNDA meeting minutes of 07-JUN-2000.

The proposed commercial capsule products are filled with 1 of 2 powder blend formulations. The Series A powder blend contains 25% Pregabalin by weight and is used to produce 25- and 50-mg capsule strengths; Series C powder blend contains 75% Pregabalin by weight and is used to produce 75-, 100-, 150-, 200-, 225-, and 300-mg capsule strengths. Note the 150- and higher capsule strengths are not being proposed for marketing at this time.

B. Description of How the Drug Product is Intended to be Used

Pregabalin is an analogue of the mammalian neurotransmitter gamma-aminobutyric acid (GABA). It interacts with an auxiliary subunit (α_2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [^{3}H]-gabapentin. Binding to the α_2-δ site is
required for analgesic, anticonvulsant and anxiolytic activity in animal models. In addition, pregabalin reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P. The significance of these effects for the clinical pharmacology of pregabalin is not known.

The Agency agrees to 25, 50, 75 or 100 mg capsule strengths to be given in three divided doses, to a maximum recommended dose of 300 mg/day.

For drug product development, the stability studies included the following configurations:

Bottle Size (cc)	Closure Type	Closure Size (mm)	Product Count	Product Strength
45	CR	24	2	All
120	CR	38	100	25, 50, 75, 100, 150, 200, 300
230	CR	45	100	150, 300
325	CR	38	500	25, 50, 75, 100
710	CT	43	500	150, 200, 225, 300

CR = Child resistant
CT = Continuous thread

The marketed drug product will use a 60 cc bottle size.

The Sponsor proposes an expiration dating period of three years for all strengths of pregabalin capsules packaged in HDPE bottles and PVC blister packs when stored at 25°C. Based on the statistical analysis of real time stability data, the Agency grants [redacted] expiration period for the recommended market dosage strengths 25, 50, 75 and 100 mg capsules.

C. Basis for Approvability or Not-Approval Recommendation

This NDA application can be Approved from a CMC perspective, pending an Acceptable EES report. Minor Chemistry issues and a resolution on the acceptability of the Comparability Protocol for the new drug substance synthetic scheme are pending. An Information Request letter was sent to the Sponsor. It is expected that the information will be submitted by the Sponsor and reviewed before a decision is made by the Agency. In the event that there are any unresolved issues pertaining to the Comparability Protocol, the Sponsor should be asked to withdraw the Comparability Protocol from the NDA.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Sharon Kelly, Ph.D. / May 24, 2004
Ravi Harapanhalli, Ph.D. /
Lisa Malandro, Project Manager /

C. CC Block

170 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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

/s/

Sharon Kelly
5/24/04 08:58:49 PM
CHEMIST

Ravi Harapanhalli
5/24/04 09:06:58 PM
CHEMIST
AP with pending resolutions on CPs

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

plication:	NDA 21446 000	Action Goal:	
amp:	31-OCT-2003	District Goal:	01-MAR-2004
gulatory Due:	31-JUL-2004	Brand Name:	LYRICA (PREGABALIN)
plicant:	PFIZER GLOBAL	Estab. Name:	CAPSULES
	2800 PLYMOUTH RD	Generic Name:	PREGABALIN
	ANN ARBOR, MI 481061047		25/50/75/100/150/200/225
iority:	1P		/300M
; Code:	170	Dosage Form:	(CAPSULE)
		Strength:	25 MG, ETC AS ABOVE

lication Comment:

Contacts:	S. KELLY	(HFD-510)	301-827-6394 , Review Chemist
	R. HARAPANHALLI	(HFD-170)	301-827-7410 , Team Leader

---

all Recommendation: ACCEPTABLE on 22-JUN-2004by S. ADAMS (HFD-322)301-827-9051

>lishment: CFN 1811098 FEI 1811098

PARKE DAVIS DIV WARNER LAMBERT CO

188 HOWARD AVE

HOLLAND, MI 49424

>: AADA:

sibilities: DRUG SUBSTANCE MANUFACTURER

e: CSN OAI Status: NONE

Comment: DET-DO PENDING ROUTINE GMP INSPECTION ASSIGNMENT IN FACTS UNDER OP ID # 1642439 AS PART OF A BLANKET FY-04 DRUG HIGH RISK ASSIGNMENT ID #

468916 IS ASSIGNED TO INVESTIGATOR TRACY SINJEN-WIERSMA. (on 15-DEC-2003 by M. ROBINSON (HFR-CE740) 313-393-8121)

PFIZER GLOBAL MANUFACTURING: RESPONSIBILITIES ARE MANUFACTURING, RELEASE TESTING, AND STABILITY TESTING OF DRUG SUBSTANCE (on 12-DEC-2003 by S. KELLY (HFD-510) 301-827-6394)

lestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
BMITTED TO OC	12-DEC-2003				KELLYS
BMITTED TO DO	15-DEC-2003	PS			DAMBROGIOJ
SIGNED INSPECTION T	15-DEC-2003	PS			MROBINSO
SPECTION PERFORMED	19-DEC-2003		19-DEC-2003		MROBINSO

P & PAI EI DATED DECEMBER 15-19, 2003 RESULTED IN NO 483 BEING ISSUED. THE REPORT IS ECTED TO BE CLASSIFIED NAI AND PROFILED ACCEPTABLE.

PECTION SCHEDULED	10-FEB-2004				MROBINSO
RECOMMENDATION	25-FEB-2004			ACCEPTABLE INSPECTION	MROBINSO

-APPROVAL INSPECTION ON 12/15-19/2003 WAS CONDUCTED AS PART OF A COMPREHENSIVE GMP EI BULK ACTIVE PHARMACEUTICAL INGREDIENT (API) DRUGS. NO FDA-483 WAS ISSUED AND THE FIRM CLASSIFIED NAI AND PROFILED ACCEPTABLE FOR PROFILE CLASS CSN.

ECOMMENDATION	25-FEB-2004			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

tablishment: CFN 2623619 FEI 3002173302
PARKE DAVIS DIV WARNER LAMBERT CO
KM 19 RD 689
VEGA BAJA, PR 00763

No: AADA:

ponsibilities: FINISHED DOSAGE MANUFACTURER

ile: CHG OAI Status: NONE

b. Comment: RESPONSIBILITIES: MANUFACTURE, PACKAGING, SECONDARY PACKAGING, LABELING, RELEASE TESTING (on 12-DEC-2003 by S. KELLY (HFD-510) 301-827-6394)

stone Name	Date	Type	Insp. Date	Decision & Reason	Creator
ITTED TO OC	12-DEC-2003				KELLYS
ITTED TO DO	15-DEC-2003	PS			DAMBROGIOJ
GNED INSPECTION T	18-DEC-2003	PS			IAYALA
CTION PERFORMED	14-APR-2004		14-APR-2004		MTORRES
COMMENDATION	16-APR-2004			ACCEPTABLE INSPECTION	MTORRES

CT TO A COMMITMENT MADE BY THE FIRM TO [illegible] BE SUBMITTED TO THE AGENCY AS
SLE CONFERENCE OF 4/8/04 WITH REVIEW CHEMISTS AND FIRM OFFICIALS.

COMMENDATION	19-APR-2004			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

tablishment: CFN 2210721 FEI 2210721

PFIZER INC

182 TABOR RD

MORRIS PLAINS, NJ 07950

F No: AADA:

sponsibilities: FINISHED DOSAGE STABILITY TESTER

ofile: CTL OAI Status: NONE

ilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
BMITTED TO OC	12-DEC-2003				KELLYS
RECOMMENDATION	15-DEC-2003			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

---

blishment: CFN 2410924 FEI 2410924

PFIZER INC

630 FLUSHING AVE

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

BROOKLYN, NY 11206

r No: AADA:

sponsibilities: FINISHED DOSAGE RELEASE TESTER

file: CTL OAI Status: NONE

ab. Comment: RELEASE TESTING, PACKAGING, SECONDARY PACKAGING, LABELING (on 12-DEC-2003 by S. KELLY (HFD-510) 301-827-6394)

estone Name	Date	Type	Insp. Date	Decision & Reason	Creator
MITTED TO OC	12-DEC-2003				KELLYS
RECOMMENDATION	15-DEC-2003			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

---

ishment: CFN 9611880 FEI 3003382089

PFIZER IRELAND PHARMACEUTICALS

LITTLE ISLAND

COUNTY CORK, , EI

AADA:

ibilities: DRUG SUBSTANCE MANUFACTURER

: CSN OAI Status: NONE

ne Name	Date	Type	Insp. Date	Decision & Reason	Creator
ION PERFORMED	07-APR-2004		07-APR-2004		

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

PFIZER IRELAND PHARMACEUTICALS INC.

RINGASKIDDY

RINGASKIDDY, COUNTY CORK, , EI

D: AADA:

isibilities: DRUG SUBSTANCE MANUFACTURER

e: CSN OAI Status: NONE

itone Name	Date	Type	Insp. Date	Decision & Reason	Creator
CTION PERFORMED	01-APR-2004		01-APR-2004		RPENTA
TED TO OC	27-APR-2004				ADAMSS
TED TO DO	27-APR-2004	PS			ADAMSS
ED INSPECTION T	27-APR-2004	PS			ADAMSS
TION SCHEDULED	27-APR-2004		31-MAR-2004		ADAMSS
OMMENDATION	22-JUN-2004			ACCEPTABLE	ADAMSS
				INSPECTION	

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

ASSIGNED INSPECTION T	23-DEC-2003	PS		DAMBROGIOJ
INSPECTION SCHEDULED	18-MAR-2004	23-MAR-2004		IRIVERA
INSPECTION PERFORMED	23-MAR-2004	23-MAR-2004		ADAMSS
DO RECOMMENDATION	23-APR-2004		ACCEPTABLE	ADAMSS
			INSPECTION	

BASED ON REVIEW OF 483 OBSERVATIONS AND INVESTIGATOR'S RECOMMENDATION. AWAITING FIRM'S RESPONSE AND EIR.

C RECOMMENDATION	23-APR-2004		ACCEPTABLE	ADAMSS
			DISTRICT RECOMMENDATION	

APPEARS THIS WAY
ON ORIGINAL

ECOMMENDATION 22-JUN 2004 ACCEPTABLE ADAMSS

DISTRICT RECOMMENDATION

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lishment: CFN [redacted] FEI [redacted]

[redacted]

[redacted]

[redacted]

): AADA:

isibilities: [redacted]

.e: CSN OAI Status: NONE

Comment: [redacted]

12-DEC-2003 by S. KELLY (HFD-510) 301-827-6394)

tone Name	Date	Type	Insp. Date	Decision & Reason	Creator
TTED TO OC	12-DEC-2003				KELLYS
TTED TO DO	15-DEC-2003	PS			DAMBROGIOJ

[redacted]

[redacted]

BMITTED TO OC	30-APR-2004				ADAMSS
BMITTED TO DO	30-APR-2004	PS			ADAMSS
SIGNED INSPECTION T	30-APR-2004	PS			ADAMSS
SPECTION SCHEDULED	30-APR-2004		07-APR-2004		ADAMSS
RECOMMENDATION	08-JUN-2004			ACCEPTABLE	ADAMSS
				INSPECTION	
RECOMMENDATION	08-JUN-2004			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	

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lishment: CFN [redacted] FEI [redacted]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-446

ENVIRONMENTAL ASSESSMENT/FONSI

REVIEW OF

ENVIRONMENTAL ASSESSMENT

FOR

PREGABALIN CAPSULES

(Management of neuropathic pain associated with peripheral neuropathy)

NDA 21-446

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Anesthetic, Critical Care, Addiction Drug Products (HFD-170)

Date Completed: February 24, 2004

EXECUTIVE SUMMARY: **FONSI for NDA 21-446 is recommended.**

Pregabalin is a new molecular entity in a drug product (Pregabalin Capsules) that is indicated for 4 different conditions.

NDA 21-446 Management of neuropathic pain associated with peripheral neuropathy
NDA 21-723 Mgt of neuropathic pain associated with herpes zoster (post-herpetic neuralgia)
NDA 21-724 Treatment of epilepsy
NDA [ ] Treatment of generalized anxiety disorder (GAD)

This EA Review pertains to the "lead" NDA 21-446 only. [ ]

The EIC, — ppb, was calculated from the maximum annual production estimate in 2006, namely, — kg of pregabalin. Therefore, ecotoxicity data was provided for pregabalin because the total amount of pregabalin required for all indications listed above gives EIC greater than 1 ppb.

Pregabalin is not volatile and will not enter the air compartment. Pregabalin does not hydrolyze or photolyze. Pregabalin is not considered to be rapidly biodegradable under standard test conditions. However, the compound is an amino acid and has the potential to be metabolized or biodegraded as other aliphatic acids and / or amino substituted aliphatic acids. Pregabalin is not expected to bind significantly to sludge in [ ]. Its log octanol water partition coefficient is -1.35 at pH 7.4 and -1.90 at pH 1.0. Pregabalin is soluble in water (32 mg/L at pH 7.4) and is expected to enter the aquatic environment through effluents discharged by publicly owned treatment works (POTW). The Expected Introduction Concentration ($EIC_{aquatic}$) is — ppb assuming no metabolism, no hydrolysis and no photolysis. The Predicted Environmental Concentration (PEC) in the aquatic environment is — ppb. The PEC was calculated using 0.24 % sorption to sludge and a dilution factor of 10 for wastewater effluents discharged into the receiving waters.

Environmental effect data were generated for aquatic species. It is unlikely that pregabalin represents a significant risk to the aquatic environment based on the available data submitted.

Pregabalin Effects, Testing Data		
Microbial Inhibition	Aspergillus niger	MIC > 1000 mg/mL
	Trichoderma viride	MIC > 1000 mg/ml
	Clostridium perfringens	MIC > 997 mg/ml
	Bacillus subtilis	MIC > 1000 mg/ml
	Nostoc sp.	MIC > 1000 mg/ml
Daphnia, acute	48 hour EC_{50} > 1000 mg/L, NOEC 1000 mg/L	
Rainbow trout	96 hour EC_{50} > 1000 mg/L, NOEC 1000 mg/L	
Green alga (the most sensitive species)	72 hour EC_{50} > 300 mg/L, NOEC 300 mg/L (based on cell density and growth rate)	

REVIEW of ENVIRONMENTAL ASSESSMENT

1. **Date:** EA dated April 11, 2003
   Chemist: Sharon L Kelly (HFD-170) (301) 827-6394
   Project Mgr: Lisa Malandro (HFD-170)

2. **Name of applicant/petitioner:** Pfizer Inc

   ADEQUATE

3. **Address:** 235 East 42nd Street, New York, NY 10017

   ADEQUATE

4. **Description of the proposed action:**

   a. Requested Approvals

   Pfizer Inc filed NDA 21-446 pursuant to section 505(b) of the Federal, Food, Drug & Cosmetic Act for Pregabalin Capsules indicated for neuropathic pain associated with diabetic peripheral neuropathy. Pregabalin Capsules contain either 25, 50, 75, 100, 150, 200, 225 or 300 mg of pregabalin. Pregabalin Capsules are packaged in HDPE bottles and PVC/foil blisters.

   ADEQUATE

   b. Need for Action:

   Management of neuropathic pain associated with peripheral neuropathy

   ADEQUATE

   c. Expected Locations of Use (Drug Product):

   Pregabalin Capsules will be used in hospitals, clinics and patients' homes throughout the U.S.

   ADEQUATE

d. **Disposal Sites**

Hospitals, pharmacies and clinics will dispose of empty or partially empty packages in accordance with their waste handling procedures. When used in the home, empty or partially empty packages containing Pregabalin Capsules will be disposed of by a community's solid waste management system, which may include landfills, incineration and recycling. Minimal quantities of unused drug may be disposed of in the sewer or septic systems.

ADEQUATE

5. **Identification of the chemical that is the subject of the proposed action**:

a. Nomenclature
   i. Established Name (USAN): pregabalin
   ii. Trade Name: Lyrica is proposed but not yet approved
   iii. Chemical Name: (S)-3-(Aminomethyl)-5-methylhexanoic acid
b. CAS Registration Number: 148553-50-8
c. Molecular Formula: $C_8H_{17}NO_2$
d. Molecular Weight, salt: 159.23
e. Chemical Structure is in Section 5e of the EA, page 4

ADEQUATE

6. **Environmental Issues:**

The EA is in NDA 21-446. Three additional NDAs (21-723, 21-724 [ ] were created administratively from NDA 21-446. These 4 NDAs pertain to the same new molecular entity (pregabalin) in a drug product (Pregabalin Capsules) that is indicated for 4 different conditions.

NDA 21-446 Management of neuropathic pain associated with peripheral neuropathy
NDA 21-723 Mgt of neuropathic pain associated with herpes zoster (post-herpetic neuralgia)
NDA 21-724 Treatment of epilepsy
NDA [ ] Treatment of generalized anxiety disorder (GAD)

The maximum annual production estimate for all indications combined is [ ] kg of pregabalin in 2006. Ecotoxicity data was provided for pregabalin because $EIC_{aquatic}$ is — ppb. GLPs and OECD or FDA EA-TAD testing procedures were used to obtain fate and effects data for pregabalin. The test reports established that scientifically sound methods were used to develop the data to support the Environmental Assessment.

Environmental Fate of Released Substances

i. Identification of Substances of Interest

Pregabalin is the active pharmaceutical ingredient. Following oral administration, pregabalin is mainly excreted in the urine (92% of the oral dose). Of the excreted amount, 89% is excreted as unchanged pregabalin with an additional 0.9% identified as the N-methylated derivative of pregabalin. As a result, pregabalin is considered to be a valid tracer for assessing environmental fate and effects in the aquatic environment.

ADEQUATE

ii. Physical and Chemical Characterization

The aqueous solubility is reported to be 32 mg/mL at pH 7.4.

The pKa for the carboxyl group is 4.2. The pKa for the amine is 10.6. Therefore, pregabalin will exist as the zwitterion at environmental conditions.

The log of the n-octanol / water partition coefficient (log P_{ow}) at environmental conditions (pH 7.4) is -1.35. Because log P_{ow} is not more than — the probability for bioaccumulation, adsorption to particulate matter, humic acids and sediments is low.

The vapor pressure of pregabalin is virtually nil. Therefore, vaporization into the atmosphere is not expected.

ADEQUATE

iii. Environmental Depletion Mechanisms

Sorption: The experimentally determined $K_{d\ sludge}$ is 13.3 in [ ] The corresponding K_{OC} is — This is a low value typically observed for substances that are moderately to highly mobile in the aquatic environment. Therefore, pregabalin is not expected to sorb to sludge or wastewater solids including particulate matter, humic acids, suspended sediments or sediments.

Biodegradation: Pregabalin is not biodegradable according to results from the "Aerobic Biodegradation in Water" test (TAD 3.11). This observation does not necessarily mean that pregabalin is not biodegradable. Indeed, aerobic biodegradation is a consequence of the normal metabolic activity of bacteria and fungi in the environment. The test result may be consistent with slow biodegradation.

Hydrolysis: The molecular structure of pregabalin is not consistent with possible hydrolysis. Pregabalin is presumed to be stable to hydrolysis under environmental conditions (pH 7.4).

Chemical transformation: Pregabalin is an amino acid that may be converted to a lactam at pH 4 or pH 10. Although this degradation pathway is possible, it is likely to be a slow process at environmental temperature and pH.

Photolysis: Pregabalin does not exhibit ultra-violet absorption above 250 nm. Therefore, pregabalin is presumed to be photolytically stable in the environment.

ADEQUATE

iv. Environmental Concentration, aquatic

The total amount of pregabalin required for all indications in the peak market year (2006) is [ ] kg/year. (Ref: Confidential Appendix 1, page 18)

The Expected Introduction Concentration ($EIC_{aquatic}$) of pregabalin entering the external aquatic environment is — ppb (— mg/L). This assumes no metabolism. This is the concentration used in the risk assessment for effects on microorganisms and acute toxicity studies.

Adjusting $EIC_{aquatic}$ for removal by sorption (0.24 %) and 10 fold dilution when pregabalin is introduced into the aquatic compartment gives — ppb for the Predicted Environmental Concentration (PEC). EIC and PEC were not adjusted for removal by photolysis and hydrolysis because these depletion mechanisms do not apply to pregabalin.

ADEQUATE

v. Summary

Pregabalin is expected to primarily enter the aquatic environment through effluents discharged by publicly owned treatment works (POTW). Pregabalin is not volatile and therefore will not enter the air compartment. Pregabalin is not expected to be present in the terrestrial environment because it does not bind significantly to sludge and only a fraction of all sludge is applied as an amendment to farm lands.

Microbial metabolism and chemical degradation are likely to remove pregabalin from the aquatic environment.

ADEQUATE

Environmental Effects of Pregabalin

Data about the environmental effects of pregabalin on aquatic species are on pages 8 to 10 of the EA dated April 11, 2003.

Pregabalin Effects, Testing Data		
Microbial Inhibition	Aspergillus niger	MIC > 1000 mg/mL
	Trichoderma viride	MIC > 1000 mg/ml
	Clostridium perfringens	MIC > 997 mg/ml
	Bacillus subtilis	MIC > 1000 mg/ml
	Nostoc sp.	MIC > 1000 mg/ml
Daphnia, acute	48 hour EC_{50} > 1000 mg/L, NOEC 1000 mg/L	
Rainbow trout, acute	96 hour EC_{50} > 1000 mg/L, NOEC 1000 mg/L	
Green alga, acute (the most sensitive species)	72 hour EC_{50} > 300 mg/L, NOEC 300 mg/L (based on cell density and growth rate)	

The introduction of the pregabalin into sewage treatment plants and into the aquatic environment through use and disposal of the product is not expected to pose an environmental risk.

Based on the Microbial Inhibition Test, pregabalin does not inhibit the growth of microbial strains or species at concentrations expected in wastewater treatment plants. Therefore it is not expected to disrupt the ecosystem.

The applicant performed acute toxicity testing with daphnia magna, rainbow trout and green alga. Green alga are the most sensitive species tested.

The 72 hour EC_{50} for green alga is > 300 mg/L; the NOEC is 300 mg/L. The Tier 1and Tier 2 Standards are satisfied because EC_{50} / EIC is greater than 1000 and the NOEC is more than 1000 times greater than the EIC —— mg/L). These calculations indicate that no effects in the aquatic environment would be expected.

The predicted no effect concentration (PNEC) is calculated by dividing the NOEC for the most sensitive species tested by 100, the assessment factor (AF). Therefore the PNEC is 3.0 mg/L.

It is unlikely that pregabalin represents a significant risk to the aquatic environment based on the available data.

Summary Evaluation: Based on the above data, a FONSI is recommended for NDA 21-446.

ADEQUATE

7. Mitigation Measures

No adverse environmental effects have been identified.
No mitigation measures are required.

ADEQUATE

8. Alternatives to the proposed action

No potential effects have been identified for this proposed action.
No alternatives to the proposed action are required.

ADEQUATE

9. Preparers

Non Confidential EA: The names and professional experience of the EA preparers are provided.
Confidential Appendices: [ ] is the contract testing lab employed by Pfizer to determine ecotoxicity data.

ADEQUATE

10. References

Four references are provided.

ADEQUATE

11. Appendices

The EA contains a 2-page data summary table in the non-confidential Appendix 1. The confidential Appendixes 1, 2, 3 and 4 include calculations of EIC (MEEC), PEC and PNEC (predicted no effect concentration) based on the maximum annual production estimate in any of the next 5 years. Projected peak market usage will occur in 2006.

Confidential Appendix 5 (Determination of Sorption and Desorption Properties, TAD 3.08) Results show that ^{14}C-pregabalin does not adsorb significantly to [ ] Sludge in [ ] solution. The test report (pages 23 to 67) shows that scientifically sound methods were used to develop the data reported in the Environmental Assessment.

Confidential Appendix 6 (Determination of Aerobic Degradation in Water, TAD 3.11)
Results show that pregabalin does not degrade significantly in water in 28 days at pH 6.9 to 7.9 at 16°C to 23°C. The test report (pages 69 to 106) shows that scientifically sound methods were used to develop the data reported in the Environmental Assessment.

Confidential Appendix 7 (Determination of Microbial Growth Inhibition, TAD 4.02)
Results show that pregabalin does not inhibit microbial growth at concentrations up to and including 1,000 mg/mL. The test report (pages 108 to 138) shows that scientifically sound methods were used to develop the data reported in the Environmental Assessment.

Confidential Appendix 8 (Acute Toxicity to Daphnia Magna Under Static Conditions, TAD 4.02)
Results show that pregabalin does not immobilize daphnids; the 48-hour EC_{50} is estimated to be greater than 1,000 mg/mL; the NOEC is 1,000 mg/mL. The test report (pages 140 to 185) shows that scientifically sound methods were used to develop the data reported in the Environmental Assessment.

Confidential Appendix 9 (Acute Toxicity to Rainbow Trout Under Static Conditions, OECD 203)
Mortality and adverse effects due to pregabalin were not observed; the 96-hour EC_{50} is estimated to be greater than 1,000 mg/mL; the 96-hour NOEC is 1,000 mg/mL. The test report (pages 187 to 230) shows that scientifically sound methods were used to develop the data reported in the Environmental Assessment.

Confidential Appendix 10 (Toxicity to Freshwater Green Alga, OECD 201)
Biomass and growth rate were not changed significantly when exposed to 300 mg/mL pregabalin for 72 hours; the 72-hour EC_{50} for biomass (cell density) and growth rate is estimated to be greater than 300 mg/mL, the highest concentration tested; the 72-hour NOEC is 300 mg/mL. The test report (pages 232 to 295) shows that scientifically sound methods were used to develop the data reported in the Environmental Assessment.

ADEQUATE

12. Certification

Certification that the information in the submitted EA is true, accurate and complete is provided by an executive of Pfizer.

ADEQUATE

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

/s/

Florian Zielinski
2/24/04 03:39:41 PM
ENV ASSESSMENT

Nancy Sager
2/25/04 08:03:22 AM
ENV ASSESSMENT

Moheb Nasr
2/25/04 10:12:27 AM
CHEMIST

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

PREGABALIN CAPSULES

NDA 21-446

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Anesthetic, Critical Care and Addiction Drug Products
(HFD-170)

February 24, 2004

FINDING OF NO SIGNIFICANT IMPACT, NDA 21-446

PREGABALIN

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

In support of its new drug application for Pregabalin Capsules containing either 25, 50, 75, 100, 150, 200, 225 or 300 mg of pregabalin, Pfizer Inc prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 (b) which evaluates the potential environmental impact from the use and disposal of the product.

Pregabalin is a chemically synthesized drug that is indicated as an analgesic for the management of neuropathic pain associated with diabetic peripheral neuropathy.

Pregabalin, a new molecular entity, may enter the environment from patient use and disposal. It is expected to enter into the aquatic environment. Data indicate that the drug will not adsorb significantly to sludge and that it is not susceptible to hydrolysis and photolysis. It is not readily biodegradable although it is likely to slowly degrade chemically and microbiologically because it is an amino acid. The toxicity of pregabalin to environmental organisms was characterized. The results indicate that pregabalin is not expected to be toxic to organisms at expected environmental concentrations.

In U.S. hospitals and clinics, empty or partially empty packages will be disposed of according to hospital/clinic procedures. When used in the home, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of the unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

PREPARED BY
Florian Zielinski
Chemist, Center for Drug Evaluation and Research

CONCURRED BY
Nancy B. Sager
Environmental Officer, Center for Drug Evaluation and Research

CONCURRED BY
Moheb M. Nasr
Acting Director, Office of New Drug Chemistry, Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Appended Electronic Signature Page

ENVIRONMENTAL ASSESSMENT

NONCONFIDENTIAL [FREEDOM OF INFORMATION ACT (FOIA)] SUBMISSION

(Referenced Confidential Information Has Been Provided Under Separate Cover)

PREGABALIN
NDA 21-446

Pregabalin for Use in the Management of Epilepsy, Neuropathic Pain, and Generalized Anxiety Disorder

April 2003

Pfizer Inc
235 East 42nd Street
New York, NY 10017

ENVIRONMENTAL ASSESSMENT

Pregabalin
25-, 50-, 75-, 100-, 150-, 200-, 225- and 300-mg Capsules

SUMMARY

Pfizer Inc. is providing an Environmental Assessment (EA) in support of Pregabalin Capsules (NDA 21-446). Pfizer Inc. anticipates no adverse effects to humans or environmental organisms as a result of excreted pregabalin entering publicly owned treatment works (POTW) and subsequent release environments.

1. **DATE:** April 11, 2003

2. **NAME OF APPLICANT/PETITIONER:** Pfizer Inc

3. **ADDRESS:** 235 East 42nd Street, New York, NY 10017

4. **DESCRIPTION OF PROPOSED ACTION:**

a. Requested Approval

Pfizer Inc. has submitted a NDA pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act for pregabalin as an oral antiepileptic, as an analgesic agent for the management of chronic pain (neuropathic pain), and for the management of generalized anxiety disorder. The pregabalin NDA includes capsules containing 25, 50, 75, 100, 150, 200, 225, and 300 mg pregabalin, which are packaged in HDPE bottles and PVC/foil blisters. An EA is being submitted pursuant to 21 CFR Part 25, following the Center for Drug Evaluation and Research, "Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications," dated July 1998.[1]

b. Need for Action

Pregabalin is an analogue of the mammalian neurotransmitter, γ-aminobutyric acid (GABA). Pregabalin has been shown to be effective as an oral antiepileptic, as an analgesic agent for the management of chronic pain (neuropathic pain), and for the management of generalized anxiety disorder. It is currently estimated that

there are more than 2 million patients in the United States requiring management of these disease states. Approval will offer qualifying patients in the United States an alternative and or additional therapy to existing treatments.

c. Locations of Use

Pregabalin will be used as a prescription agent in home, clinic, and hospital environments throughout the world.

d. Disposal Sites

End-user disposal of empty or partially empty packages at US hospitals, pharmacies, or clinics will follow hospital, pharmacy, or clinic procedures. Empty or partially empty containers in residences will typically be disposed of by a community's solid waste management system, which may include landfills, incineration, and/or recycling. Minimal quantities of unused drug may be disposed of in sewer or septic systems.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT OF THE PROPOSED ACTION:

a. Nomenclature

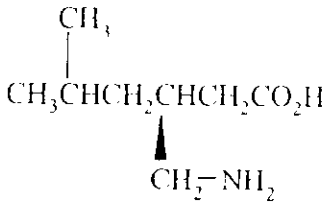
i. Established Name (USAN): Pregabalin
ii. Trade Name: LYRICA ™
iii. Chemical Name: (S)-3-(Aminomethyl)-5-methylhexanoic acid

b. Chemical Abstracts Service (CAS) Registration Number: 148553-50-8

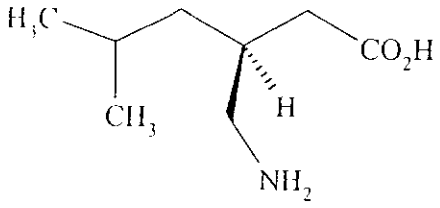
c. Molecular Formula: $C_8H_{17}NO_2$

d. Molecular Weight: 159.23

e. Structural Formula:



Structural Formula



Stereochemical Formula

6. ENVIRONMENTAL ISSUES:

Section One — Assessing Toxicity to Environmental Organisms

This EA focuses on the fate and effects of the active moiety pregabalin, for which the estimated concentration in the aquatic environment is projected to exceed 1 ppb at the point of entry. A tiered approach to testing was used. The physical-chemical, fate, and ecotoxicity protocols used in testing pregabalin followed the Technical Assistance Documents (TAD) as published in FDA's EA Technical Assistance Handbook and OECD (Organization for Economic Co-Operation and Development) Test Guidelines.

a. Environmental Fate of Released Substances

i. Identification of Substance of Interest:

Pregabalin is mainly excreted in the urine (92% of the oral dose). Of the excreted amount, 89% is excreted as unchanged pregabalin with an additional 0.9% identified as an N-methylated derivative of pregabalin.[2] Pregabalin is the primary entity released into the environment and is therefore a valid environmental tracer for assessing fate and effects. Pregabalin will reside mainly in the aquatic compartment, as described in Section 6.a.v.

ii. Physical and Chemical Characterization:

Refer to Data Summary Table (Appendix 1) for an overview of physical/chemical data for pregabalin.

- Water Solubility - The solubility of pregabalin ranges from 47 mg/mL at pH 10.1 to 107 mg/mL at pH 3.7. At pH's <3.7, pregabalin mainly exists

as a cation and is considered freely soluble. Refer to Section 3.2.S.1.3 General Properties

- Dissociation Constant - Two pKa values were determined for pregabalin, 4.2 for the carboxyl group and 10.6 for the amine. Pregabalin will therefore exist as a zwitterion at environmental pH's. Refer to Section 3.2.S.1.3 General Properties.

- Octanol/Water Partition Coefficient - Log K_{ow} values range from -1.90 at pH 1 to -1.35 at pH 7.4. Pregabalin is not likely to partition into lipid based tissues or organic matter in the environment. Refer to Section 3.2.S.1.3 General Properties.

- Vapor Pressure (Vp estimate) - $<1 \times 10^{-7}$ mm Hg at 25°C. Vapor pressure estimates are based on the group and bond contribution methods of Hine and Mookerjee.[3] Pregabalin is not volatile and therefore would not enter the air compartment.

iii. Environmental Depletion Mechanisms

Based on the criteria defined in the Guidance for Industry document, pregabalin will not rapidly deplete in the aquatic environment by sorption, biodegradation, hydrolysis, or photolysis. Refer to Data Summary Table (Appendix 1) for an overview of depletion mechanism data for pregabalin.

- Sorption - Based on an experimentally determined $K_{d\ sludge}$ value of 13.3, pregabalin is unlikely to significantly sorb to wastewater solids and be removed through wastewater treatment. It is also not expected to highly sorb to particulate matter, humic acids, suspended sediments, and sediments due to its low $K_{d\ sludge}$ value, high solubility, and small molecular size. Refer to Confidential Appendix 5.

- Biodegradation - Based on the Guidance for Industry's aerobic biodegradation rapid depletion criteria of t½ ≤8 hours, pregabalin is not a readily biodegradable substance (no biodegradation observed in 28 days). Refer to Confidential Appendix 6.

- Hydrolysis - Formal hydrolysis experiments were not conducted as pregabalin has no constituents capable of being hydrolyzed. Based on the Guidance for Industry's hydrolysis rapid depletion criteria of t½ ≤24 hours, pregabalin will not deplete by this mechanism.

- Chemical Depletion (lactamization) - Pregabalin is essentially an amino acid. The main degradation pathway, although minimal, is lactamization. Based on the demonstrated degradation of pregabalin to lactam at approximately pH 4 and pH 10, there is a potential for pregabalin to slowly deplete at environmental pH's. Refer to Section 3.2.S.7.3.4 Stability Data Tables for additional stability data.

Exposure Conditions	% Pregabalin (w/w)	% Lactam (w/w)
0.1N HCL, 80°C, 24 hours	94.9	3.3
0.1N NaOH, 80°C, 6 hours	81.8	15.0

- Photolysis - The ultraviolet spectra of pregabalin dissolved in an aqueous media demonstrates no absorption occurring above 250 nm. With no chromophores present, normal mechanisms for photodegradation in the environment are not likely to apply. Refer to Section 3.2.S.1.3 General Properties.

iv. Environmental Concentrations

(1) Expected Introduction Concentration (EIC):

$$EIC_{aquatic}\ (ppm) = A \times B \times C \times D$$

Where: A = kg/yr produced for direct use (Confidential Appendix 1).
B = 1/L/day entering POTWs*.
C = years/365 days.
D = 1×10^6 mg/kg (conversion factor).

* 1.214×10^{11} L/day entering POTWs

The EIC entering the external aquatic environment ($EIC_{aquatic}$) from POTWs has been calculated (Confidential Appendix 2). The calculations are based on total projected usage of pregabalin. Using a conservative approach, no adjustments have been made to account for metabolism, other environmental depletion mechanisms, or for the dilution of wastewater effluents into the receiving waters.

(2) Expected Environmental Concentration (EEC):

The Expected Environmental Concentration (EEC), which is sometimes referred to as the Predicted Environmental Concentration (PEC), is calculated as follows:

$$PEC = EIC_{aquatic} \times [(100 - R)/(100 \times DF)]$$

Where: %Removal (R) = 0.24.
Dilution Factor (DF) = 10.

The PEC refines the original EIC estimate by accounting for removal on sludge during wastewater treatment and subsequent dilution into the receiving waters. The PEC was calculated using 0.24% for removal on sludge, based on an experimentally determined sludge sorption coefficient (K_d), and a dilution factor of 10 for dilution of waste water effluents into receiving waters (Confidential Appendix 3).

v. Summary

Pregabalin will enter the aquatic environment through effluents discharged by POTWs. Pregabalin is not volatile and therefore will not enter the air compartment. As noted in the Guidance for Industry document, generally, only a fraction of sludge from POTWs would be applied to soil. Based on the $K_{d\ sludge}$ for pregabalin, sludge applied to land would not result in a significant concentration of pregabalin in the soil compartment. Based on these environmental transport considerations, and an assessment of the physical-chemical properties, pregabalin will reside in the aquatic compartment. Consequently, environmental effects data were generated on aquatic species.

Pregabalin is not anticipated to be rapidly removed from the aquatic compartment through the depletion mechanisms of sorption, biodegradation, hydrolysis, and photolysis. Its removal from the environment is likely to result from microbial biotransformation and chemical degradation. Pregabalin, as an amino acid, has the potential to be co-metabolized or biodegraded as other aliphatic acids and/or amino substituted aliphatic acids.[4] Based on the stability data, there is also a

potential for pregabalin to slowly degrade in the environment through lactamization.

b. Environmental Effects of Released Substances

Refer to Data Summary Table (Appendix 1) for an overview of the environmental effects data for pregabalin.

i. Microbial Inhibition Testing - The microbial inhibition concentration (MIC) for all microorganisms tested is >995 mg/L. Based on this data, pregabalin has no significant potential to inhibit microorganisms and therefore would not disrupt wastewater treatment processes. Refer to Confidential Appendix 7.

ii. Tiered Ecotoxicity Testing - Tiered testing followed the approach described in the EA Guidance for Industry Document.[2] Effects testing was conducted in a tiered sequence, starting with acute testing. Testing progresses to more advanced tiers when the $L(E)C_{50}$/EIC ratios meet or exceed the decision criteria set for each tier. Advanced tiers require either acute testing on additional species or chronic testing in the most sensitive species previously tested.

Using a conservative approach, the acute toxicity of pregabalin was determined using 3 species from different taxonomic classes and with different functions within the aquatic ecosystem. Refer to Confidential Appendices 8 through 10.

Tier 1 and Tier 2 (Acute Ecotoxicity - Base Set Aquatic) - 3 Species

Decision criteria $L(E)C_{50}$/EIC ratio is ≥100.

Species	$L(E)C_{50}$
Daphnia magna	>1000 mg/L
Rainbow trout	>1000 mg/L
Green alga	>300 mg/L

The $L(E)C_{50}$/EIC ratio for green alga is >100 indicating no further testing is required.

iii. Predicted No Effect Concentration (PNEC)

The PNEC is calculated by applying an assessment factor (AF) to the effects data developed during the tiered testing.

$$PNEC = NOEC \text{ or } L(E)C_{50}/AF$$

The assessment factor represents the extent of uncertainty in extrapolating test data on a limited number of species to the natural environment. In general, the greater number of species tested and the longer the duration of the tests, the smaller the degree of uncertainty and the size of the assessment factor.

The PNEC for pregabalin is based on green alga, the most sensitive species and was calculated using the standard tier 2 assessment factor of 100. The PNEC for pregabalin is 3 mg/L.

iv. Summary

The ecotoxicity of pregabalin to 3 aquatic species was determined using either a FDA TAD Test Protocol or an OECD Test Guideline. Green alga was the most sensitive environmental species tested and therefore was used to determine the PNEC. For each species tested, the No Observable Effect Concentration (NOEC) is >300 mg/L and significantly greater than the EIC. It is therefore anticipated that pregabalin would not have an adverse affect on the environment.

c. Summary

Upon approval of the subject NDA, introduction of pregabalin into the environment through use and disposal by consumers is projected to result in an insignificant amount of pregabalin in the environment.

Based on the PEC/PNEC risk assessment, it is unlikely that pregabalin represents a risk to the aquatic environment. The PEC/PNEC risk assessment for total pregabalin usage was based on green alga, the most sensitive species tested. This risk assessment was conducted using a conservative estimate for the PEC. No adverse environmental effect was identified in this assessment, as demonstrated by a calculated PEC/PNEC ratio of approximately 4 orders of magnitude <1.0, the

threshold of concern. The PEC/PNEC risk assessment based on pregabalin usage is provided in Confidential Appendix 4.

Analysis of current data provides that "**No Further Action**" is required since the PEC/PNEC is substantially <1.0, and the green alga NOEC is substantially less than the PEC.

Section Two—Use of Fauna or Flora

The subject application does not include the use of fauna or flora.

7. MITIGATION MEASURES:

No adverse environmental effects have been identified. No mitigation measures are required.

8. ALTERNATIVES TO THE PROPOSED ACTION:

No potential effects have been identified for this proposed action. No alternatives to the proposed action are required.

9. LIST OF PREPARERS:

Richard T. Williams, Assistant Director, Environmental Sciences, Chemical Research and Development, Pfizer Global Research and Development. PhD in Microbiology/Ecology with 21 years of experience in EH&S, including 11 years experience with Chemical Research and Development.

Jon F. Ericson, Project Leader, Environmental Sciences, Chemical Research and Development, Pfizer Global Research and Development. Analytical chemist with MS and 17 years experience in drug metabolism and environmental sciences.

Lisa A. Constantine, Senior Chemical Safety and Control Coordinator, Environmental Sciences, Chemical Research and Development, Pfizer Global Research and Development. BS in Chemistry; MBA, Certified Industrial Hygienist with 18 years experience in EH&S, including 4 years experience with Chemical Research and Development.

The contract testing laboratory used for all studies is included in the relevant confidential appendices.

10. REFERENCES:

[1] "Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications," Center for Drug Evaluation and Research (CDER), Jul 1998.

[2] "A Study of the Mass Balance and Metabolism of [^{14}C] CI-1008 (Pregabalin) in Healthy Volunteers: Protocol 1008-5," Total Renal Pharmaceutical Research Institute, Inc, Feb 2000.

[3] "Hine J, Mookerjee PK. "The Intrinsic Hydrophilic Character of Organic Compounds. Correlations in Terms of Structural Contributions," *J. Org. Chem.* 1975;40:292-98 (Available upon request).

[4] Dias FF, Alexander M. "Effect of Chemical Structure on the Biodegradability of Aliphatic Acids and Alcohols," *Applied Microbiology*, 1971;22:1114-8

11. APPENDICES:

Nonconfidential:

1. Data Summary Table
2. Abbreviations

Confidential:

Projected Usage:

1. Projected Total Usage of Pregabalin

EIC/PEC/PNEC:

2. Basis for Expected Introduction Concentration (EIC) From Use Into the External Aquatic Environment
3. Basis for Predicted Environmental Concentration (PEC) From Use Into the External Aquatic Environment
4. Basis for PEC/PNEC Calculation

Environmental Fate Studies:

5. Determination of Sorption and Desorption Properties, TAD 3.08

6. Determination of Aerobic Biodegradation in Water, TAD 3.11

Environmental Effect Studies:

7. Determination of Microbial Growth Inhibition, TAD 4.02
8. Acute Toxicity to Daphnids (*Daphnia Magna*) Under Static Conditions, TAD 4.08
9. Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions, OECD 203
10. Toxicity to Freshwater Green Alga (*Pseudokirchneriella subcapitata*), OECD 201

12. **CERTIFICATION:**

The undersigned official certifies that the information presented is true, accurate, and complete to the best of Pfizer Inc's knowledge.

Name: Richard T. Williams, Ph.D.

Title:
Assistant Director,
Environmental Sciences

Department:
Chemical Research and Development
Pfizer Global Research and Development,
Groton, CT 06340

Richard T. Williams

Signature

15 April 2003

Date

APPENDIX 1

Data Summary Table
(Page 1 of 2)

Physical/Chemical Characterization	
Melting Point	190°C
Ultraviolet - Visible Spectrum	**Ext. Coefficient (L/mol-cm)**
194 nm	256
207 nm	40.1
216 nm	44.2
Water Solubility	**(mg/mL)**
pH 3.7	107
pH 7.4	32
pH 10.1	47
Dissociation Constant (pKa)	4.2
	10.6
Octanol/Water Partition Coefficient	**(log K_{ow})**
pH 1	-1.90
pH 4	-1.43
pH 7.4	-1.35
Vapor Pressure (estimate)	1×10^{-7} mm Hg
Sludge Sorption Coefficient (K_d)	13.3
Depletion Mechanisms	
Hydrolysis at Environmental Conditions	Stable
Aerobic Sludge Biodegradation (B.A.S.)	-2.19% after 28 days
Photolysis: half life (days)	Not applicable

Data Summary Table
(Page 2 of 2)

Environmental Effects	
Microbial Inhibition (MIC)	**(mg/L)**
Aspergillus niger	>1000
Trichoderma viride	>1000
Clostridium perfringens	>997
Bacillus subtilis	>1000
Nostoc sp.	>1000
Acute Toxicity	
Daphnia Magna 48-hour EC_{50}	>1000
Rainbow trout 96-hour LC_{50}	>1000
Green alga 72-hour EC_{50}	>300
Daphnia Magna 48-hour NOEC	1000
Rainbow trout 96-hour NOEC	1000
Green alga 72-hour NOEC	>300

APPENDIX 2

Abbreviations

The following is a list of abbreviations and their definitions. They are grouped according to their use in the Environmental Assessment.

Regulatory

EA	Environmental Assessment
FDA	Food and Drug Administration
CDER	Center for Drug Evaluation and Research
NDA	New Drug Application
FOIA	Freedom of Information Act

Dosage Form, Packaging and Containers

HDPE	High Density Polyethylene
IM	Intramuscular
IV	Intravenous
PVC	Polyvinyl Chloride

Environmental Tests

C_{ss}	Concentration of substance on POTW suspended solids
C_{ww}	Concentration of substance in POTW aqueous phase
EC_{50}	Effective Concentration for 50% of test population
K_d	Sludge sorption coefficient
K_{oc}	Sorption coefficient corrected for organic content
LC50	Lethal Concentration to 50% of test population
$L(E)C_{50}$	Lethal or Effective Concentration for 50% of test population
Log K_{ow}	Log value of the octanol-water partition coefficient
MIC	Minimum Inhibitory Concentration
NOEC	No Observed Effect Concentration
OECD	Organization for Economic Co-operation and Development
pKa	Dissociation Constant
SW	Sludge wasted in grams
TAD	Technical Assistance Document
Vp	Vapor Pressure
POTW	Publicly Owned Treatment Works

Abbreviations (con't)

Environmental Models

A	Usage in Mature Market in Kilograms (Kg)
AF	Assessment Factor
D	Dilution
DF	Dilution Factor
EEC	Expected Environmental Concentration
EIC	Expected Introduction Concentration
P	Population in millions
PEC_{air}	Predicted Environmental Concentration in air
PEC_{soil}	Predicted Environmental Concentration in soil
PEC_{water}	Predicted Environmental Concentration in water
PEC/PNEC	Ratio of Predicted Environmental Concentration to Predicted No Effect Concentration
PNEC	Predicted No Effect Concentration
R	Percent removed via sorption, hydrolysis, biodegradation
t½	Half life
V	Volume (L) /capita/day

Units

C	Celsius
kg/yr	Kilograms per year
mg	Milligrams
mg/kg	Milligrams per kilogram
mg/mL	Milligrams per milliliter
mg/L	Milligrams per liter
mg a.i./L	Milligrams of activity per liter
ng/L	Nanograms per liter
nm	Nanometers
ppb	Parts per billion (µg/L)
ppt	Parts per trillion (ng/L)
µg/kg	Micrograms per kilogram
µg/L	Micrograms per liter

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