CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-427

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

NDA 20-427

Sabril (vigabatrin)
Tablets

Ovation Pharmaceuticals, Inc.

Monica D. Cooper, Ph.D.
ONDQA Pre-Marketing Assessment
Division I/Branch I

Reviewed for the Division of Neurology Products (DNP)
HFD-120

Table of Contents

Chemistry Review Data Sheet

1. NDA 20-427

2. REVIEW #: 10

3. REVIEW DATE: 04-Jun-2009

4. REVIEWER: Monica D. Cooper, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 20-427 (Original Submission)	29-Apr-1994
Amendment N000 BZ (CMC update here)	23-Dec-2005
Amendment N000 BZ (CMC update here)	10-Oct-2006
Amendment N000 BZ	01-Mar-2007
Major Amendment N000 AZ	28-Dec-2007
Amendment N000 BC (Response to IR Letter)	26-Jun-2008
Amendment N000 BC (Revised DP Specification)	25-Jul-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment N000 BZ (Stability Update)	30-Jan-2009
Amendment N000 BC (Updated Facility Information)	05-Feb-2009
Amendment N000 BC (Information on Product Launch Batches)	25-Mar-2009
Amendment N000 BC (Syringe Durability Studies for Sabril for Oral Solution – *Note*: This amendment was sent to both Sabril NDAs by mistake and will be evaluated in NDA 22-006 CMC Review #1)	02-Apr-2009
Amendment (N000 BC) (New DP Facilities and Supporting Data)	30-Apr-2009

7. NAME & ADDRESS OF APPLICANT:

Name	Ovation Pharmaceuticals, Inc.
Address	4 Parkway North, Suite 200 Deerfield, IL 60015
Representative	Jenny Swalec Director, Global Regulatory Affairs
Telephone	847-282-1066
FAX Number	847-317-9112

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name	Sabril
Non-Proprietary Name (USAN)	vigabatrin
Code Names	MDL 71,754
Chemistry Type	1
Submission Priority	P

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

10. PHARMACOL. CATEGORY: Anticonvulsant (for complex partial seizures)

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 500 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X__Rx _____OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

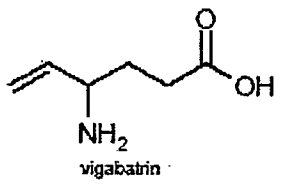
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

Chemical Names: (1) 4-amin-5-hexenoic acid,
(2) (±)-4-amino-hexenoic acid,
(3) dl-4-amino-5-hexanoic acid,
(4) vinyl γ-aminobutyric acid, and
(5) vinyl GABA

US Adopted Name (USAN): vigabatrin
International Nonproprietary Name (INN): vigabatrin
Laboratory Codes: MDL 71,754



vigabatrin

Chemical Formula: $C_6H_{11}NO_2$
Molecular Weight: 129.16
CAS Number: 60643-86-9

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED
[redacted]	III	[redacted]	[redacted]	1	Adequate	05-Jun-2008
	III			3	Adequate	N/A
	III			3	Adequate	N/A
	III			3	Adequate	N/A
	III			3	Adequate	N/A

b(4)

Chemistry Review Data Sheet

[redacted]	III	[redacted]	3	Adequate	N/A
	III		3	Adequate	N/A
	III		3	Adequate	N/A

b(4)

[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
N/A		

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	20-May-2009	M. Stock
LNC	N/A	----	----
Methods Validation	*Not Necessary*	----	----
DMEPA	Tradename: Sabril Acceptable	01-May-2009	T. Jones-Smith
EA	Categorical Exclusion: Acceptable	05-Aug-2008	H. Sarker (CMC Review #9)
Microbiology	N/A		

The Chemistry Review for NDA 20-427

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This new drug application (20-427) is recommended for **APPROVAL** from the perspective of chemistry, manufacturing, and controls. All CMC deficiencies were resolved in NDA 20-427 CMC Review #9 (H. Sarker, 05-Aug-2008).

Due to the postponement of the Sabril Advisory Committee meeting until January 2009, the NDA review cycle was extended beyond the closure of the drug product manufacturing facility at the end of 2008. The applicant submitted new drug product facilities and supporting data in the amendment dated 30-Apr-2009.

The Office of Compliance has given an overall acceptable recommendation for the manufacturing and testing facilities (see Establishment Evaluation Summary at the end of this review).

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

There are no Phase 4 commitments.

II. Summary of Chemistry Assessments

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

Vigabatrin is an oral anti-epilepsy drug, which was first approved in the United Kingdom in 1989 and is currently approved in over 50 countries. Approved indications include monotherapy for the treatment of Infantile Spasms and for the treatment of partial epilepsy in subjects who have not responded adequately to other anti-epilepsy drugs. Vigabatrin is a selective and irreversible inhibitor of gamma-aminobutyric acid transaminase (GABA-T), which is the enzyme responsible for the metabolism of the central nervous system (CNS) inhibitory neurotransmitter gamma-aminobutyric acid (GABA). The mechanism of action is dose-dependent inhibition of GABA-T and consequent increased levels of GABA in the CNS.

Drug Substance

The drug substance, vigabatrin, is a small, chemically-synthesized, organic molecule with the chemical name (±)-4-amino-5-hexenoic acid. Vigabatrin has one chiral center and is a racemic mixture of the R and S enantiomers. It is a white to off-white [redacted] powder with a melting point of 171 – 176°C. Vigabatrin is not hygroscopic; however, it is highly soluble in aqueous media. Since vigabatrin is an amino acid, it has two ionizable groups – a carboxylic acid (pKa = 4.0) and an amine (pKa = 9.7). [redacted] polymorphs (Form I and Form [redacted] have been identified – [redacted] is metastable, has been rarely observed (not in any production lots), and converts to Form I under ambient storage conditions over a period of months. Form I is the thermodynamically stable form and is the form developed by the applicant. Forms I [redacted] are readily distinguished by IR. b(4)

The drug substance manufacturing process involves a [redacted] A retest date of [redacted] granted for the bulk drug substance when stored at controlled room temperature (see NDA 20-427 CMC Review #9, H. Sarker). The drug substance is stored in [redacted] b(4)

Drug Product

The drug product is an oval, biconvex, white to off-white, film-coated tablet with a score line on one side and "OV 111" engraved on the other side. Each tablet contains 500 mg of vigabatrin. The drug product is manufactured using [redacted] b(4)

Sabril Tablets (500 mg) will be supplied in 100-count (commercial configuration) and 6-count (physician samples) [redacted] closures. The applicant proposed a 36-month expiration date for the drug product. In a stability update **(Amendment dated 30-Jan-2009)**, 36 months of long-term stability data were provided for the 3 primary registration batches. Thus, **a 36-month shelf-life is appropriate** for the drug product when stored in [redacted] bottles at controlled room temperature. b(4)

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

As noted above, Sabril (vigabatrin) Tablets (500 mg) will be supplied in one commercial configuration – a 100-count [redacted] bottle (120 cc). In addition, physician samples will be supplied in 6-count [redacted] bottles (30 cc). The usual adult dose is 3 g per day in BID dosage. The dose is gradually increased, beginning at 1 g per day and increasing to 3 g per day (as the maximum daily dose). b(4)

C. Basis for Approvability or Not-Approval Recommendation

This new drug application (20-427) is recommended for **APPROVAL** from the perspective of chemistry, manufacturing, and controls. All of the CMC deficiencies were resolved in CMC Review #9 (H. Sarker, 05-Aug-2008).

III. Administrative

A. Reviewer's Signature

/s/ M.D. Cooper, Ph.D.

B. Endorsement Block

Chemistry Reviewer:	Monica D. Cooper, Ph.D.
Pharmaceutical Assessment Lead:	Martha Heimann, Ph.D.
Branch Chief:	Ramesh Sood, Ph.D.
Project Manager:	Tamy Kim

C. CC Block

Orig. NDA 20-427
HFD-120/Division File

43 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry 34

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/s/

Monica Cooper
6/4/2009 03:47:16 PM
CHEMIST

Ramesh Sood
6/5/2009 07:48:42 AM
CHEMIST

NDA 20-427

Sabril
(vigabatrin)
Tablets

Ovation Pharmaceuticals, Inc.

Haripada Sarker, Ph.D.
ONDQA, DPA I

Reviewed for the Division of Neurology Products (DNP)
HFD-120

N20-427
CMC Review #9

Table of Contents

Chemistry Review Data Sheet

1. NDA 20-427

2. REVIEW #9

3. REVIEW DATE: 05-Aug-2008

4. REVIEWER: Haripada Sarker, Ph.D. (Revisions by M. Cooper, Ph.D.)

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 17,213	February 19, 1980
NDA 20-427 (original submission)	April 29, 1994

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (N-000) BZ (CMC update here)	December 23, 2005
Amendment (N-000) BZ (CMC update here)	October 10, 2006
Amendment (N-000) BZ	March 1, 2007
Major Amendment (N-000) AZ	December 28, 2007
Amendment (N-000) BC (Response to IR Letter)	June 26, 2008
Amendment (N-000) BC (Revised DP Spec)	July 25, 2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Ovation Pharmaceuticals, Inc.
Address:	4 Parkway North, Suite 200 Deerfield, IL 60015
Representative:	Jenny Swalec
Telephone:	847-282-1066

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Sabril
b) Non-Proprietary Name (USAN): Vigabatrin
c) Code Name/#: MDL 71,754
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 1
- Submission Priority: P

e) Proposed Trade Name: Sabril

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

10. PHARMACOL. CATEGORY: Anticonvulsant (indicated as an add-on therapy for the treatment of complex partial seizures with or without secondary generalization in adults)

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 500 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

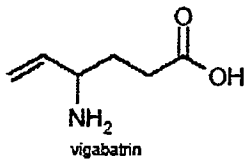
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

Structure:



vigabatrin

Name (drug substance)	Vigabatrin
Chemical Name (USAN)	Vigabatrin
Chemical Name	(±)-4-amino-5-hexenoic acid, 4-amino-5-hexenoic acid, dl-4-amino-5-hexanoic acid, vinyl γ-aminobutyric acid, vinyl GABA
CAS number	60643-86-9
Molecular Weight	129.16
Molecular Formula	$C_6H_{11}NO_2$
Structural formula	As above

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COM-PLETED	COMMENTS (LOA date)
[redacted]	III	[redacted]	[redacted]	1	Adequate	05-Jun-2008	01-Jun-2005
	III			3	Adequate	N/A	24-May-2005
	III			3	Adequate	N/A	24-May-2005
	III			3	Adequate	N/A	26-Aug-2005
	III			3	Adequate	N/A	30-Aug-2005
	III			3	Adequate	N/A	30-Aug-2005
	III			3	Adequate	N/A	31-Aug-2005
	III			3	Adequate	N/A	01-Jun-2006

b(4)

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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: None

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	27-Oct-2006	J. D. Ambrogio
Biopharm	N/A	N/A	N/A
DMETS	Acceptable	18-Dec-2006	Judy Parker
Methods Validation	*Not Necessary*	--	--
EA (Categorical Exclusion)	Acceptable	See Review Date Above	Haripada Sarker
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 20-427

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for **APPROVAL** from the standpoint of chemistry, manufacturing and controls.

A letter was sent to the applicant on 10-Jun-2008 outlining the information needed to complete this application. The applicant responded to the issues in amendments dated 26-Jun-2008 and 25-Jul-2008. All of the CMC deficiencies were resolved satisfactorily.

The Office of Compliance has given an overall acceptable recommendation for the manufacturing and testing facilities (see Establishment Evaluation Summary at the end of this review).

The following item should be included in the action letter –

- **Based on your primary and supportive stability data, a 36-month expiration date is granted for the drug product when stored at controlled room temperature in 100-count [redacted] bottles and 6-count [redacted] bottles (physician samples).** b(4)

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

N/A

II. Summary of Chemistry Assessments

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

Vigabatrin is an oral anti-epilepsy drug, which was first approved in the United Kingdom in 1989 and is currently approved in over 50 countries. Approved indications include monotherapy for the treatment of Infantile Spasms and for the treatment of partial epilepsy in subjects who have not responded adequately to other anti-epilepsy drugs. Vigabatrin is a selective and irreversible inhibitor of gamma-aminobutyric acid transaminase (GABA-T), which is the enzyme responsible for the metabolism of the central nervous system (CNS) inhibitory neurotransmitter gamma-aminobutyric acid (GABA). The mechanism of action is dose-dependent inhibition of GABA-T and consequent increased levels of GABA in the CNS.

Drug Substance

The drug substance, vigabatrin, is a small, chemically-synthesized, organic molecule with the chemical name (±)-4-amino-5-hexenoic acid. Vigabatrin has one chiral center and is a racemic mixture of the R- and S-enantiomers. It is a white to off-white [redacted] powder with a melting point of 171 – 176°C. Vigabatrin is not hygroscopic; however, it is highly soluble in aqueous media. Since vigabatrin is an amino acid, it has two ionizable groups – a carboxylic acid (pKa = 4.0) and an amine (pKa = 9.7). [redacted] polymorphs (Form I [redacted] have been identified - [redacted] is metastable, has been rarely observed (not in any production lots), and converts to Form I under ambient storage conditions over a period of months. Form I is the thermodynamically stable form and is the form developed by the applicant. Forms I [redacted] are readily distinguished by IR. b(4)

The drug substance manufacturing process involves a [redacted] A retest date of [redacted] is appropriate for the bulk drug substance when stored at controlled room temperature. The drug substance is stored in [redacted] b(4)

Drug Product

The drug product is an oval, biconvex, white to off-white, film-coated tablet with a score line on one side and "OV 111" engraved on the other side. Each tablet contains 500 mg of vigabatrin. The drug product is manufactured using [redacted] b(4)

Sabril Tablets (500 mg) will be supplied in 100-count (commercial configuration) and 6-count (physician samples) [redacted] bottles, [redacted] closures. The applicant proposed a 36-month expiration date for the drug product. Based on the primary and supportive stability data provided to-date, **a 36-month shelf-life is appropriate** for the drug product when stored at controlled room temperature. b(4)

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

As noted above, Sabril (vigabatrin) Tablets (500 mg) will be supplied in one commercial configuration – a 100-count [redacted] bottle (120 cc). In addition, physician samples will be supplied in 6-count [redacted] bottles (30 cc). The usual adult dose is 3 g per day in BID dosage. The dose is gradually increased, beginning at 1 g per day and increasing to 3 g per day (as the maximum daily dose). b(4)

C. Basis for Approvability Recommendation

This new drug application (20-427) is recommended for **APPROVAL** from the perspective of chemistry, manufacturing, and controls. A letter was sent to the applicant on 10-Jun-2008 outlining the information needed to complete this application. The applicant responded to the

issues in amendments dated 26-Jun-2008 and 25-Jul-2008. All of the CMC deficiencies were resolved.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name: Haripada Sarker, Ph.D. (Revisions by M. Cooper, Ph.D.)
Chemistry Branch Chief: Ramesh Sood, Ph.D.
Project Manager Name: Tamy Kim

C. CC Block

83 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 3B

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/s/

Monica Cooper
8/5/2008 02:34:09 PM
CHEMIST
For revisions to the draft review by Hari Sarker, Ph.D.

Haripada Sarker
8/5/2008 02:47:59 PM
CHEMIST

Ramesh Sood
8/5/2008 03:14:03 PM
CHEMIST

Sabril™
(vigabatrin)
Tablet

NDA 20-427

Division Director Review
Chemistry, Manufacturing, and Controls

Applicant: Ovation Pharmaceuticals, Inc.
4 Parkway North, Suite 200
Deerfield, IL 60015

Indication: Anticonvulsant, indicated as an add-on therapy for the treatment of complex partial seizures with or without secondary generalization in adults

Presentation: Film-coated, white, oval, biconvex, immediate release, tablet for oral administration. Each tablet contains 500 mg vigabatrin, is scored on one side, and debossed with "OV 111" on the other side.

Tablets are packaged in white, opaque, [redacted] bottles, at 100 count (commercial) and at 6-count (physician sample), both with [redacted] closures. b(4)

EER Status:		Acceptable	27-OCT-2006
Consults:	EA – OPS	No significant impact	23-AUG-2002
	Methods Validation –	Revalidation by Agency not requested.	
Original Submission:		29-APR-1994	
Post-Approval Agreements:		None	

Drug Substance:

Vigabatrin is an irreversible inhibitor of gamma-aminobutyric acid transaminase (GABA-T) developed for treatment of epilepsy. The drug substance, vigabatrin, is a small, synthetic, New Molecular Entity (NME) with an empirical formula of $C_6H_{11}NO_2$ and a molecular weight of 129.16. Vigabatrin has one chiral center and is a racemic mixture of the R- and S- enantiomers. Known chemically as (±)-4-amino-5-hexenoic acid, it is a white to off-white, non-hygroscopic, [redacted] powder with a melting range of 171-176°C. Vigabatrin is freely soluble in water (330 mg/mL) and in aqueous solvents; slightly soluble in methanol; very slightly in ethanol and chloroform; and practically insoluble in toluene and n-hexane. The n-octanol/water partition coefficient of vigabatrin is about 0.011 at physiologic pH. Vigabatrin is an amino acid with two b(4)

ionizable groups, a carboxylic acid (pKa = 4.0) and an amine (pKa = 9.7); the pH of an aqueous solution of vigabatrin ranges from 6.342 to 6.972. [redacted] polymorphs and one metastable form have been identified, with form I being the thermodynamically stable form and that form manufactured by the applicant.

b(4)

The bulk drug substance is [redacted]

The structure of vigabatrin was elucidated using several analytical and spectrophotometric techniques, including elemental analysis, infrared spectroscopy (IR), multinuclear (^{1}H and ^{13}C) magnetic resonance (NMR) spectroscopy, ultraviolet (UV) spectroscopy, mass spectrometry, optical rotation, [redacted]

The proposed release specification for vigabatrin includes appearance, identification by IR spectroscopy, melting range, water content by Karl-Fischer, heavy metals, residue on ignition, residual solvents by gas chromatography (GC), impurities and related substances by reverse phase – high performance liquid chromatography (RP-HPLC), specific optical rotation, particle size by sieve analysis, and assay by RP-HPLC. The proposed regulatory methods are either compendial or were developed and validated for their intended purpose. The primary reference standard for drug substance, manufactured by commercial process, has been characterized by the proposed regulatory methods as well as additional methods. The impurity and degradation profiles have been investigated. Reference standards for known impurities have been synthesized and fully characterized.

The stability data for a dozen commercial batches support a [redacted] retest period for the bulk drug substance stored inside [redacted] contained in [redacted] controlled room temperature, 25°C/60% RH.

b(4)

Conclusion: Drug substance is acceptable.

Drug Product:

Sabril (vigabatrin) tablets are film-coated, white, oval, biconvex, immediate release, tablets available in one strength of 500 mg. Each tablet is scored on one side and debossed with "OV 111" on the other side. Tablets are packaged in white, opaque, [redacted] bottles, at 100-count and at 6-count (physician samples), both with [redacted] closures.

The drug product is manufactured beginning with [redacted]

b(4)

The composition of the 500 mg strength, oval tablet is vigabatrin (500.00 mg), microcrystalline cellulose NF [redacted] sodium starch glycolate NF [redacted], povidone [redacted]

mg), magnesium stearate NF [redacted], to give a core tablet weight of [redacted] Following [redacted] film-coating, the total film-coated tablet weight is 685.00 mg. b(4)

The release specification for drug product includes: appearance, identification by RP-HPLC, identification by IR, related substances by RP-HPLC, dissolution, assay by RP-HPLC, content uniformity, weight, and microbial limits. The vigabatrin reference standard for drug product is the same as that for drug substance. The proposed regulatory methods are either compendial or were developed and validated for their intended purpose.

The stability data support expiration dating of 36 months for all strengths of drug product stored at controlled room temperature conditions [25° C (77° F); excursion permitted to 15-30° C (59-86° F)], and packaged in 100-count [redacted] bottles and in 6-count [redacted] bottles (physician samples). b(4)

Conclusion: Drug product is acceptable.

Additional Items:

- The applicant agreed to place one batch of drug substance per year on stability under long term conditions at 25°C/60% RH and tested throughout the commercial life of the drug substance.
- The applicant agreed to place on stability the first three commercial scale lots of the drug product, following the approved stability protocol, to firmly establish the proposed shelf life.
- The sponsor agreed to place on stability at least one commercial production lot of drug product, per year, following the approved stability protocol.
- All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.
- The analytical methods used for testing (release, stability, and in-process) are well known and widely used by the pharmaceutical industry; revalidation by Agency laboratories will not be requested.

Overall Conclusion:

From a CMC perspective, the application is recommended for **Approval.**

Blair A. Fraser, Ph.D.
Director
DPA I/ONDQA

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/s/

Blair Fraser
8/5/2008 03:52:26 PM
CHEMIST

JUL 27 1998

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-427	**CHEM. REVIEW # 12**	**REVIEW DATE**	21-JUL-98
SUBMISSION TYPE	**DOCUMENT DATE**	**CDER DATE**	**ASSIGNED DATE**
ORIGINAL	12-AUG-95	17-AUG-95	
AMENDMENT N(AZ)	24-APR-98	29-MAY-97	02-JUN-97

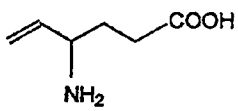
NAME AND ADDRESS OF APPLICANT

HOECHST MARION ROUSSEL, Inc.
10236 Marion Merell Park Drive
P.O. Box 9627
Kansas City, Missouri 64134-0627

DRUG PRODUCT NAME

Proprietary:	**SABRIL®** Tablets
USAN [1985]:	Vigabatrin
Code Name/Number:	MDL 71,754, RMI 71,754
Chem. Type/Ther. Class:	
PHARMACOLOGICAL CATEGORY/INDICATION	Epilepsy
DOSAGE FORM	Tablets
STRENGTHS	500 mg
ROUTE OF ADMINISTRATION	Oral
DISPENSED	XXX RX ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA
d,l-4-Amino-5-hexenoic acid (VG, GVG, VGB, Vinyl GABA)



$C_6H_{11}NO_2$ Mol. Wt. 129.16

Registry #: 60643-86-9, 68506-85-5

SUPPORTING & RELATED DOCUMENTS: IND 17,213 (Vigabatrin Tablets, Marion), [redacted] b(4)
Lepetit, Garessio, Italy - Vigabatrin manufacturer), 21 DMFs for containers/closures.

CONSULTS: According to the CDER Labeling and Nomenclature Committee, there is a potential conflict between proprietary names SABRIL and GABITRIL (AP NDA 20-646). The CGMP compliance status of the manufacturing facilities is ACCEPTABLE as of 11-SEP-97 (EER report is attached). Analytical methods for SABRIL Tablets and vigabatrin bulk drug substance are ACCEPTABLE for quality control and regulatory purposes.

REMARKS/COMMENTS: This amendment provides for responses to the approvable letter of November 26, 1997. The sponsor believes that the potential for medication errors related to similarities between the names Sabril (vigabatrin) and Gabitril (tiagabine HCl) is negligible, and that these two products are distinguishable. The sponsor agrees to adopt the following dissolution methodology and specification for Sabril 500 mg tablets: Q = [redacted] in 30 min (900 mL water at 37° ± 0.5°C, USP Apparatus II, paddle at 50 rpm). The expiration dating period is 36 months. Recommended storage conditions are: "Store at Controlled Room Temperature, 20°C to 25°C (68°F to 77°F) and [redacted] The REVIEW NOTES are attached. b(4)

CONCLUSIONS & RECOMMENDATIONS: Recommend APPROVAL of NDA 20-427.

M. Guzewska, Ph.D.

cc: Orig. NDA 20-427
HFD-120
HFD-120/MGuzewska
HF-120/Ware
HFD-810/JSimmons
R/D Init by: JSimmons/ 7.27.98

Filename: n20427.012

ER Establishment Evaluation Report for July 21, 1998

Application: NDA 20427/000
Stamp: 02-MAY-1994 Regulatory Due: 27-OCT-1998
Applicant: HOECHST MARION RSSL
9707
KANSAS CITY, MO 641340707

Priority: 1S
Action Goal:
Brand Name: SABRIL (VIGABATRIN) TABLET 500MG
Established Name:
Generic Name: VIGABATRIN
Dosage Form: TAB (TABLET)
Strength: 500 MG

Org Code: 120
District Goal: 30-JUL-1997

FDA Contacts: M. GUZEWSKA (HFD-120) 301-594-5571 , Review Chemist

Overall Recommendation:

ACCEPTABLE on 11-SEP-1997 by J. D AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 27-DEC-1995 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: [redacted]
DMF No:
AADA No:

b(4)

Profile: [redacted] OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 11-SEP-1997
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: [redacted]

Establishment: [redacted]
DMF No: [redacted]
AADA No.

b(4)

Profile: [redacted] OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 11-SEP-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment: 1510437
HOECHST MARION ROUSSEL
2110 EAST GALBRAITH RD
CINCINNATI, OH 45215

DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 11-SEP-1997
Decision: ACCEPTABLE

Responsibilities: FINISHED DOSAGE MANUFACTURER

Reason: **BASED ON FILE REVIEW**
DISTRICT RECOMMENDATION

Establishment: [redacted]

DMF No:
AADA No:

b(4)

Profile: [redacted] OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **11-SEP-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

FEB 2 1 1998

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-427 **CHEM.REVIEW #:** 11 **REVIEW DATE:** 05-Feb-98

SUBMISSION TYPE		DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL		12-Aug-95	17-Aug-95	
AMENDMENT	N(EL)	28-Oct-97	29-Oct-97	02-Feb-98
	N(EL)	13-Nov-97	14-Nov-97	02-Feb-98

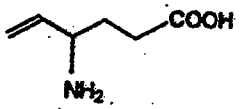
NAME & ADDRESS OF APPLICANT: HOECHST MARION ROUSSEL, Inc.
10236 Marion Merell Park Drive
P.O. Box 9627
Kansas City, MO 64134-0627

DRUG PRODUCT NAME
Proprietary: SABRIL® Tablets
Nonproprietary/USAN: Vigabatrin
Code Name/#: MDL 71,754, RMI 71,754
Chem.Type/Ther.Class:

PHARMACOL.CATEGORY/INDICATION: Epilepsy

DOSAGE FORM: Tablets
STRENGTHS: 500 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X Rx ____ OTC

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



Chemical Name(s):

d,l-4-Amino-5-hexenoic acid (VG, GVG, VGB, Vinyl GABA)

Molecular Formula: $C_6H_{11}NO_2$ Molecular Weight: 129.16

Registry #: 60643-86-9, 68506-85-5

SUPPORTING & RELATED DOCUMENTS:

IND 17,213 (Vigabatrin Tablets, Marion), [redacted], Garessio, Italy - Vagabatrin manufacturer), 21 DMFs for containers/closures. b(4)

CONSULTS:

According to the CDER Labeling and Nomenclature Committee, there is a potential conflict between proprietary names SABRIL and GABITRIL (AP NDA 20-646). The CGMP compliance status of the manufacturing facilities is ACCEPTIBLE as of 11-SEP-97. Analytical methods for SABRIL Tablets and vigabatrin bulk drug substance are ACCEPTABLE for quality control and regulatory purposes. The EA is adequate.

REMARKS/COMMENTS:

In these amendments, the sponsor included copy of the carton labeling for SABRIL (10/28/97) which could be found in the original NDA and had the old name Marion Merrell Dow Inc. and the final carton labeling (11/13/97).

CONCLUSIONS & RECOMMENDATIONS:

Recommend APPROVAL of NDA 20-427.

cc:
Orig. NDA 20-427
HFD-120/Division File
HFD-110/CunninghamD/2/5/98
HFD-120/MGuzewska
HFD-120/Ware
HFD-810/JSimmons

R/D Init by: SUPERVISOR 2.11.98

Danute G. Cunningham, Review Chemist
filename: 20427R11.NDA

OCT 28 1997

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-427

CHEM. REVIEW # 10 | **REVIEW DATE** 24-OCT-97

SUBMISSION TYPE	**DOCUMENT DATE**	**CDER DATE**	**ASSIGNED DATE**
ORIGINAL	12-AUG-95	17-AUG-95	
AMENDMENT N(AZ)	29-MAY-97	29-MAY-97	02-JUN-97

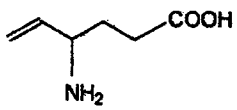
NAME AND ADDRESS OF APPLICANT

HOECHST MARION ROUSSEL, Inc.
10236 Marion Merell Park Drive
P.O. Box 9627
Kansas City, Missouri 64134-0627

DRUG PRODUCT NAME

Proprietary:	**SABRIL®** Tablets
USAN [1985]:	Vigabatrin
Code Name/Number:	MDL 71,754, RMI 71,754
Chem. Type/Ther. Class:	
PHARMACOLOGICAL CATEGORY/INDICATION	Epilepsy
DOSAGE FORM	Tablets
STRENGTHS	500 mg
ROUTE OF ADMINISTRATION	Oral
DISPENSED	XXX RX ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA
d,l-4-Amino-5-hexenoic acid (VG, GVG, VGB, Vinyl GABA)



$C_6H_{11}NO_2$ Mol. Wt. 129.16

Registry #: 60643-86-9, 68506-85-5

SUPPORTING & RELATED DOCUMENTS: IND 17,213 (Vigabatrin Tablets, Marion), [redacted] b(4)
Lepetit, Garessio, Italy - Vigabatrin manufacturer), 21 DMFs for containers/closures.

CONSULTS: According to the CDER Labeling and Nomenclature Committee, there is a potential conflict between proprietary names SABRIL and GABITRIL (AP NDA 20-646). The CGMP compliance status of the manufacturing facilities is ACCEPTABLE as of 11-SEP-97 (report attached). Analytical methods for SABRIL Tablets and vigabatrin bulk drug substance are ACCEPTABLE for quality control and regulatory purposes. The EA is adequate

REMARKS/COMMENTS: In this submission, the sponsor addresses deficiencies listed in the Agency's Not Approvable Letter dated April 28, 1995. All issues in the biopharmaceutics section of this letter have been satisfactorily resolved. The sponsor agrees to adopt the following dissolution methodology and specification for Vigabatrin 500 mg film-coated tablet: Q = [redacted] in 30 min (900 mL water at 37° ± 0.5°C, USP Apparatus II, paddle at 50 rpm). The proposed expiration dating of 36 months is acceptable (see Review #8 for stability data). Recommended storage conditions are: "Store at Controlled Room Temperature, 20°C to 25°C (68°F to 77°F) [redacted] b(4)

CONCLUSIONS & RECOMMENDATIONS: Recommend APPROVAL of NDA 20-427.

cc: Orig. NDA 20-427
[redacted]
HFD-120/MGuzewska 10.24.97
HF-120/Ware
HFD-810/JSimmons
R/D Init by: JSimmons/ 10-28-97

M. Guzewska, Ph.D., Chemist

Filename: n20427.010

for October 24, 1997

Application: NDA 20427/000 Priority: 1S Org Code: 120
Stamp: 02-MAY-1994 Regulatory Due: 29-NOV-1997 Action Goal: District Goal: 30-JUL-1997
Applicant: HOECHST MARION RSSL
9707
KANSAS CITY, MO 641340707
Brand Name: SABRIL (VIGABATRIN) TABLET 500M
Established Name:
Generic Name: VIGABATRIN
Dosage Form: TAB (TABLET)
Strength: 500 MG

FDA Contacts: M. GUZEWSKA (HFD-120) 301-594-5571 ;Review Chemist

Overall Recommendation:

WITHHOLD on 27-DEC-1995 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 11-SEP-1997 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 1810030
DOW CHEMICAL CO MICHIGAN DI
1803 BLDG/2030 WH DOW CENTER
MIDLAND, MI 48674
DMF No:
AADA No:

Profile: [redacted] OAI Status: NONE
Last Milestone: OC RECOMMENDAT 11-SEP-1997
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Responsibilities: [redacted]

b(4)

Establishment: [redacted]
DMF No: [redacted]
AADA No:

b(4)

Profile: [redacted] OAI Status: NONE
Last Milestone: OC RECOMMENDAT 11-SEP-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment: 1510437
HOECHST MARION ROUSSEL
2110 EAST GALBRAITH RD
CINCINNATI, OH 45215
DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDAT 11-SEP-1997
Decision: ACCEPTABLE
Reason: BASED ON FILE REVIEW
DISTRICT RECOMMENDATION
Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment: [redacted]
DMF No:

b(4)

AADA No:

Responsibilities:
DRUG SUBSTANCE MANUFACTURER

Profile: [redacted] OAI Status: NONE
Last Milestone: OC RECOMMENDAT 11-SEP-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

b(4)

OCT 24 1997

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-427

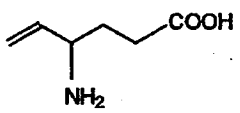
CHEM. REVIEW #9 **REVIEW DATE** 24-OCT-97

SUBMISSION TYPE	**DOCUMENT DATE**
Methods Validation Results (PHI-DO, HFR-MA100)	01-MAY-96
Methods Validation Results (DDA, St. Louis, MO, HFH-300)	05-APR-96
NAME AND ADDRESS OF APPLICANT	HOECHST MARION ROUSSEL, Inc. 10236 Marion Merell Park Drive P.O. Box 9627 Kansas City, Missouri 64134-0627
DRUG PRODUCT NAME	
Proprietary:	**SABRIL®** Tablets
Nonproprietary/USAN:	Vigabatrin
Code Name/Number:	MDL 71,754, RMI 71,754
Chem. Type/Ther. Class:	
PHARMACOLOGICAL CATEGORY/INDICATION	Epilepsy
DOSAGE FORM	Tablets
STRENGTHS	500 mg
ROUTE OF ADMINISTRATION	Oral
DISPENSED	XXX RX ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA
d,l-4-Amino-5-hexenoic acid (VG, GVG, VGB, Vinyl GABA)

$C_6H_{11}NO_2$ Mol. Wt. 129.16

Registry #: 60643-86-9, 68506-85-5



REMARKS/COMMENTS: The NDA methodology for SABRIL® (vigabatrin) Tablets has been evaluated as ACCEPTABLE for quality control and regulatory purposes by two laboratories: [redacted] The content of residual solvents was determined by the [redacted] lab only (The [redacted] lab did not have sufficient amount of the sample to do it). The completed worksheets are attached. b(4)

CONCLUSIONS & RECOMMENDATIONS: Analytical methods for SABRIL® Tablets and vigabatrin bulk drug substance are acceptable for quality control and regulatory purposes.

M. Guzewska, Ph.D., Chemist

cc: Orig. NDA 20-427
[redacted]
HFD-120/MGuzewska
HF-120/Ware

Filename: n20427.mv

DF

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

DEC 22 1995

NDA 20-427

CHEM. REVIEW # 8

REVIEW DATE 14-DEC-95

SUBMISSION TYPE	**DOCUMENT DATE**	**CDER DATE**	**ASSIGNED DATE**
ORIGINAL	12-AUG-95	17-AUG-95	
AMENDMENT .BC	17-JUL-95	19-JUL-95	19-JUL-95
AMENDMENT .BC	26-SEP-95	27-SEP-95	23-NOV-95

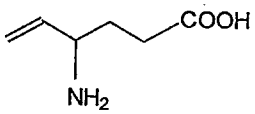
NAME AND ADDRESS OF APPLICANT

HOECHST MARION ROUSSEL, Inc.
10236 Marion Merell Park Drive
P.O. Box 9627
Kansas City, Missouri 64134-0627

DRUG PRODUCT NAME
Proprietary: **SABRIL®** Tablets
Nonproprietary/USAN: Vigabatrin
Code Name/Number: MDL 71,754, RMI 71,754
Chem. Type/Ther. Class:

PHARMACOLOGICAL CATEGORY/INDICATION Epilepsy
DOSAGE FORM Tablets
STRENGTHS 500 mg
ROUTE OF ADMINISTRATION Oral
DISPENSED XXX RX ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA
d,l-4-Amino-5-hexenoic acid (VG, GVG, VGB, Vinyl GABA)



$C_6H_{11}NO_2$ Mol. Wt. 129.16

Registry #: 60643-86-9, 68506-85-5

SUPPORTING & RELATED DOCUMENTS: see previous reviews
CONSULTS: Methods' Validation and evaluations of the CGMP Compliance Status of facilities are ongoing.
REMARKS/COMMENTS: A stability report on Sabril tablets is provided in the Amendment of 17-JUL-95. Based on the submitted data, the applicant requests the Agency to extend the expiration dating period for the tablets to **36 months** when packaged and stored as per the original NDA submission. In the NA letter of 28-APR-95, the Agency requested that the dissolution method and specification be changed to Q= [redacted] in 0.1N HCl (from Q= [redacted] in water). Based on the *in vitro/in vivo* results provided by the sponsor on 13-JUN-95, the Agency agreed to **water** as the medium but maintained its position of changing the specification to **Q=** [redacted] The updated Sabril tablet specifications to reflect the change in the dissolution spec from Q= [redacted] are provided in the Amendment of 26-SEP-95. As a result of the change in the dissolution spec, the stability data provided earlier, i.e. in the Amendment of 17-JUL-95, were re-evaluated to reflect the new dissolution spec of [redacted] The updated stability report as well as the request to approve a 36-month expiration dating for Sabril tablets are provided in the Amendment of 26-SEP-95. The provided data support the requested extention of the expiration dating period to 36 months. Statistical analysis of the results obtained at 25°C and 30°C suggests the expected shelf-life of at least 48 months for both of these storage conditions. The REVIEW NOTES are attached.

b(4)

CONCLUSIONS & RECOMMENDATIONS: Recommend that the expiration dating period for Sabril Tablets be extended to 36 months when packaged and stored as per the original NDA submission.

cc: Orig. NDA 20-427
HFD-120
HFD-120/MGuzewska/ 12.14.95
HFD-120/RPitts/CSO
HFD-120/SBlum
R/D Init by: SWB

SWB 12/22/95

M. Guzewska, Ph.D., Chemist

Filename: n20427.008

13 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 4

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS HFD-120

REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-427 **CHEM. REVIEW** #7 **REVIEW DATE** 04-APR-95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	29-APR-94	02-MAY-94	
AMENDMENT	26-JUL-94	28-JUL-94	
AMENDMENT .BC	09-FEB-95	10-FEB-95	
AMENDMENT .BC	24-MAR-95	27-MAR-95	
AMENDMENT .BC	15-FEB-95	28-FEB-95	
AMENDMENT .NC	27-FEB-95	28-FEB-95	
AMENDMENT .BC	08-MAR-95	09-MAR-95	10-MAR-95

NAME AND ADDRESS OF APPLICANT

MARION MERRELL DOW Inc.
10236 Marion Park Drive
P.O. Box 9707
Kansas City, Missouri 64134-0707

DRUG PRODUCT NAME

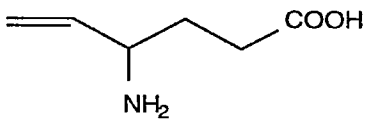
Proprietary: **SABRIL®** Tablets
Nonproprietary/USAN: Vigabatrin
Code Name/Number: MDL 71,754, RMI 71,754
Chem.Type/Ther.Class:

PHARMACOLOGICAL CATEGORY / INDICATION Epilepsy
DOSAGE FORM Tablets
STRENGTHS 500 mg
ROUTE OF ADMINISTRATION Oral
DISPENSED XXX RX ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

d,l - 4-Amino-5-hexenoic acid (VG, GVG, VGB, Vinyl GABA)

$C_6H_{11}NO_2$ Mol. Weight 129.16
CAS Registry Number 60643-86-9, 68506-85-5



SUPPORTING/RELATED DOCUMENTS: see Review #4

CONSULTS: The EER was requested on 12-JAN-95. The MV Package is ready to be send out.

REMARKS/COMMENTS: In response to the reviewer's request of 06-MAR-95 (telecon memo: .T09), revised stability protocols for vigabatrin produced at MMD's Garessio and Midland facilities are provided. Copies of Vigabatrin Stability Study Protocols are attached.

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-427, as amended, APPROVABLE subject to a satisfactory evaluation of all facilities. In addition, we expect sponsor's full cooperation in resolving problems that may arise during the validation of analytical methods.

cc: Orig. NDA 20-427
HFD-120
HFD-120/MGuzewska/MG 4.4.95
HFD-120/RPitts
HFD-120/SBlum
R/D Init by: SWB/ SWB 4/10/95

Maria E. Guzewska, Ph.D. Chemist

Filename: N020427.007

2 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 5

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS HFD-120

REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-427 **CHEM. REVIEW #6** **REVIEW DATE** 04-APR-95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	29-APR-94	02-MAY-94	
AMENDMENT	26-JUL-94	28-JUL-94	
AMENDMENT .BC	09-FEB-95	10-FEB-95	
AMENDMENT .BC	24-MAR-95	27-MAR-95	
AMENDMENT .BC	15-FEB-95	28-FEB-95	
AMENDMENT .NC	27-FEB-95	28-FEB-95	02-MAR-95

NAME AND ADDRESS OF APPLICANT

MARION MERRELL DOW Inc.
10236 Marion Park Drive
P.O. Box 9707
Kansas City, Missouri 64134-0707

DRUG PRODUCT NAME

Proprietary: **SABRIL®** Tablets
Nonproprietary/USAN: Vigabatrin
Code Name/Number: MDL 71,754, RMI 71,754
Chem.Type/Ther.Class:

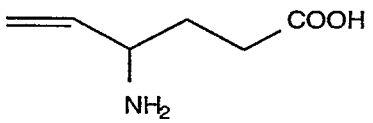
PHARMACOLOGICAL CATEGORY / INDICATION Epilepsy
DOSAGE FORM Tablets
STRENGTHS 500 mg
ROUTE OF ADMINISTRATION Oral
DISPENSED XXX RX ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

d,l - 4-Amino-5-hexenoic acid (VG, GVG, VGB, Vinyl GABA)

$C_6H_{11}NO_2$ Mol. Weight 129.16

CAS Registry Number 60643-86-9, 68506-85-5



SUPPORTING/RELATED DOCUMENTS: see Review #4

CONSULTS: The EER was requested on 12-JAN-95. The MV Package is ready to be send out.

REMARKS / COMMENTS: In response to the reviewer's request of 22-FEB-95 (telecon memo: .T07), stability protocols for the drug substance manufactured at both locations, i.e. in Midland, MI and in Garessio, Italy, are provided. The protocol for the Garessio material was originally submitted in the Amendment of 09-FEB-95, and the protocol for the drug substance from Midland is new. Both protocols are still inadequate since the proposed [redacted] for Garessio and Midland, resp.) do not comply with the ICH Guidelines. Stability samples from both manufacturing sites are also stored at 30°C (RH unknown) at the [redacted] facility. The deficiencies identified in the provided stability protocols were communicated to the sponsor by phone on 06-MAR-95 (telecon memo: T09). Stability protocols for vigabatrin drug substance, and a copy of the telecon memo are attached. b(4)

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-427, as amended, APPROVABLE subject to a satisfactory evaluation of all facilities, and a submission of adequate stability protocols for the drug substance. In addition, we expect sponsor's full cooperation in resolving problems that may arise during the validation of analytical methods.

cc: Orig. NDA 20-427
HFD-120
HFD-120/MGuzewska 4.4.95
HFD-120/RPitts
HFD-120/SBlum
R/D Init by: SWB/ 4/10/95

Maria E. Guzewska, Ph.D. Chemist

Filename: N020427.006

3 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 6

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS HFD-120

REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-427 **CHEM. REVIEW** #5 **REVIEW DATE** 04-APR-95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	29-APR-94	02-MAY-94	
AMENDMENT	26-JUL-94	28-JUL-94	
AMENDMENT .BC	09-FEB-95	10-FEB-95	
AMENDMENT .BC	24-MAR-95	27-MAR-95	
AMENDMENT .BC	15-FEB-95	28-FEB-95	02-MAR-95

NAME AND ADDRESS OF APPLICANT

MARION MERRELL DOW Inc.
10236 Marion Park Drive
P.O. Box 9707
Kansas City, Missouri 64134-0707

DRUG PRODUCT NAME

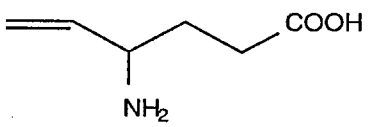
Proprietary: **SABRIL®** Tablets
Nonproprietary/USAN: Vigabatrin
Code Name/Number: MDL 71,754, RMI 71,754
Chem.Type/Ther.Class:

PHARMACOLOGICAL CATEGORY / INDICATION Epilepsy
DOSAGE FORM Tablets
STRENGTHS 500 mg
ROUTE OF ADMINISTRATION Oral
DISPENSED XXX RX ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

d,l - 4-Amino-5-hexenoic acid (VG, GVG, VGB, Vinyl GABA)

$C_6H_{11}NO_2$ Mol. Weight 129.16



CAS Registry Number 60643-86-9, 68506-85-5

SUPPORTING DOCUMENTS: see Review #4
RELATED DOCUMENTS: see Review #4

CONSULTS: The EER was requested on 12-JAN-95. The MV Package is ready to be send out.

REMARKS / COMMENTS: Information on a new, previously unidentified polymorph of vigabatrin is provided [redacted] This polymorph has appeared in only one production lot of the drug substance (Lot OP 196, [redacted] February 1994), is metastable, and converts to Form I upon storage at ambient conditions. Additional [redacted] polymorph [redacted] The polymorphic forms of vigabatrin (Form I [redacted] are readily distinguished using IR [redacted] The applicant proposes to take no action in the routine manufacture of vigabatrin drug substance for the following reasons: [redacted]

b(4)

[redacted]

CONCLUSIONS & RECOMMENDATIONS: NAI

cc: Orig. NDA 20-427
HFD-120
HFD-120/MGuzewska/mg 4.4.95
HFD-120/RPitts
HFD-120/SBlum
R/D Init by: SWB/ SWB 4/10/95

Maria E. Guzewska, Ph.D. Chemist

Filename: N020427.005

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS HFD-120

REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-427 **CHEM. REVIEW** #4 **REVIEW DATE** 04-APR-95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	29-APR-94	02-MAY-94	
AMENDMENT	26-JUL-94	28-JUL-94	
AMENDMENT .BC	09-FEB-95	10-FEB-95	
AMENDMENT .BC	24-MAR-95	27-MAR-95	28-MAR-95

NAME AND ADDRESS OF APPLICANT

MARION MERRELL DOW Inc.
10236 Marion Park Drive
P.O. Box 9707
Kansas City, Missouri 64134-0707

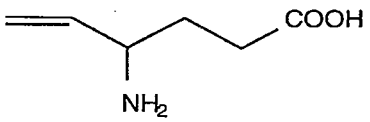
DRUG PRODUCT NAME

Proprietary: **SABRIL®** Tablets
Nonproprietary/USAN: Vigabatrin
Code Name/Number: MDL 71,754, RMI 71,754
Chem.Type/Ther.Class:

PHARMACOLOGICAL CATEGORY / INDICATION Epilepsy
DOSAGE FORM Tablets
STRENGTHS 500 mg
ROUTE OF ADMINISTRATION Oral
DISPENSED XXX RX ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

d,l - 4-Amino-5-hexenoic acid (VG, GVG, VGB, Vinyl GABA)



$C_6H_{11}NO_2$ Mol. Weight 129.16
CAS Registry Number 60643-86-9, 68506-85-5

SUPPORTING DOCUMENTS: IND 17,213 (Vigabatrin Tablets, Marion), [redacted] Gruppo Lepetit, Garessio, Italy - Vigabatrin manufacturer), 21 DMFs for containers/closures.

RELATED DOCUMENTS: [redacted] b(4)

CONSULTS: The EER was requested on 12-JAN-95. The MV Package is ready for mailing.

REMARKS / COMMENTS: This Amendment provides for the revised Analytical Methods Validation Package (2 volumes). The following information is included: a list of samples to be collected for the MV, address where the samples can be collected, CoAs for all validation samples, descriptions and Applicant's validation results for all analytical methods for the drug substance, [redacted] the drug product. Copies of the MV request for SABRIL® (vigabatrin) Tablets are attached. b(4)

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-427, as amended, APPROVABLE subject to a satisfactory evaluation of all facilities. In addition, we expect sponsor's full cooperation in resolving problems that may arise during the validation of analytical methods.

cc: Orig. NDA 20-427
HFD-120
HFD-120/MGuzewska/MG 4.3.95
HFD-120/RPitts
HFD-120/SBlum
R/D Init by: SWB/SWB 4/10/95

M. Guzewska
Maria E. Guzewska, Ph.D. Chemist

Filename: N020427.004

2 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 7

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS HFD-120

REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-427 **CHEM. REVIEW #3** **REVIEW DATE** 22-FEB-95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	29-APR-94	02-MAY-94	
AMENDMENT	26-JUL-94	28-JUL-94	
AMENDMENT. BC	09-FEB-95	10-FEB-95	13-FEB-95

NAME AND ADDRESS OF APPLICANT

MARION MERRELL DOW Inc.
10236 Marion Park Drive
P.O. Box 9707
Kansas City, Missouri 64134-0707

DRUG PRODUCT NAME

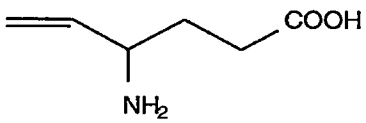
Proprietary: **SABRIL®** Tablets
Nonproprietary/USAN: Vigabatrin
Code Name/Number: MDL 71,754, RMI 71,754
Chem.Type/Ther.Class:

PHARMACOLOGICAL CATEGORY / INDICATION Epilepsy
DOSAGE FORM Tablets
STRENGTHS 500 mg
ROUTE OF ADMINISTRATION Oral
DISPENSED XXX RX __OTC

FEB 24 1995

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

d,l - 4-Amino-5-hexenoic acid (VG, GVG, VGB, Vinyl GABA)



$C_6H_{11}NO_2$ Mol. Weight 129.16
CAS Registry Number 60643-86-9, 68506-85-5

SUPPORTING DOCUMENTS: see Review #1
RELATED DOCUMENTS: see Review #1

CONSULTS: The EER was sent on 12-JAN-95. The EA review is pending. A new Methods Validation package will be prepared and submitted to the Agency.

REMARKS / COMMENTS: The Amendment provides for responses to the CM&C deficiencies identified in the original submission. The results of analytical examination of the [redacted] batches received from each supplier [redacted] and Midland) are provided. Validation data for all analytical methods are given. Stability protocol for vigabatrin manufactured at Garessio, Italy, needs to be revised to include a defined storage temperature (it is "ambient" now). Stability protocol for the drug substance produced at Midland, MI is not given. The new MV package and stability protocols for the drug substance were requested today by phone. The REVIEW NOTES, a copy of the EER, and a memo of the telecon are attached.

b(4)

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-427, as amended, APPROVABLE subject to a satisfactory evaluation of all facilities, and a submission of stability protocols for the drug substance. In addition, we expect sponsor's full cooperation in resolving problems that may arise during the validation of analytical methods.

cc: Orig. NDA 20-427
HFD-120
HFD-120/MGuzewska/MG 2.22.95
HFD-120/RPitts
HFD-120/SBlum
R/D Init by: SWB/ SWB 2/24/95

Maria E. Guzewska, Ph.D. Chemist

Filename: N020427.003

12 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 8

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS HFD-120

REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-427 **CHEM. REVIEW** # 2 **REVIEW DATE** 13-JAN-95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	29-APR-94	02-MAY-94	
AMENDMENT	26-JUL-94	28-JUL-94	29-JUL-94

NAME AND ADDRESS OF APPLICANT

MARION MERRELL DOW Inc.
10236 Marion Park Drive
P.O. Box 9707
Kansas City, Missouri 64134-0707

DRUG PRODUCT NAME

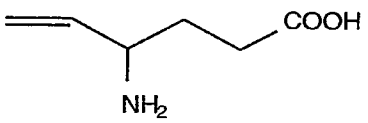
Proprietary: **SABRIL®** Tablets
Nonproprietary/USAN: Vigabatrin
Code Name/Number: MDL 71,754, RMI 71,754
Chem.Type/Ther.Class:

PHARMACOLOGICAL CATEGORY / INDICATION Epilepsy
DOSAGE FORM Tablets
STRENGTHS 500 mg
ROUTE OF ADMINISTRATION Oral
DISPENSED XXX RX __ OTC

JAN 19 1995

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

d,l - 4-Amino-5-hexenoic acid (VG, GVG, VGB, Vinyl GABA)



$C_6H_{11}NO_2$ Mol. Weight 129.16
CAS Registry Number 60643-86-9, 68506-85-5

SUPPORTING DOCUMENTS: IND 17,213 (Vigabatrin Tablets, Marion), [redacted] b(4)
Gruppo Lepetit, Garessio, Italy - Vigabatrin manufacturer), 21 DMFs for containers/closures.
RELATED DOCUMENTS: see Review #1
CONSULTS: The EER was requested on 12-JAN-95. The MV Package is unsatisfactory. The EA review is pending.
REMARKS / COMMENTS: This amendment to the original submission is provided in response to the request of Dr. Tamara of the Biopharmaceutics Division to provide the composition of four batches of SABRIL Tablets that were used in various bioavability studies. The composition and the batch production records (BPRs) for the following batches are provided: No. C46848 (uncoated), C49844 (uncoated), C49982 and 8001.

CONCLUSIONS & RECOMMENDATIONS: N.A.I.

cc: Orig. NDA 20-427
HFD-120
HFD-120/MGuzewska/mg 13-JAN-95
HFD-120/RPitts
HFD-120/SBlum
R/D Init by: SWB/ SWB 1/18/95

Maria E. Guzewska, Ph.D. Chemist

Filename: N020427.002

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS HFD-120

REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-427 | **CHEM. REVIEW** # 1 | **REVIEW DATE** 12-JAN-95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	29-APR-94	02-MAY-94	17-MAY-94

NAME AND ADDRESS OF APPLICANT

MARION MERRELL DOW Inc.
10236 Marion Park Drive
P.O. Box 9707
Kansas City, Missouri 64134-0707

DRUG PRODUCT NAME

Proprietary:	**SABRIL®** Tablets
Nonproprietary/USAN:	Vigabatrin
Code Name/Number:	MDL 71,754, RMI 71,754
Chem.Type/Ther.Class:	

PHARMACOLOGICAL CATEGORY / INDICATION	Epilepsy
DOSAGE FORM	Tablets
STRENGTHS	500 mg
ROUTE OF ADMINISTRATION	Oral
DISPENSED	XXX RX __ OTC

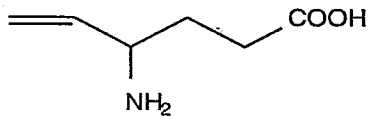
JAN 23 1995

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

d,l - 4-Amino-5-hexenoic acid (VG, GVG, VGB, Vinyl GABA)

$C_6H_{11}NO_2$ Mol. Weight 129.16

CAS Registry Number 60643-86-9, 68506-85-5



SUPPORTING DOCUMENTS: IND 17,213 (Vigabatrin Tablets, Marion), [redacted] b(4)
Gruppo Lepetit, Garessio, Italy - Vigabatrin manufacturer), 21 DMFs for containers/closures.

RELATED DOCUMENTS: [redacted]

CONSULTS: The EER was requested on 12-JAN-95. The MV Package is unsatisfactory and should be revised. The EA review is pending. b(4)

REMARKS / COMMENTS: Specifications for [redacted] can not be evaluated due to the lack of information on the purity profile of this material. Validation methods for the current (NDA) analytical methods used for the drug substance and drug product are not provided. The drug substance batches and [redacted] sources should be identified for all tablets used in stability studies. The post-approval stability protocol should be revised to include tablets made from [redacted] The REVIEW NOTES are attached.

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-427 NOT APPROVABLE. Satisfactory correction of all deficiencies is required.

cc: Orig. NDA 20-427
HFD-120
HFD-120/MGuzewska/MG 1.13.95
HFD-120/RPitts
HFD-120/SBlum
HFD-100/
R/D Init by: SWB/ SWB 1/13/95

Maria E. Guzewska, Ph.D. Chemist

Filename: N020427.000

27 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 9