CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 209822

Name: Vigabatrin Tablets USP, 500 mg

Sponsor: Teva Pharmaceuticals USA, Inc.

Approval Date: January 14, 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209822

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209822

APPROVAL LETTER

ANDA 209822

ANDA APPROVAL

Teva Pharmaceuticals USA, Inc.
400 Interpace Parkway, Building A
Parsippany, NJ 07054
Attention: Bernard Domnic
Associate Director, Regulatory Affairs

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 16, 2016, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Vigabatrin Tablets USP, 500 mg.

Reference is also made to the complete response letter issued by this office on September 10, 2018, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is **approved**, effective on the date of this letter. We have determined your Vigabatrin Tablets USP, 500 mg to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Sabril Tablets, 500 mg, of Lundbeck Pharmaceuticals, LLC.

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Section 505-1 of the FD&C Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA under section 505(j) is subject to certain elements of the REMS required for the applicable listed drug.

The details of the REMS requirements were outlined in our REMS notification letter dated January 11, 2017. In that letter, you were also notified that pursuant to section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA and the listed drug it references must use a single, shared system for elements to assure safe use (ETASU), unless FDA waives that requirement.

Your final proposed REMS, submitted on April 6, 2018; is approved, and will be posted on the FDA REMS website: http://www.fda.gov/rems

The REMS consists of a ETASU and an implementation system.

Your REMS must be fully operational before you introduce Vigabatrin into interstate commerce.

The Vigabatrin REMS uses a shared system for the ETASU. This shared system REMS Program currently includes the products listed on the FDA REMS website, available at http://www.fda.gov/rems. Other products may be added in the future if additional NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

We remind you that you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FD&C Act.

We also remind you that section 505-1(f)(8) of the FD&C Act prohibits holders of an approved covered application from using any element to assure safe use to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing a REMS assessment or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

ANDA 209822 REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA 209822/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 209822/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 209822/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR ANDA 209822

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

In addition to submitting the proposed REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS submission.

For more information on submitting REMS in SPL format, please email REMSWebsite@fda.hhs.gov

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient

package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, Pharm.D.
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Sarah Kurtz

Digitally signed by Sarah Kurtz
Date: 1/14/2019 07:00:21PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209822

OTHER ACTION LETTERS

ANDA 209822

COMPLETE RESPONSE

Teva Pharmaceuticals USA Inc
200 Elmora Avenue, Suite B
Elizabeth, NJ 07207
Attention: Janak Jadeja
Director, Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) received for review on December 16, 2016, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Vigabatrin Tablet USP, 500 mg.

We acknowledge receipt of the March 12, 2018 submission, which constituted a complete response to our October 12, 2017 action letter, and to any amendments thereafter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PHARMACEUTICAL QUALITY

(b) (4)

(b) (4)

[redacted]

PROCESS/BIOPHARMACEUTICS/FACILITY INSPECTION/BIOEQUIVALENCE/ LABELING/REMS

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally the compliance status of each facility named in the application may be re-evaluated upon re-submission.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements.

To ensure you are using the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence, as required by FDA regulations (21 CFR320.24(a)), please continue to monitor for the availability of new and revised product specific guidances in the *Federal Register* and on the FDA Web site at the following address: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

We remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling. It is also your responsibility to ensure that your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Also, ensure that your labeling aligns with your patent and exclusivity statements.

OTHER

The resubmission to this CR letter will be considered to represent a **MINOR** AMENDMENT, given that the deficiencies have been classified as **MINOR**.

Provided that the amendment contains no additional information that requires a substantial expenditure of resources to review, prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission:

RESUBMISSION
MINOR
COMPLETE RESPONSE AMENDMENT
DRUG SUBSTANCE/DRUG PRODUCT

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. Additionally, a partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date

specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

If you have any questions, call Kimberly McCullough, Regulatory Project Manager, Division of Project Management, at (240) 402 - 9021.

Sincerely yours,

{See appended electronic signature page}

For Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Mandy Kwong

Digitally signed by Mandy Kwong
Date: 9/10/2018 01:20:47PM
GUID: 529372550000cc96a0a98e57d06862e5

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 209822

COMPLETE RESPONSE

Teva Pharmaceuticals USA Inc.
200 Elmora Avenue, Suite B
Elizabeth, NJ 07207
Attention: Janak Jadeja, R.Ph.
Director, Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on December 16, 2016, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Vigabatrin Tablet USP, 500 mg.

Reference is also made to any amendments submitted prior to the issuance of this letter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PHARMACEUTICAL QUALITY

Drug Substance

(b) (4)

[redacted]

Following this page, 2 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

Biopharmaceutics

20. Your proposed acceptance criterion of "Q=75% dissolved in 30 minutes" is permissive and NOT acceptable. Based on the provided dissolution data, we recommend a dissolution acceptance criterion of "Q= (b) (4) % in 15 minutes" for your proposed drug products. Note that sometimes dissolution Stage 2 testing, and occasional Stage 3 testing, may be needed.

21. Submit a copy of the updated drug product specification table with the revised acceptance criterion for the dissolution test and update other section of your submission as appropriate.

BIOEQUIVALENCE

Dissolution Testing

1. Per the CDER *Guidance for Industry, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (BCS)*, May 2015, the reference listed drug (RLD) must meet the criteria for BCS class 1, and the test product should exhibit a similar dissolution profile to the reference product. The RLD dissolution does not demonstrate that the product is rapidly dissolving because not all units dissolve >85% in 30 minutes in water and the three other media tested. The f2 values comparing the test and reference product dissolution are <15; therefore, the test and reference product dissolution profiles are not similar and do not meet the BCS guidance recommendations for classification as BCS class 1.

Medium	**F2 Metric for Test vs RLD**
Water (Batch#1115900057)	13.88
Water (Batch#1115900058)	11.78
Water (Batch#1115900060)	12.74
0.1N HCl	13.44
pH 4.5 Acetate Buffer	14.04
pH 6.8 Phosphate Buffer	14.98

Solubility and Gastrointestinal Tract Stability Testing

2. You referenced but did not provide experimental protocol E15-47 "Evaluation of pH Solubility Profile and Stability Studies in Simulated Gastric Fluid (SGF) and Simulated Intestinal fluid (SIF) of Vigabatrin According to BCS Guidance." Please provide this document.

3. You referenced the assay method (b) (4); however, you provided analytical method (b) (4) "Vigabatrin Tablets: Assay, Content Uniformity, and Blend Uniformity for Release and Stability." Please identify the changes between the document version referenced and the version submitted.

4. Per the BCS Guidance, simulated fluids such as Gastric and Intestinal Fluids, USP are acceptable to use for GI stability studies. You used Simulated Gastric Fluid (SGF) and Simulated Intestinal Fluid (SIF) but did not include enzymes in these fluids. Per USP, SGF should contain pepsin, and SIF should contain pancreatin. Your SGF and SIF do not meet USP requirements; therefore, the GI stability results are not adequate. Please repeat your GI stability experiments using SGF and SIF that conform to USP requirements (including enzymes).

Analytical Method for Solubility and Gastrointestinal Tract Stability Testing

(b) (4)

In Situ Rat Intestinal Perfusion Studies

(b) (4)

(b) (4)

Analytical Method for In Situ Rat Intestinal Permeability Studies

(b) (4)

(b) (4)

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are using the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence, as required by FDA regulations (21 CFR 320.24(a)), please continue to monitor for the availability of new and revised product-specific guidances in the *Federal Register* and on the FDA Web site at the following address: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

LABELING

1. PRESCRIBING INFORMATION

   A. Please revise your insert labeling to be in accordance with the most recently approved labeling for the reference-listed drug (RLD), Sabril®, NDA 020427/S-016 approved April 27, 2017.

   B. FULL PRESCRIBING INFORMATION

      1) ADVERSE REACTIONS: Please include as the second bullet "• Magnetic Resonance Imaging (MRI) Abnormalities in Infants *[see Warnings and Precautions (5.3)]*"

      2) OVERDOSAGE, 10.1 Signs, Symptoms, and Laboratory Findings of Overdosage, second paragraph, second sentence: Please revise "veltigo" to read "vertigo".

      3) DESCRIPTION, third paragraph, first sentence: Please revise "vely" to read "very".

      4) CLINICAL PHARMACOLOGY, 12.1 Mechanism of Action, first paragraph, first sentence: Please revise "neurotrans1nitter" to read "neurotransmitter".

      5) CLINICAL PHARMACOLOGY, 12.2 Pharmacodynamics, first paragraph: Please revise "a." to read "a". [Two instances].

6) CLINICAL STUDIES, 14.1 Complex Partial Seizures, first paragraph after Table 9: Please revise “pa1tial” to read “partial” and “pa1ticular” to read “particular”.

2. MEDICATION GUIDE

Please revise your Medication Guide to be in accordance with the most recently approved Medication Guide for the reference listed drug (RLD), Sabril®, NDA 020427/S-016 approved April 27, 2017.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address – http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

FACILITY INSPECTION/REMS

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally the compliance status of each facility named in the application may be re-evaluated upon re-submission.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

As described in our letter dated January 11, 2017, section 505-1 of the FD&C Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA under section 505(j) is subject to certain elements of the REMS required for the applicable reference listed drug (RLD).

There is an approved REMS for the applicable RLD, Sabril (vigabatrin), to ensure the benefits of the drug outweigh the risk of vision loss associated with vigabatrin.

We acknowledge receipt of your proposed REMS included in your June 22, 2017 submission, which contains elements to assure safe use, an implementation system and timetable for submission of assessments.

(b) (4)

The REMS, should your application be approved, will create enforceable obligations.
For administrative purposes, designate the proposed REMS submission "**PROPOSED REMS for ANDA 209822**" and all subsequent submissions related to the proposed REMS "**PROPOSED REMS for ANDA 209822 -AMENDMENT**."

To facilitate review of your submission, we request that you submit your proposed REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

OTHER

The resubmission to this CR letter will be considered to represent a **MAJOR** AMENDMENT, given that the deficiencies have been classified as **MAJOR.**

Prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission:

RESUBMISSION
MAJOR
COMPLETE RESPONSE AMENDMENT
DRUG SUBSTANCE/DRUG PRODUCT/PROCESS/BIOPHARMACEUTICS/ BIOEQUIVALENCE/LABELING

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. Additionally, a partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information, please visit: www.fda.gov/ectd.

If you have any questions, call Kimberly McCullough, Regulatory Project Manager, Division of Project Management, at (240) 402-9021.

Sincerely yours,

{See appended electronic signature page}

Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Denise
Toyer McKan

Digitally signed by Denise Toyer McKan
Date: 10/12/2017 09:43:45AM
GUID: 5277df670008860f7e1231f730a8684c

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209822

LABELING

NDC 0591-**3851**-01

Vigabatrin Tablets, USP
500 mg

PHARMACIST: Dispense the accompanying Medication Guide to each patient.

℞ only

100 Tablets

TEVA

Each Film-Coated Tablet Contains:
Vigabatrin, USP..... 500 mg

Usual Dosage: See accompanying product literature for full prescribing information.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container with a child-resistant closure.

Keep this and all drugs out of the reach of children.

Manufactured in India by:
Watson Pharma Private Limited
Verna, Salcette Goa 403 722 INDIA
Manufactured for:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

Rev. 10/17

LOT/EXP. BELOW

N 3 0591-3851-01 6

237138

Non Varnish/Coding Area

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VIGABATRIN TABLETS safely and effectively. See full prescribing information for VIGABATRIN TABLETS.

VIGABATRIN tablets, for oral use
Initial U.S. Approval: 2009

WARNING: PERMANENT VISION LOSS
See full prescribing information for complete boxed warning.

- **Vigabatrin can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, vigabatrin may also decrease visual acuity (5.1).**
- **Risk increases with increasing dose and cumulative exposure, but there is no dose or exposure to vigabatrin known to be free of risk of vision loss (5.1).**
- **Risk of new and worsening vision loss continues as long as vigabatrin is used, and possibly after discontinuing vigabatrin (5.1).**
- **Baseline and periodic vision assessment is recommended for patients on vigabatrin. However, this assessment cannot always prevent vision damage (5.1).**
- **Vigabatrin tablets are available only through a restricted program called the Vigabatrin REMS Program (5.2).**

----------INDICATIONS AND USAGE----------
Vigabatrin tablets are indicated for the treatment of:

- Refractory Complex Partial Seizures as adjunctive therapy in patients greater than or equal to 10 years of age who have responded inadequately to several alternative treatments; Vigabatrin tablets are not indicated as a first line agent (1.1)

----------DOSAGE AND ADMINISTRATION----------
Refractory Complex Partial Seizures

- Adults (17 years of age and older): Initiate at 1,000 mg/day (500 mg twice daily); increase total daily dose weekly in 500 mg/day increments, to the recommended dose of 3,000 mg/day (1,500 mg twice daily) (2.2)
- Pediatric (10 to 16 years of age): Initiate at 500 mg/day (250 mg twice daily); increase total daily dose weekly in 500 mg/day increments, to recommended maintenance dose of 2,000 mg/day (1,000 mg twice daily); dose patients weighing more than 60 kg according to adult recommendations (2.2)

Renal Impairment: Dose adjustment recommended (2.4, 8.5, 8.6)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablet: 500 mg (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------

- Abnormal MRI signal changes have been reported in some infants with Infantile Spasms receiving vigabatrin (5.3)
- Suicidal behavior and ideation: Antiepileptic drugs, including vigabatrin, increase the risk of suicidal thoughts and behavior (5.5)
- Withdrawal of AEDs: Taper dose to avoid withdrawal seizures (5.6)
- Anemia: Monitor for symptoms of anemia (5.7)
- Somnolence and fatigue: Advise patients not to drive or operate machinery until they have gained sufficient experience on vigabatrin (5.8)

----------ADVERSE REACTIONS----------
Refractory Complex Partial Seizures
Most common adverse reactions in controlled studies include (incidence greater than or equal to 5% over placebo):

- Adults: in addition to permanent vision loss, fatigue, somnolence, nystagmus, tremor, blurred vision, memory impairment, weight gain, arthralgia, abnormal coordination, and confusional state (6.1)
- Pediatric patients (10 to 16 years of age): weight gain, upper respiratory tract infection, tremor, fatigue, aggression, and diplopia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals USA, Inc. at 1-888-838-2872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Decreased phenytoin plasma levels: dosage adjustment may be needed (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Nursing Mothers: Vigabatrin is excreted in human milk (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2018

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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: PERMANENT VISION LOSS

- **Vigabatrin can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, vigabatrin also can damage the central retina and may decrease visual acuity *[see Warnings and Precautions (5.1)]*.**
- **The onset of vision loss from vigabatrin is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time after starting treatment, even after months or years.**
- **Symptoms of vision loss from vigabatrin are unlikely to be recognized by patients or caregivers before vision loss is severe.**
  Vision loss of milder severity, while often unrecognized by the patient or caregiver, can still adversely affect function.
- **The risk of vision loss increases with increasing dose and cumulative exposure, but there is no dose or exposure known to be free of risk of vision loss.**
- **Vision assessment is recommended at baseline (no later than 4 weeks after starting vigabatrin), at least every 3 months during therapy, and about 3 to 6 months after the discontinuation of therapy.**
- **Once detected, vision loss due to vigabatrin is not reversible. It is expected that, even with frequent monitoring, some patients will develop severe vision loss.**
- **Consider drug discontinuation, balancing benefit and risk, if vision loss is documented.**
- **Risk of new or worsening vision loss continues as long as vigabatrin is used. It is possible that vision loss can worsen despite discontinuation of vigabatrin.**
- **Because of the risk of vision loss, vigabatrin should be withdrawn from patients with refractory complex partial seizures who fail to show substantial clinical benefit within 3 months of initiation and within 2 to 4 weeks of initiation for patients with infantile spasms, or sooner if treatment failure becomes obvious. Patient response to and continued need for vigabatrin should be periodically reassessed.**
- **Vigabatrin should not be used in patients with, or at high risk of, other types of irreversible vision loss unless the benefits of treatment clearly outweigh the risks.**
- **Vigabatrin should not be used with other drugs associated with serious adverse ophthalmic effects such as retinopathy or glaucoma unless the benefits clearly outweigh the risks.**
- **Use the lowest dosage and shortest exposure to vigabatrin consistent with clinical objectives *[see Dosage and Administration (2.1)]*.**

Because of the risk of permanent vision loss, vigabatrin is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Vigabatrin REMS Program *[see Warnings and Precautions (5.2)]*. Further information is available at www.vigabatrinREMS.com or 1-866-244-8175.

1 INDICATIONS AND USAGE

1.1 Refractory Complex Partial Seizures (CPS)

Vigabatrin tablets are indicated as adjunctive therapy for adults and pediatric patients 10 years of age and older with refractory complex partial seizures who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss *[see Warnings and Precautions (5.1)]*.
Vigabatrin tablets are not indicated as a first line agent for complex partial seizures.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing and Administration Instructions

Dosing

Use the lowest dosage and shortest exposure to vigabatrin tablets consistent with clinical objectives *[see Warnings and Precautions (5.1)]*.

The vigabatrin tablet dosing regimen depends on the age group and weight *[see Dosage and Administration (2.2,)]*. Patients with impaired renal function require dose adjustment *[see Dosage and Administration (2.4)]*.

Vigabatrin tablets and powder for oral solution are bioequivalent. Either tablet or powder can be used for CPS.

Monitoring of vigabatrin plasma concentrations to optimize therapy is not helpful.

Administration

Vigabatrin tablets are given orally with or without food.

If a decision is made to discontinue vigabatrin tablets, the dose should be gradually reduced *[see Dosage and Administration (2.2) and Warnings and Precautions (5.6)]*.

2.2 Refractory Complex Partial Seizures

Adults (Patients 17 Years of Age and Older)

Treatment should be initiated at 1,000 mg/day (500 mg twice daily). Total daily dose may be increased in 500 mg increments at weekly intervals, depending on response. The recommended dose of vigabatrin tablets in adults is 3,000 mg/day (1,500 mg twice daily). A 6,000 mg/day dose has not been shown to confer additional benefit compared to the 3,000 mg/day dose and is associated with an increased incidence of adverse events.

In controlled clinical studies in adults with complex partial seizures, vigabatrin was tapered by decreasing the daily dose 1,000 mg/day on a weekly basis until discontinued *[see Warnings and Precautions (5.6)]*.

Pediatric (Patients 10 to 16 Years of Age)

Treatment is based on body weight as shown in Table 1. Treatment should be initiated at a total daily dose of 500 mg/day (250 mg twice daily) and may be increased weekly in 500 mg/day increments to a total maintenance dose of 2,000 mg/day (1,000 mg twice daily). Patients weighing more than 60 kg should be dosed according to adult recommendations.

Table 1. Pediatric CPS Dosing Recommendations

Body Weight [kg]	Total Daily* **Starting Dose** [mg/day]	Total Daily* **Maintenance Dose**† [mg/day]
25 to 60††	500	2,000

*Administered in two divided doses.

†Maintenance dose is based on 3,000 mg/day adult-equivalent dose

†† Patients weighing more than 60 kg should be dosed according to adult recommendations

In patients with refractory complex partial seizures, vigabatrin tablets should be withdrawn if a substantial clinical benefit is not observed within 3 months of initiating treatment. If, in the clinical judgment of the prescriber, evidence of treatment failure becomes obvious earlier than 3 months, treatment should be discontinued at that time *[see Warnings and Precautions (5.1)]*.

In a controlled study in pediatric patients with complex partial seizures, vigabatrin tablets were tapered by decreasing the daily dose by one third every week for three weeks *[see Warnings and Precautions (5.6)]*.

2.4 Patients with Renal Impairment
Vigabatrin is primarily eliminated through the kidney.

Adult and pediatric patients 10 years and older

- Mild renal impairment (CLcr greater than 50 to 80 mL/min): dose should be decreased by 25%
- Moderate renal impairment (CLcr greater than 30 to 50 mL/min): dose should be decreased by 50%
- Severe renal impairment (CLcr greater than 10 to 30 mL/min): dose should be decreased by 75%

CLcr in mL/min may be estimated from serum creatinine (mg/dL) using the following formulas:

- Patients 10 to less than 12 years old: CLcr (mL/min/1.73 m^2) = (K × Ht) / Scr

  height (Ht) in cm; serum creatinine (Scr) in mg/dL
  K (proportionality constant): Female Child (less than 12 years): K=0.55;
  Male Child (less than 12 years): K=0.70

- Adult and pediatric patients 12 years or older: CLcr (mL/min) = [140-*age (years)*] × *weight (kg)* / [72 × *serum creatinine (mg/dL)*] (×0.85 *for female patients*)

The effect of dialysis on vigabatrin clearance has not been adequately studied *[see Clinical Pharmacology (12.3) and Use in Specific Populations (8.6)]*.

3 DOSAGE FORMS AND STRENGTHS
Vigabatrin tablets, USP are available for oral administration and are supplied as follows:

500 mg — Each white to off-white, film-coated, oval biconvex tablet functionally-scored on one side and debossed with A314 on the other side contains 500 mg of vigabatrin, USP.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Permanent Vision Loss
Vigabatrin can cause permanent vision loss. Because of this risk and because, when it is effective, vigabatrin provides an observable symptomatic benefit; patient response and continued need for treatment should be periodically assessed.

Based upon adult studies, 30 percent or more of patients can be affected with bilateral concentric visual field constriction ranging in severity from mild to severe. Severe cases may be characterized by tunnel vision to within 10 degrees of visual fixation, which can result in disability. In some cases, vigabatrin also can damage the central retina and may decrease visual acuity. Symptoms of vision loss from vigabatrin are unlikely to be recognized by patients or caregivers before vision loss is severe. Vision loss of milder severity, while often unrecognized by the patient or caregiver, can still adversely affect function.

Because assessing vision may be difficult in children, the frequency and extent of vision loss is poorly characterized in these patients. For this reason, the understanding of the risk is primarily based on the adult

experience. The possibility that vision loss from vigabatrin may be more common, more severe, or have more severe functional consequences in children than in adults cannot be excluded.

The onset of vision loss from vigabatrin is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time after starting treatment, even after months or years.

The risk of vision loss increases with increasing dose and cumulative exposure, but there is no dose or exposure known to be free of risk of vision loss.

In patients with refractory complex partial seizures, vigabatrin should be withdrawn if a substantial clinical benefit is not observed within 3 months of initiating treatment. If, in the clinical judgment of the prescriber, evidence of treatment failure becomes obvious earlier than 3 months, treatment should be discontinued at that time *[see Dosage and Administration (2.2) and Warnings and Precautions (5.6)]*.

Vigabatrin should not be used in patients with, or at high risk of, other types of irreversible vision loss unless the benefits of treatment clearly outweigh the risks. The interaction of other types of irreversible vision damage with vision damage from vigabatrin has not been well-characterized, but is likely adverse.

Vigabatrin should not be used with other drugs associated with serious adverse ophthalmic effects such as retinopathy or glaucoma unless the benefits clearly outweigh the risks.

Monitoring of Vision

Monitoring of vision by an ophthalmic professional with expertise in visual field interpretation and the ability to perform dilated indirect ophthalmoscopy of the retina is recommended *[see Warnings and Precautions (5.2)]*. For patients receiving vigabatrin, vision assessment is recommended at baseline (no later than 4 weeks after starting vigabatrin), at least every 3 months while on therapy, and about 3 to 6 months after the discontinuation of therapy. The diagnostic approach should be individualized for the patient and clinical situation.

In adults and cooperative pediatric patients, perimetry is recommended, preferably by automated threshold visual field testing. Additional testing may also include electrophysiology (e.g., electroretinography [ERG]), retinal imaging (e.g., optical coherence tomography [OCT]), and/or other methods appropriate for the patient. In patients who cannot be tested, treatment may continue according to clinical judgment, with appropriate patient counseling. Because of variability, results from ophthalmic monitoring must be interpreted with caution, and repeat assessment is recommended if results are abnormal or uninterpretable. Repeat assessment in the first few weeks of treatment is recommended to establish if, and to what degree, reproducible results can be obtained, and to guide selection of appropriate ongoing monitoring for the patient.

The onset and progression of vision loss from vigabatrin is unpredictable, and it may occur or worsen precipitously between assessments. Once detected, vision loss due to vigabatrin is not reversible. It is expected that even with frequent monitoring, some vigabatrin patients will develop severe vision loss. Consider drug discontinuation, balancing benefit and risk, if vision loss is documented. It is possible that vision loss can worsen despite discontinuation of vigabatrin.

5.2 Vigabatrin REMS Program

Vigabatrin tablets are available only through a restricted distribution program called the Vigabatrin REMS Program, because of the risk of permanent vision loss.

Notable requirements of the Vigabatrin REMS Program include the following:

- Prescribers must be certified by enrolling in the program, agreeing to counsel patients on the risk of vision loss and the need for periodic monitoring of vision, and reporting any event suggestive of vision loss to Teva Pharmaceuticals USA, Inc.
- Patients must enroll in the program.
- Pharmacies must be certified and must only dispense to patients authorized to receive vigabatrin tablets.

Further information is available at www.vigabatrinREMS.com or call 1-866-244-8175.

5.3 Magnetic Resonance Imaging (MRI) Abnormalities in Infants

Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated with vigabatrin for infantile spasms. In a retrospective epidemiologic study in infants with IS (N=205), the prevalence of these changes was 22% in vigabatrin treated patients versus 4% in patients treated with other therapies.

In the study above, in post marketing experience, and in published literature reports, these changes generally resolved with discontinuation of treatment. In a few patients, the lesion resolved despite continued use. It has been reported that some infants exhibited coincident motor abnormalities, but no causal relationship has been established and the potential for long-term clinical sequelae has not been adequately studied.

Neurotoxicity (brain histopathology and neurobehavioral abnormalities) was observed in rats exposed to vigabatrin during late gestation and the neonatal and juvenile periods of development, and brain histopathological changes were observed in dogs exposed to vigabatrin during the juvenile period of development. The relationship between these findings and the abnormal MRI findings in infants treated with vigabatrin for infantile spasms is unknown *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.1)]*.

The specific pattern of signal changes observed in IS patients was not observed in older pediatric and adult patients treated with vigabatrin for refractory CPS. In a blinded review of MRI images obtained in prospective clinical trials in patients with refractory CPS 3 years and older (N=656), no difference was observed in anatomic distribution or prevalence of MRI signal changes between vigabatrin treated and placebo treated patients.

For adults treated with vigabatrin, routine MRI surveillance is unnecessary as there is no evidence that vigabatrin causes MRI changes in this population.

5.4 Neurotoxicity

Vacuolation, characterized by fluid accumulation and separation of the outer layers of myelin, has been observed in brain white matter tracts in adult and juvenile rats and adult mice, dogs, and possibly monkeys following administration of vigabatrin. This lesion, referred to as intramyelinic edema (IME), was seen in animals at doses within the human therapeutic range. A no-effect dose was not established in rodents or dogs. In the rat and dog, vacuolation was reversible following discontinuation of vigabatrin treatment, but, in the rat, pathologic changes consisting of swollen or degenerating axons, mineralization, and gliosis were seen in brain areas in which vacuolation had been previously observed. Vacuolation in adult animals was correlated with alterations in MRI and changes in visual and somatosensory evoked potentials (EP).

Administration of vigabatrin to rats during the neonatal and juvenile periods of development produced vacuolar changes in the brain gray matter (including the thalamus, midbrain, deep cerebellar nuclei, substantia nigra, hippocampus, and forebrain) which are considered distinct from the IME observed in vigabatrin treated adult

animals. Decreased myelination and evidence of oligodendrocyte injury were additional findings in the brains of vigabatrin-treated rats. An increase in apoptosis was seen in some brain regions following vigabatrin exposure during the early postnatal period. Long-term neurobehavioral abnormalities (convulsions, neuromotor impairment, learning deficits) were also observed following vigabatrin treatment of young rats. Administration of vigabatrin to juvenile dogs produced vacuolar changes in the brain gray matter (including the septal nuclei, hippocampus, hypothalamus, thalamus, cerebellum, and globus pallidus). Neurobehavioral effects of vigabatrin were not assessed in the juvenile dog. These effects in young animals occurred at doses lower than those producing neurotoxicity in adult animals and were associated with plasma vigabatrin levels substantially lower than those achieved clinically in infants and children *[see Use in Specific Populations (8.1, 8.4)]*.

In a published study, vigabatrin (200, 400 mg/kg/day) induced apoptotic neurodegeneration in the brain of young rats when administered by intraperitoneal injection on postnatal days 5 to 7.

Administration of vigabatrin to female rats during pregnancy and lactation at doses below those used clinically resulted in hippocampal vacuolation and convulsions in the mature offspring.

Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated for IS with vigabatrin. Studies of the effects of vigabatrin on MRI and EP in adult epilepsy patients have demonstrated no clear-cut abnormalities *[see Warnings and Precautions (5.3)]*.

5.5 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including vigabatrin, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive-therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI: 1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED treated patients was 0.43%, compared to 0.24% among 16,029 placebo treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug treated patients in the trials and none in placebo treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed. Table 4 shows absolute and relative risk by indication for all evaluated AEDs.

Table 4. Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events per 1,000 Patients	Drug Patients with Events per 1,000 Patients	Relative Risk: Incidence of Drug Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1,000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing vigabatrin or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.6 Withdrawal of Antiepileptic Drugs (AEDs)

As with all AEDs, vigabatrin should be withdrawn gradually. However, if withdrawal is needed because of a serious adverse event, rapid discontinuation can be considered. Patients and caregivers should be told not to suddenly discontinue vigabatrin therapy.

In controlled clinical studies in adults with complex partial seizures, vigabatrin was tapered by decreasing the daily dose 1,000 mg/day on a weekly basis until discontinued.

In a controlled study in pediatric patients with complex partial seizures, vigabatrin was tapered by decreasing the daily dose by one third every week for three weeks.

5.7 Anemia

In North American controlled trials in adults, 6% of patients (16/280) receiving vigabatrin and 2% of patients (3/188) receiving placebo had adverse events of anemia and/or met criteria for potentially clinically important hematology changes involving hemoglobin, hematocrit, and/or RBC indices. Across U.S. controlled trials, there were mean decreases in hemoglobin of about 3% and 0% in vigabatrin and placebo treated patients, respectively, and a mean decrease in hematocrit of about 1% in vigabatrin treated patients compared to a mean gain of about 1% in patients treated with placebo.

In controlled and open label epilepsy trials in adults and pediatric patients, 3 vigabatrin patients (0.06%, 3/4855) discontinued for anemia and 2 vigabatrin patients experienced unexplained declines in hemoglobin to below 8 g/dL and/or hematocrit below 24%.

5.8 Somnolence and Fatigue
Vigabatrin causes somnolence and fatigue. Patients should be advised not to drive a car or operate other complex machinery until they are familiar with the effects of vigabatrin on their ability to perform such activities.

Pooled data from two vigabatrin controlled trials in adults demonstrated that 24% (54/222) of vigabatrin patients experienced somnolence compared to 10% (14/135) of placebo patients. In those same studies, 28% of vigabatrin patients experienced fatigue compared to 15% (20/135) of placebo patients. Almost 1% of vigabatrin patients discontinued from clinical trials for somnolence and almost 1% discontinued for fatigue.

Pooled data from three vigabatrin controlled trials in pediatric patients demonstrated that 6% (10/165) of vigabatrin patients experienced somnolence compared to 5% (5/104) of placebo patients. In those same studies, 10% (17/165) of vigabatrin patients experienced fatigue compared to 7% (7/104) of placebo patients. No vigabatrin patients discontinued from clinical trials due to somnolence or fatigue.

5.9 Peripheral Neuropathy
Vigabatrin causes symptoms of peripheral neuropathy in adults. Pediatric clinical trials were not designed to assess symptoms of peripheral neuropathy, but observed incidence of symptoms based on pooled data from controlled pediatric studies appeared similar for pediatric patients on vigabatrin and placebo. In a pool of North American controlled and uncontrolled epilepsy studies, 4.2% (19/457) of vigabatrin patients developed signs and/or symptoms of peripheral neuropathy. In the subset of North American placebo-controlled epilepsy trials, 1.4% (4/280) of vigabatrin treated patients and no (0/188) placebo patients developed signs and/or symptoms of peripheral neuropathy. Initial manifestations of peripheral neuropathy in these trials included, in some combination, symptoms of numbness or tingling in the toes or feet, signs of reduced distal lower limb vibration or position sensation, or progressive loss of reflexes, starting at the ankles. Clinical studies in the development program were not designed to investigate peripheral neuropathy systematically and did not include nerve conduction studies, quantitative sensory testing, or skin or nerve biopsy. There is insufficient evidence to determine if development of these signs and symptoms was related to duration of vigabatrin treatment, cumulative dose, or if the findings of peripheral neuropathy were completely reversible upon discontinuation of vigabatrin.

5.10 Weight Gain
Vigabatrin causes weight gain in adult and pediatric patients.

Data pooled from randomized controlled trials in adults found that 17% (77/443) of vigabatrin patients versus 8% (22/275) of placebo patients gained greater than or equal to 7% of baseline body weight. In these same trials, the mean weight change among vigabatrin patients was 3.5 kg compared to 1.6 kg for placebo patients.

Data pooled from randomized controlled trials in pediatric patients with refractory complex partial seizures found that 47% (77/163) of vigabatrin patients versus 19% (19/102) of placebo patients gained greater than or equal to 7% of baseline body weight.

In all epilepsy trials, 0.6% (31/4855) of vigabatrin patients discontinued for weight gain. The long term effects of vigabatrin related weight gain are not known. Weight gain was not related to the occurrence of edema.

5.11 Edema
Vigabatrin causes edema in adults. Pediatric clinical trials were not designed to assess edema, but observed incidence of edema based pooled data from controlled pediatric studies appeared similar for pediatric patients on vigabatrin and placebo.

Pooled data from controlled trials demonstrated increased risk among vigabatrin patients compared to placebo patients for peripheral edema (vigabatrin 2%, placebo 1%), and edema (vigabatrin 1%, placebo 0%). In these studies, one vigabatrin and no placebo patients discontinued for an edema related AE. In adults, there was no apparent association between edema and cardiovascular adverse events such as hypertension or congestive heart failure. Edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

6 ADVERSE REACTIONS

The following serious and otherwise important adverse reactions are described elsewhere in labeling:

- Permanent Vision Loss *[see BOXED WARNING and Warnings and Precautions (5.1)]*
- Magnetic Resonance Imaging (MRI) Abnormalities in Infants *[see Warnings and Precautions (5.3)]*
- Neurotoxicity *[see Warnings and Precautions (5.4)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.5)]*
- Withdrawal of Antiepileptic Drugs (AEDs) *[see Warnings and Precautions (5.6)]*
- Anemia *[see Warnings and Precautions (5.7)]*
- Somnolence and Fatigue *[see Warnings and Precautions (5.8)]*
- Peripheral Neuropathy *[see Warnings and Precautions (5.9)]*
- Weight Gain *[see Warnings and Precautions (5.10)]*
- Edema *[see Warnings and Precautions (5.11)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In U.S. and primary non-U.S. clinical studies of 4,079 vigabatrin treated patients, the most common (greater than or equal to 5%) adverse reactions associated with the use of vigabatrin in combination with other AEDs were headache, somnolence, fatigue, dizziness, convulsion, nasopharyngitis, weight gain, upper respiratory tract infection, visual field defect, depression, tremor, nystagmus, nausea, diarrhea, memory impairment, insomnia, irritability, abnormal coordination, blurred vision, diplopia, vomiting, influenza, pyrexia, and rash.

The adverse reactions most commonly associated with vigabatrin treatment discontinuation in greater than or equal to 1% of patients were convulsion and depression.

Refractory Complex Partial Seizures

Adults

Table 5 lists the adverse reactions that occurred in greater than or equal to 2% and more than one patient per vigabatrin treated group and that occurred more frequently than in placebo patients from 2 U.S. add-on clinical studies of refractory CPS in adults.

Table 5. Adverse Reactions in Pooled, Add-On Trials in Adults with Refractory Complex Partial Seizures

	Vigabatrin Dosage (mg/day)		
Body System Adverse Reaction	**3000 [N=134] %**	**6000 [N=43] %**	**Placebo [N=135] %**
Ear Disorders			
Tinnitus	2	0	1
Vertigo	2	5	1

Eye Disorders			
Blurred vision	13	16	5
Diplopia	7	16	3
Asthenopia	2	2	0
Eye pain	0	5	0
Gastrointestinal Disorders			
Diarrhea	10	16	7
Nausea	10	2	8
Vomiting	7	9	6
Constipation	8	5	3
Upper abdominal pain	5	5	1
Dyspepsia	4	5	3
Stomach discomfort	4	2	1
Abdominal pain	3	2	1
Toothache	2	5	2
Abdominal distension	2	0	1
General Disorders			
Fatigue	23	40	16
Gait disturbance	6	12	7
Asthenia	5	7	1
Edema peripheral	5	7	1
Fever	4	7	3
Chest pain	1	5	1
Thirst	2	0	0
Malaise	0	5	0
Infections			
Nasopharyngitis	14	9	10
Upper respiratory tract infection	7	9	6
Influenza	5	7	4
Urinary tract infection	4	5	0
Bronchitis	0	5	1
Injury			
Contusion	3	5	2
Joint sprain	1	2	1
Muscle strain	1	2	1
Wound secretion	0	2	0
Metabolism and Nutrition Disorders			
Increased appetite	1	5	1
Weight gain	6	14	3
Musculoskeletal Disorders			
Arthralgia	10	5	3
Back pain	4	7	2
Pain in extremity	6	2	4
Myalgia	3	5	1
Muscle twitching	1	9	1
Muscle spasms	3	0	1
Nervous System Disorders			
Headache	33	26	31
Somnolence	22	26	13
Dizziness	24	26	17
Nystagmus	13	19	9
Tremor	15	16	8
Memory impairment	7	16	3
Abnormal coordination	7	16	2
Disturbance in attention	9	0	1
Sensory disturbance	4	7	2
Hyporeflexia	4	5	1
Paraesthesia	7	2	1
Lethargy	4	7	2
Hyperreflexia	4	2	3

Hypoaesthesia	4	5	1
Sedation	4	0	0
Status epilepticus	2	5	0
Dysarthria	2	2	1
Postictal state	2	0	1
Sensory loss	0	5	0
Psychiatric Disorders			
Irritability	7	23	7
Depression	6	14	3
Confusional state	4	14	1
Anxiety	4	0	3
Depressed mood	5	0	1
Abnormal thinking	3	7	0
Abnormal behavior	3	5	1
Expressive language disorder	1	7	1
Nervousness	2	5	2
Abnormal dreams	1	5	1
Reproductive System			
Dysmenorrhea	9	5	3
Erectile dysfunction	0	5	0
Respiratory and Thoracic Disorders			
Pharyngolaryngeal pain	7	14	5
Cough	2	14	7
Pulmonary congestion	0	5	1
Sinus headache	6	2	1
Skin and Subcutaneous Tissue Disorders			
Rash	4	5	4

Pediatrics 10 to 16 years of age

Table 6 lists adverse reactions from controlled clinical studies of pediatric patients receiving vigabatrin or placebo as add-on therapy for refractory complex partial seizures. Adverse reactions that are listed occurred in at least 2% of vigabatrin treated patients and more frequently than placebo. The median vigabatrin dose was 49.4 mg/kg (range of 8.0 to 105.9 mg/kg).

Table 6. Adverse Reactions in Pooled, Add-On Trials in Pediatric Patients 10 to 16 Years of Age with Refractory Complex Partial Seizures

Body System Adverse Reaction	All Vigabatrin [N=109] %	Placebo [N=46] %
Eye Disorders		
Diplopia	5	0
Blurred vision	3	0
Gastrointestinal Disorders		
Diarrhea	6	2
Upper abdominal pain	3	0
Constipation	3	2
General Disorders		
Fatigue	9	4
Infections and Infestations		
Upper respiratory tract infection	10	4
Influenza	6	2
Otitis media	6	2
Investigations		
Weight gain	17	2
Nervous System Disorders		
Somnolence	6	2
Tremor	6	0

Nystagmus	5	2
Psychomotor hyperactivity	4	2
Psychiatric Disorders		
Abnormal behavior	6	2
Aggression	5	0
Disorientation	4	0
Reproduction and Breast Disorders		
Dysmenorrhea	3	0
Skin and Subcutaneous Tissue Disorders		
Acne	3	0

6.2 Postmarketing Experience

The following adverse reactions have been reported during post approval use of vigabatrin worldwide. All adverse reactions that are not listed above as adverse reactions reported in clinical trials, that are not relatively common in the population and are not too vague to be useful are listed in this section. These reactions are reported voluntarily from a population of uncertain size; therefore, it is not possible to estimate their frequency or establish a causal relationship to drug exposure. Adverse reactions are categorized by system organ class.

Birth Defects: Congenital cardiac defects, congenital external ear anomaly, congenital hemangioma, congenital hydronephrosis, congenital male genital malformation, congenital oral malformation, congenital vesicoureteric reflux, dentofacial anomaly, dysmorphism, fetal anticonvulsant syndrome, hamartomas, hip dysplasia, limb malformation, limb reduction defect, low set ears, renal aplasia, retinitis pigmentosa, supernumerary nipple, talipes

Ear Disorders: Deafness

Endocrine Disorders: Delayed puberty

Gastrointestinal Disorders: Gastrointestinal hemorrhage, esophagitis

General Disorders: Developmental delay, facial edema, malignant hyperthermia, multi-organ failure

Hepatobiliary Disorders: Cholestasis

Nervous System Disorders: Dystonia, encephalopathy, hypertonia, hypotonia, muscle spasticity, myoclonus, optic neuritis, dyskinesia

Psychiatric Disorders: Acute psychosis, apathy, delirium, hypomania, neonatal agitation, psychotic disorder

Respiratory Disorders: Laryngeal edema, pulmonary embolism, respiratory failure, stridor

Skin and Subcutaneous Tissue Disorders: Angioedema, maculo-papular rash, pruritus, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), alopecia

7 DRUG INTERACTIONS

7.1 Antiepileptic Drugs

Phenytoin

Although phenytoin dose adjustments are not routinely required, dose adjustment of phenytoin should be considered if clinically indicated, since vigabatrin may cause a moderate reduction in total phenytoin plasma levels *[see Clinical Pharmacology (12.3)]*.

Clonazepam
Vigabatrin may moderately increase the C_{max} of clonazepam resulting in an increase of clonazepam-associated adverse reactions *[see Clinical Pharmacology (12.3)]*.

Other AEDs
There are no clinically significant pharmacokinetic interactions between vigabatrin and either phenobarbital or sodium valproate. Based on population pharmacokinetics, carbamazepine, clorazepate, primidone, and sodium valproate appear to have no effect on plasma concentrations of vigabatrin *[see Clinical Pharmacology (12.3)]*.

7.2 Oral Contraceptives
Vigabatrin is unlikely to affect the efficacy of steroid oral contraceptives *[see Clinical Pharmacology (12.3)]*.

7.3 Drug-Laboratory Test Interactions
Vigabatrin decreases alanine transaminase (ALT) and aspartate transaminase (AST) plasma activity in up to 90% of patients. In some patients, these enzymes become undetectable. The suppression of ALT and AST activity by vigabatrin may preclude the use of these markers, especially ALT, to detect early hepatic injury.

Vigabatrin may increase the amount of amino acids in the urine, possibly leading to a false positive test for certain rare genetic metabolic diseases (e.g., alpha aminoadipic aciduria).

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C.
Vigabatrin produced developmental toxicity, including teratogenic and neurohistopathological effects, when administered to pregnant animals at clinically relevant doses. In addition, developmental neurotoxicity was observed in rats treated with vigabatrin during a period of postnatal development corresponding to the third trimester of human pregnancy. There are no adequate and well-controlled studies in pregnant women. Vigabatrin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of vigabatrin (oral doses of 50 to 200 mg/kg) to pregnant rabbits throughout the period of organogenesis was associated with an increased incidence of malformations (cleft palate) and embryo-fetal death; these findings were observed in two separate studies. The no-effect dose for teratogenicity and embryolethality in rabbits (100 mg/kg) is approximately 1/2 the maximum recommended human dose (MRHD) of 3 g/day on a body surface area (mg/m^2) basis. In rats, oral administration of vigabatrin (50, 100, or 150 mg/kg) throughout organogenesis resulted in decreased fetal body weights and increased incidences of fetal anatomic variations. The no-effect dose for embryo-fetal toxicity in rats (50 mg/kg) is approximately 1/5 the MRHD on a mg/m^2 basis. Oral administration of vigabatrin (50, 100, 150 mg/kg) to rats from the latter part of pregnancy through weaning produced long-term neurohistopathological (hippocampal vacuolation) and neurobehavioral (convulsions) abnormalities in the offspring. A no-effect dose for developmental neurotoxicity in rats was not established; the low-effect dose (50 mg/kg) is approximately 1/5 the MRHD on a mg/m^2 basis.

In a published study, vigabatrin (300 or 450 mg/kg) was administered by intraperitoneal injection to a mutant mouse strain on a single day during organogenesis (day 7, 8, 9, 10, 11, or 12). An increase in malformations (including cleft palate) was observed at both doses.

Oral administration of vigabatrin (5, 15, or 50 mg/kg) to young rats during the neonatal and juvenile periods of development (postnatal days 4 to 65) produced neurobehavioral (convulsions, neuromotor impairment, learning deficits) and neurohistopathological (brain vacuolation, decreased myelination, and retinal dysplasia) abnormalities in treated animals. The early postnatal period in rats is generally thought to correspond to late pregnancy in humans in terms of brain development. The no-effect dose for developmental neurotoxicity in

juvenile rats (5 mg/kg) was associated with plasma vigabatrin exposures (AUC) less than 1/30 of those measured in pediatric patients receiving an oral dose of 50 mg/kg.

Pregnancy Registry
To provide information regarding the effects of *in utero* exposure to vigabatrin, physicians are advised to recommend that pregnant patients taking vigabatrin enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

8.3 Nursing Mothers
Vigabatrin is excreted in human milk. Because of the potential for serious adverse reactions from vigabatrin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother *[see Warnings and Precautions (5.3, 5.4)]*.

8.4 Pediatric Use
The safety and effectiveness of vigabatrin as adjunctive treatment of refractory complex partial seizures in pediatric patients aged 10 to 16 years of age have been established *[see Clinical Studies (14.1)]*. The dosing recommendation in this population varies according to age group and is weight based *[see Dosage and Administration (2.2)]*. Adverse reactions in this pediatric population are similar to those observed in the adult population *[see Adverse Reactions (6.1)]*.

The safety and effectiveness of vigabatrin have not been established in pediatric patients under 10 years of age with refractory complex partial seizures.

Abnormal MRI signal changes were observed in infants *[see Warnings and Precautions (5.3, 5.4)]*.

Oral administration of vigabatrin (5, 15, or 50 mg/kg) to young rats during the neonatal and juvenile periods of development (postnatal days 4 to 65) produced neurobehavioral (convulsions, neuromotor impairment, learning deficits) and neurohistopathological (brain gray matter vacuolation, decreased myelination, and retinal dysplasia) abnormalities. The no-effect dose for developmental neurotoxicity in juvenile rats (the lowest dose tested) was associated with plasma vigabatrin exposures (AUC) substantially less than those measured in pediatric patients at recommended doses. In dogs, oral administration of vigabatrin (30 or 100 mg/kg) during selected periods of juvenile development (postnatal days 22 to 112) produced neurohistopathological abnormalities (brain gray matter vacuolation). Neurobehavioral effects of vigabatrin were not assessed in the juvenile dog. A no-effect dose for neurohistopathology was not established in juvenile dogs; the lowest effect dose (30 mg/kg) was associated with plasma vigabatrin exposures lower than those measured in pediatric patients at recommended doses *[see Warnings and Precautions (5.4)]*.

8.5 Geriatric Use
Clinical studies of vigabatrin did not include sufficient numbers of patients aged 65 and over to determine whether they responded differently from younger patients.

Vigabatrin is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Oral administration of a single dose of 1.5 g of vigabatrin to elderly (greater than or equal to 65 years) patients with reduced creatinine clearance (less than 50 mL/min) was associated with moderate to severe sedation and confusion in 4 of 5 patients, lasting up to 5 days. The renal clearance of vigabatrin was 36% lower in healthy

elderly subjects (greater than or equal to 65 years) than in young healthy males. Adjustment of dose or frequency of administration should be considered. Such patients may respond to a lower maintenance dose *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

8.6 Renal Impairment

Dose adjustment, including initiating treatment with a lower dose, is necessary in pediatric patients 10 years of age and older and adults with mild (creatinine clearance greater than 50 to 80 mL/min), moderate (creatinine clearance greater than 30 to 50 mL/min) and severe (creatinine clearance greater than 10 to 30 mL/min) renal impairment *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Vigabatrin is not a controlled substance.

9.2 Abuse

Vigabatrin did not produce adverse events or overt behaviors associated with abuse when administered to humans or animals. It is not possible to predict the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of vigabatrin (e.g., incrementation of dose, drug-seeking behavior).

9.3 Dependence

Following chronic administration of vigabatrin to animals, there were no apparent withdrawal signs upon drug discontinuation. However, as with all AEDs, vigabatrin should be withdrawn gradually to minimize increased seizure frequency *[see Warnings and Precautions (5.6)]*.

10 OVERDOSAGE

10.1 Signs, Symptoms, and Laboratory Findings of Overdosage

Confirmed and/or suspected vigabatrin overdoses have been reported during clinical trials and in post marketing surveillance. No vigabatrin overdoses resulted in death. When reported, the vigabatrin dose ingested ranged from 3 g to 90 g, but most were between 7.5 g and 30 g. Nearly half the cases involved multiple drug ingestions including carbamazepine, barbiturates, benzodiazepines, lamotrigine, valproic acid, acetaminophen, and/or chlorpheniramine.

Coma, unconsciousness, and/or drowsiness were described in the majority of cases of vigabatrin overdose. Other less commonly reported symptoms included vertigo, psychosis, apnea or respiratory depression, bradycardia, agitation, irritability, confusion, headache, hypotension, abnormal behavior, increased seizure activity, status epilepticus, and speech disorder. These symptoms resolved with supportive care.

10.2 Management of Overdosage

There is no specific antidote for vigabatrin overdose. Standard measures to remove unabsorbed drug should be used, including elimination by emesis or gastric lavage. Supportive measures should be employed, including monitoring of vital signs and observation of the clinical status of the patient.

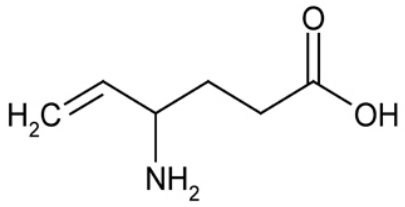
In an *in vitro* study, activated charcoal did not significantly adsorb vigabatrin.

The effectiveness of hemodialysis in the treatment of vigabatrin overdose is unknown. In isolated case reports in renal failure patients receiving therapeutic doses of vigabatrin, hemodialysis reduced vigabatrin plasma concentrations by 40% to 60%.

11 DESCRIPTION

Vigabatrin tablets, USP are an oral antiepileptic drug and are available as white film-coated 500 mg tablets.

The chemical name of vigabatrin USP, a racemate consisting of two enantiomers, is (±) 4-amino-5-hexenoic acid. The molecular formula is $C_6H_{11}NO_2$ and the molecular weight is 129.16. It has the following structural formula:



Vigabatrin, USP is a white to off-white powder which is freely soluble in water, slightly soluble in methyl alcohol, very slightly soluble in ethyl alcohol and chloroform, and insoluble in toluene and hexane. The pH of a 1% aqueous solution is about 6.9. The n-octanol/water partition coefficient of vigabatrin, USP is about 0.011 (log *P*=-1.96) at physiologic pH. Vigabatrin, USP melts with decomposition in a 3-degree range within the temperature interval of 171°C to 176°C. The dissociation constants (pK_a) of vigabatrin, USP are 4 and 9.7 at room temperature (25°C).

Each vigabatrin tablet contains 500 mg of vigabatrin, USP. The inactive ingredients are hypromellose 2910, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, polyethylene glycol 8000, polysorbate 80, povidone, sodium starch glycolate, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism of vigabatrin's anti-seizure effect is unknown, but it is believed to be the result of its action as an irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the metabolism of the inhibitory neurotransmitter GABA. This action results in increased levels of GABA in the central nervous system.

No direct correlation between plasma concentration and efficacy has been established. The duration of drug effect is presumed to be dependent on the rate of enzyme re-synthesis rather than on the rate of elimination of the drug from the systemic circulation.

12.2 Pharmacodynamics

Effects on Electrocardiogram

There is no indication of a QT/QTc prolonging effect of vigabatrin in single doses up to 6.0 g. In a randomized, placebo-controlled, crossover study, 58 healthy subjects were administered a single oral dose of vigabatrin (3 g and 6 g) and placebo. Peak concentrations for 6.0 g vigabatrin were approximately 2-fold higher than the peak concentrations following the 3.0 g single oral dose.

12.3 Pharmacokinetics

Vigabatrin displayed linear pharmacokinetics after administration of single doses ranging from 0.5 g to 4 g, and after administration of repeated doses of 0.5 g and 2.0 g twice daily. Bioequivalence has been established

between the oral solution and tablet formulations. The following PK information (T_{max}, half-life, and clearance) of vigabatrin was obtained from stand-alone PK studies and population PK analyses.

Absorption

Following oral administration, vigabatrin is essentially completely absorbed. The time to maximum concentration (T_{max}) is approximately 1 hour for children (10 years to 16 years) and adults. There was little accumulation with multiple dosing in adult and pediatric patients. A food effect study involving administration of vigabatrin to healthy volunteers under fasting and fed conditions indicated that the C_{max} was decreased by 33%, T_{max} was increased to 2 hours, and AUC was unchanged under fed conditions.

Distribution

Vigabatrin does not bind to plasma proteins. Vigabatrin is widely distributed throughout the body; mean steady-state volume of distribution is 1.1 L/kg (CV = 20%).

Metabolism and Elimination

Vigabatrin is not significantly metabolized; it is eliminated primarily through renal excretion. The terminal half-life of vigabatrin is about 9.5 hours for children (10 years to 16 years), and 10.5 hours for adults. Following administration of $^{[14]}$C-vigabatrin to healthy male volunteers, about 95% of total radioactivity was recovered in the urine over 72 hours with the parent drug representing about 80% of this. Vigabatrin induces CYP2C9, but does not induce other hepatic cytochrome P450 enzyme systems.

Specific Populations

Geriatric

The renal clearance of vigabatrin in healthy elderly patients (greater than or equal to 65 years of age) was 36% less than those in healthy younger patients. This finding is confirmed by an analysis of data from a controlled clinical trial *[see Use in Specific Populations (8.5)]*.

Pediatric

The clearance of vigabatrin is 5.8 L/hr for children (10 years to 16 years) and 7 L/hr for adults.

Gender

No gender differences were observed for the pharmacokinetic parameters of vigabatrin in patients.

Race

No specific study was conducted to investigate the effects of race on vigabatrin pharmacokinetics. A cross study comparison between 23 Caucasian and 7 Japanese patients who received 1, 2, and 4 g of vigabatrin indicated that the AUC, C_{max}, and half-life were similar for the two populations. However, the mean renal clearance of Caucasians (5.2 L/hr) was about 25% higher than the Japanese (4.0 L/hr). Inter-subject variability in renal clearance was 20% in Caucasians and was 30% in Japanese.

Renal Impairment

Mean AUC increased by 30% and the terminal half-life increased by 55% (8.1 hr vs 12.5 hr) in adult patients with mild renal impairment (CLcr from greater than 50 to 80 mL/min) in comparison to normal subjects.

Mean AUC increased by two-fold and the terminal half-life increased by two-fold in adult patients with moderate renal impairment (CLcr from greater than 30 to 50 mL/min) in comparison to normal subjects.

Mean AUC increased by 4.5-fold and the terminal half-life increased by 3.5-fold in adult patients with severe renal impairment (CLcr from greater than 10 to 30 mL/min) in comparison to normal subjects.

Adult patients with renal impairment
Dosage adjustment, including starting at a lower dose, is recommended for adult patients with any degree of renal impairment *[see Use in Specific Populations (8.6) and Dosage and Administration (2.4)]*.

Pediatric patients 10 years and older with renal impairment
Although information is unavailable on the effects of renal impairment on vigabatrin clearance in pediatric patients 10 years and older, dosing can be calculated based upon adult data and an established formula *[see Use in Specific Populations (8.6) and Dosage and Administration (2.4)]*.

Hepatic Impairment
Vigabatrin is not significantly metabolized. The pharmacokinetics of vigabatrin in patients with impaired liver function has not been studied.

Drug Interactions
Phenytoin
A 16% to 20% average reduction in total phenytoin plasma levels was reported in adult controlled clinical studies. *In vitro* drug metabolism studies indicate that decreased phenytoin concentrations upon addition of vigabatrin therapy are likely to be the result of induction of cytochrome P450 2C enzymes in some patients. Although phenytoin dose adjustments are not routinely required, dose adjustment of phenytoin should be considered if clinically indicated *[see Drug Interactions (7.1)]*.

Clonazepam
In a study of 12 healthy adult volunteers, clonazepam (0.5 mg) co-administration had no effect on vigabatrin (1.5 g twice daily) concentrations. Vigabatrin increases the mean C_{max} of clonazepam by 30% and decreases the mean T_{max} by 45% *[see Drug Interactions (7.1)]*.

Other AEDs
When co-administered with vigabatrin, phenobarbital concentration (from phenobarbital or primidone) was reduced by an average of 8% to 16%, and sodium valproate plasma concentrations were reduced by an average of 8%. These reductions did not appear to be clinically relevant. Based on population pharmacokinetics, carbamazepine, clorazepate, primidone, and sodium valproate appear to have no effect on plasma concentrations of vigabatrin *[see Drug Interactions (7.1)]*.

Alcohol
Co-administration of ethanol (0.6 g/kg) with vigabatrin (1.5 g twice daily) indicated that neither drug influences the pharmacokinetics of the other.

Oral Contraceptives
In a double-blind, placebo-controlled study using a combination oral contraceptive containing 30 mcg ethinyl estradiol and 150 mcg levonorgestrel, vigabatrin (3 g/day) did not interfere significantly with the cytochrome P450 isoenzyme (CYP3A)-mediated metabolism of the contraceptive tested. Based on this study, vigabatrin is unlikely to affect the efficacy of steroid oral contraceptives. Additionally, no significant difference in pharmacokinetic parameters (elimination half-life, AUC, C_{max}, apparent oral clearance, time to peak, and apparent volume of distribution) of vigabatrin were found after treatment with ethinyl estradiol and levonorgestrel *[see Drug Interactions (7.2)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Vigabatrin showed no carcinogenic potential in mouse or rat when given in the diet at doses up to 150 mg/kg/day for 18 months (mouse) or at doses up to 150 mg/kg/day for 2 years (rat). These doses are less

than the maximum recommended human dose (MRHD) for refractory complex partial seizures (3 g/day) on a mg/m^2 basis.

Vigabatrin was negative in *in vitro* (Ames, CHO/HGPRT mammalian cell forward gene mutation, chromosomal aberration in rat lymphocytes) and in *in vivo* (mouse bone marrow micronucleus) assays.

No adverse effects on male or female fertility were observed in rats at oral doses up to 150 mg/kg/day (approximately 1/2 the MRHD of 3 g/day on a mg/m^2 basis) for adults treated with refractory complex partial seizures.

14 CLINICAL STUDIES

14.1 Complex Partial Seizures

Adults

The effectiveness of vigabatrin as adjunctive therapy in adult patients was established in two U.S. multicenter, double-blind, placebo-controlled, parallel-group clinical studies. A total of 357 adults (age 18 to 60 years) with complex partial seizures, with or without secondary generalization were enrolled (Studies 1 and 2). Patients were required to be on an adequate and stable dose of an anticonvulsant, and have a history of failure on an adequate regimen of carbamazepine or phenytoin. Patients had a history of about 8 seizures per month (median) for about 20 years (median) prior to entrance into the study. These studies were not capable by design of demonstrating direct superiority of vigabatrin over any other anticonvulsant added to a regimen to which the patient had not adequately responded. Further, in these studies, patients had previously been treated with a limited range of anticonvulsants.

The primary measure of efficacy was the patient's reduction in mean monthly frequency of complex partial seizures plus partial seizures secondarily generalized at end of study compared to baseline.

Study 1

Study 1 (N=174) was a randomized, double-blind, placebo-controlled, dose-response study consisting of an 8-week baseline period followed by an 18-week treatment period. Patients were randomized to receive placebo or 1, 3, or 6 g/day vigabatrin administered twice daily. During the first 6 weeks following randomization, the dose was titrated upward beginning with 1 g/day and increasing by 0.5 g/day on days 1 and 5 of each subsequent week in the 3 g/day and 6 g/day groups, until the assigned dose was reached.

Results for the primary measure of effectiveness, reduction in monthly frequency of complex partial seizures, are shown in Table 8. The 3 g/day and 6 g/day dose groups were statistically significantly superior to placebo, but the 6 g/day dose was not superior to the 3 g/day dose.

Table 8. Median Monthly Frequency of Complex Partial Seizures[+]

	N	Baseline	End-study
Placebo	45	9.0	8.8
1 g/day vigabatrin	45	8.5	7.7
3 g/day vigabatrin	41	8.5	3.7[*]
6 g/day vigabatrin	43	8.5	4.5[*]

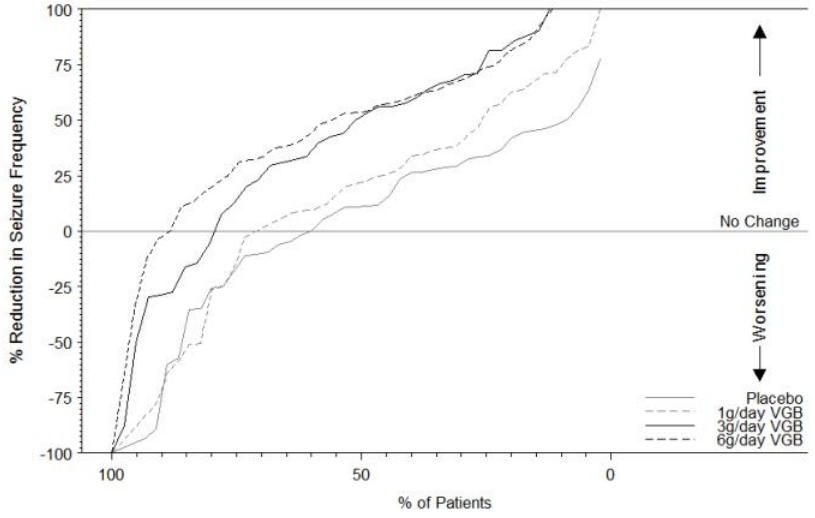
[*] $p<0.05$ compared to placebo

[+] Including one patient with simple partial seizures with secondary generalization only

Figure 1 presents the percentage of patients (X-axis) with a percent reduction in seizure frequency (responder rate) from baseline to the maintenance phase at least as great as that represented on the Y-axis. A positive value on the Y-axis indicates an improvement from baseline (i.e., a decrease in complex partial seizure frequency), while a negative value indicates a worsening from baseline (i.e., an increase in complex partial seizure frequency). Thus, in a display of this type, a curve for an effective treatment is shifted to the left of the curve for

placebo. The proportion of patients achieving any particular level of reduction in complex partial seizure frequency was consistently higher for the vigabatrin 3 and 6 g/day groups compared to the placebo group. For example, 51% of patients randomized to vigabatrin 3 g/day and 53% of patients randomized to vigabatrin 6 g/day experienced a 50% or greater reduction in seizure frequency, compared to 9% of patients randomized to placebo. Patients with an increase in seizure frequency greater than 100% are represented on the Y-axis as equal to or greater than -100%.

Figure 1. Percent Reduction from Baseline in Seizure Frequency



Study 2

Study 2 (N=183 randomized, 182 evaluated for efficacy) was a randomized, double-blind, placebo-controlled, parallel study consisting of an 8-week baseline period and a 16-week treatment period. During the first 4 weeks following randomization, the dose of vigabatrin was titrated upward beginning with 1 g/day and increased by 0.5 g/day on a weekly basis to the maintenance dose of 3 g/day.

Results for the primary measure of effectiveness, reduction in monthly complex partial seizure frequency, are shown in Table 9. Vigabatrin 3 g/day was statistically significantly superior to placebo in reducing seizure frequency.

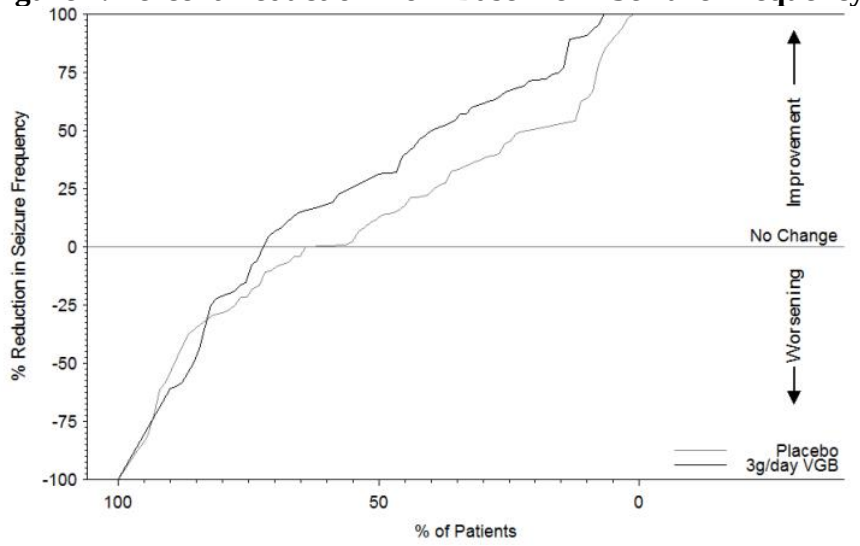
Table 9. Median Monthly Frequency of Complex Partial Seizures

	N	Baseline	End-study
Placebo	90	9.0	7.5
3 g/day vigabatrin	92	8.3	5.5*

*p<0.05 compared to placebo

Figure 2 presents the percentage of patients (X-axis) with a percent reduction in seizure frequency (responder rate) from baseline to the maintenance phase at least as great as that represented on the Y-axis. A positive value on the Y-axis indicates an improvement from baseline (i.e., a decrease in complex partial seizure frequency), while a negative value indicates a worsening from baseline (i.e., an increase in complex partial seizure frequency). Thus, in a display of this type, a curve for an effective treatment is shifted to the left of the curve for placebo. The proportion of patients achieving any particular level of reduction in seizure frequency was consistently higher for the vigabatrin 3 g/day group compared to the placebo group. For example, 39% of patients randomized to vigabatrin (3 g/day) experienced a 50% or greater reduction in complex partial seizure frequency, compared to 21% of patients randomized to placebo. Patients with an increase in seizure frequency greater than 100% are represented on the Y-axis as equal to or greater than -100%.

Figure 2. Percent Reduction from Baseline in Seizure Frequency



For both studies, there was no difference in the effectiveness of vigabatrin between male and female patients. Analyses of age and race were not possible as nearly all patients were between the ages of 18 to 65 and Caucasian.

Pediatric patients 10 to 16 years of age

Vigabatrin was studied in three double-blind, placebo-controlled, parallel-group studies in 269 patients who received vigabatrin and 104 patients who received placebo. No individual study was considered adequately powered to determine efficacy in pediatric patients age 10 years and above. The data from all three pediatric studies were pooled and used in a pharmacometric bridging analysis using weight-normalized doses to establish efficacy and determine appropriate dosing. All three studies were randomized, double-blind, placebo-controlled, parallel-group, adjunctive-treatment studies in patients aged 3 to 16 years with uncontrolled complex partial seizures with or without secondary generalization. The study period included a 6 to 10 week baseline phase and a 14 to 17 week treatment phase (composed of a titration and maintenance period).

The pharmacometric bridging approach consisted of defining a weight-normalized dose-response, and showing that a similar dose-response relationship exists between pediatric patients and adult patients when vigabatrin was given as adjunctive therapy for complex partial seizures. Dosing recommendations in pediatric patients 10 to 16 years of age were derived from simulations utilizing these pharmacometric dose-response analyses *[see Dosage and Administration (2.2)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Vigabatrin tablets, USP are available for oral administration and are supplied as follows:

500 mg — Each white to off-white, film-coated, oval biconvex tablet functionally-scored on one side and debossed with A314 on the other side contains 500 mg of vigabatrin, USP. Tablets are supplied in bottles of 100 (NDC 0591-3851-01).

16.2 Storage and Handling

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container that is defined in the USP.

17 PATIENT COUNSELING INFORMATION

Advise patients and caregivers to read the FDA-approved patient labeling (Medication Guide).

Permanent Vision Loss

Inform patients and caregivers of the risk of permanent vision loss, particularly loss of peripheral vision, from vigabatrin tablets, and the need for monitoring vision *[see Warnings and Precautions (5.1)]*.

Monitoring of vision, including assessment of visual fields and visual acuity, is recommended at baseline (no later than 4 weeks after starting vigabatrin tablets), at least every 3 months while on therapy, and about 3 to 6 months after discontinuation of therapy. In patients for whom vision testing is not possible, treatment may continue without recommended testing according to clinical judgment with appropriate patient or caregiver counseling. Patients or caregivers should be informed that if baseline or subsequent vision is not normal, vigabatrin tablets should only be used if the benefits of vigabatrin tablet treatment clearly outweigh the risks of additional vision loss.

Advise patients and caregivers that vision testing may be insensitive and may not detect vision loss before it is severe. Also advise patients and caregivers that if vision loss is documented, such loss is irreversible. Ensure that both of these points are understood by patients and caregivers.

Patients and caregivers should be informed that if changes in vision are suspected, they should notify their physician immediately.

Vigabatrin REMS Program

Vigabatrin tablets are available only through a restricted program called the Vigabatrin REMS Program *[see Warnings and Precautions (5.2)]*. Inform patients/caregivers of the following:

- Patients/caregivers must be enrolled in the program.
- Vigabatrin tablets are only available through pharmacies that are enrolled in the Vigabatrin REMS Program.

Suicidal Thinking and Behavior

Counsel patients, their caregiver(s), and families that AEDs, including vigabatrin tablets, may increase the risk of suicidal thoughts and behavior. Also advise patients and caregivers of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts of self-harm. Behaviors of concern should be reported immediately to healthcare providers *[see Warnings and Precautions (5.5)]*.

Use in Pregnancy

Instruct patients to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding or intend to breast feed during therapy *[see Use in Specific Populations (8.1, 8.3)]*.

Encourage patients to enroll in the NAAED Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/ *[see Use in Specific Populations (8.1)]*.

Withdrawal of Vigabatrin Tablet Therapy

Instruct patients and caregivers not to suddenly discontinue vigabatrin tablet therapy without consulting with their healthcare provider. As with all AEDs, withdrawal should normally be gradual *[see Warnings and Precautions (5.6)]*.

Manufactured in India by:
Watson Pharma Private Limited
Verna, Salcette Goa 403 722 INDIA

Manufactured for:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

Revised — August 2018

MEDICATION GUIDE
Vigabatrin (vye ga' ba trin) Tablets, USP

What is the most important information I should know about vigabatrin?
Vigabatrin can cause serious side effects, including:

- **Permanent vision loss**
- **Risk of suicidal thoughts or actions**

1. Permanent vision loss:
Vigabatrin can damage the vision of anyone who takes it. People who take vigabatrin do not lose all of their vision, but some people can have severe loss particularly to their ability to see to the side when they look straight ahead (peripheral vision). With severe vision loss, you may only be able to see things straight in front of you (sometimes called "tunnel vision"). You may also have blurry vision. If this happens, it will not get better.

- **Vision loss and use of vigabatrin in adults and children 10 years and older:** Because of the risk of vision loss, vigabatrin is used to treat complex partial seizures (CPS) only in people who do not respond well enough to several other medicines.

Tell your healthcare provider right away if you (or your child):

- might not be seeing as well as before starting vigabatrin
- start to trip, bump into things, or are more clumsy than usual
- are surprised by people or things coming in front of you that seem to come out of nowhere

- These changes can mean that you (or your child) have damage to your vision.
- It is recommended that your healthcare provider test your (or your child's) vision (including peripheral vision) and visual acuity (ability to read an eye chart) before you (or your child) start vigabatrin or within 4 weeks after starting vigabatrin, and at least every 3 months after that until vigabatrin is stopped. It is also recommended that you (or your child) have a vision test about 3 to 6 months after vigabatrin is stopped.
- Some people are not able to complete testing of vision. Your healthcare provider will determine if you (or your child) can be tested. If you (or your child) cannot complete vision testing, your healthcare provider may continue prescribing vigabatrin, but your healthcare provider will not be able to watch for any vision loss you (or your child) may get.
- Even if your vision (or your child's vision) seems fine, it is important that you get these regular vision tests because vision damage can happen before you (or your child) notice any changes.
- These vision tests cannot prevent the vision damage that can happen with vigabatrin, but they do allow the healthcare provider to decide if you (or your child) should stop vigabatrin if vision has gotten worse, which usually will lessen further damage.
- If you do not have these vision tests regularly, your healthcare provider may stop prescribing vigabatrin.
- If you drive and your vision is damaged by vigabatrin, driving might be more dangerous, or you may not be able to drive safely at all. Talk about this with your healthcare provider.

All people who take vigabatrin:

- You are at risk for permanent vision loss with any amount of vigabatrin.
- Your risk of vision loss may be higher the more vigabatrin you take daily and the longer you take it.
- It is not possible for your healthcare provider to know when vision loss will happen. It could happen soon after starting vigabatrin or any time during treatment. It may even happen after treatment has stopped.

- Because vigabatrin might cause permanent vision loss, it is available to healthcare providers and patients only under a special program called the Vigabatrin Risk Evaluation and Mitigation Strategy (REMS)

Program. Vigabatrin can only be prescribed to people who are enrolled in this program. As part of the Vigabatrin REMS Program, it is recommended that your healthcare provider test your (or your child's) vision from time to time (periodically) while you (or your child) are being treated with vigabatrin, and even after you (or your child) stop treatment. Your healthcare provider will explain the details of the Vigabatrin REMS Program to you. For more information, go to www.vigabatrinREMS.com or call 1-866-244-8175.

2. Risk of suicidal thoughts or actions:

Like other antiepileptic drugs, vigabatrin may cause suicidal thoughts or actions in a very small number of people, about 1 in 500 people taking it. Call a healthcare provider right away if you or your child have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- new or worse depression
- feeling agitated or restless
- trouble sleeping (insomnia)
- acting aggressive, being angry, or violent
- an extreme increase in activity and talking (mania)
- attempts to commit suicide
- new or worse anxiety
- panic attacks
- new or worse irritability
- acting on dangerous impulses
- other unusual changes in behavior or mood

Suicidal thoughts or actions can be caused by things other than medicines. If you or your child have suicidal thoughts or actions, your healthcare provider may check for other causes.

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.
- Call your healthcare provider between visits as needed, especially if you are worried about symptoms.
- **Do not stop vigabatrin without first talking to a healthcare provider.**
- Stopping vigabatrin suddenly can cause serious problems. Stopping a seizure medicine suddenly can cause seizures that will not stop (status epilepticus) in people who are being treated for seizures.

What is vigabatrin?

- Vigabatrin is a prescription medicine used along with other treatments to treat adults and children 10 years and older with complex partial seizures (CPS) if:
  - The CPS does not respond well enough to several other treatments, and
  - You and your healthcare provider decide the possible benefit of taking vigabatrin is more important than the risk of vision loss.

Vigabatrin should not be the first medicine used to treat CPS.

What should I tell my healthcare provider before starting vigabatrin?

If you or your child has CPS, before taking vigabatrin tell your healthcare provider if you or your child have or had:

- depression, mood problems or suicidal thoughts or behavior
- an allergic reaction to vigabatrin, such as hives, itching, or trouble breathing
- any vision problems
- any kidney problems
- low red blood cell counts (anemia)
- any nervous or mental illnesses, such as depression, thoughts of suicide, or attempts at suicide
- any other medical conditions
- are breastfeeding or planning to breastfeed. Vigabatrin can pass into breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take vigabatrin.
- are pregnant or plan to become pregnant. It is not known if vigabatrin will harm your unborn baby. You and your healthcare provider will have to decide if you should take vigabatrin while you are pregnant.

Pregnancy Registry:

If you become pregnant while taking vigabatrin, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic medicine during pregnancy.

Tell your healthcare provider about all the medicines you or your child take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Vigabatrin and other medicines may affect each other causing side effects.

How should I take vigabatrin?

- Vigabatrin comes as tablets.
- You or your child will receive vigabatrin from a specialty pharmacy.
- Take vigabatrin exactly as your healthcare provider tells you to. Vigabatrin is usually taken 2 times each day.
- Vigabatrin may be taken with or without food.
- Before starting to take vigabatrin, talk to your healthcare provider about what you or your child should do if a vigabatrin dose is missed.
- If you or your child are taking vigabatrin for CPS and the seizures do not improve enough within 3 months, your healthcare provider will stop prescribing vigabatrin.
- **Do not stop taking vigabatrin suddenly.** This can cause serious problems. Stopping vigabatrin or any seizure medicine suddenly can cause seizures that will not stop (status epilepticus) in people who are being treated for seizures. You should follow your healthcare provider's instructions on how to stop taking vigabatrin.
- **Tell your healthcare provider right away about any increase in seizures when vigabatrin treatment is being stopped.** Before your child starts taking vigabatrin, speak to your child's healthcare provider about what to do if your child misses a dose, vomits, spits up, or only takes part of the dose of vigabatrin.
- **Do not stop taking vigabatrin without talking to your healthcare provider.** If vigabatrin improves your (or your child's) seizures, you and your healthcare provider should talk about whether the benefit of taking vigabatrin is more important than the risk of vision loss, and decide if you (or your child) will continue to take vigabatrin.

What should I avoid while taking vigabatrin?

Vigabatrin causes sleepiness and tiredness. Adults taking vigabatrin should not drive, operate machinery, or perform any hazardous task, unless you and your healthcare provider have decided that you can do these things safely.

What are the possible side effects of vigabatrin?

Vigabatrin can cause serious side effects, including:

- **See "What is the most important information I should know about vigabatrin?"**
- **sleepiness and tiredness. See "What should I avoid while taking vigabatrin?"**
- **weight gain that happens without swelling**

The following serious side effects happen in **adults**. It is not known if these side effects also happen in babies who take vigabatrin.

- **low red blood cell counts (anemia)**
- **nerve problems.** Symptoms of a nerve problem can include numbness and tingling in your toes or feet. It is not known if nerve problems will go away after you stop taking vigabatrin.
- **swelling**

If you or your child has CPS, vigabatrin may make certain types of seizures worse. Tell your healthcare provider right away if your (or your child's) seizures get worse.

The most common side effects of vigabatrin in **adults** include:

- problems walking or feeling uncoordinated
- shaking (tremor)
- memory problems and not thinking clearly
- feeling dizzy
- joint pain
- eye problems: blurry vision, double vision and eye movements that you cannot control

The most common side effects of vigabatrin in **children 10 to 16 years of age** include:

- weight gain
- tiredness
- Also expect side effects like those seen in adults
- upper respiratory tract infection
- aggression

Tell your healthcare provider if you or your child have any side effect that bothers you or that does not go away. These are not all the possible side effects of vigabatrin.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store vigabatrin?

- Store vigabatrin tablets at room temperature, between 68°F to 77°F (20°C to 25°C).
- Keep vigabatrin tablets in the container they come in.

Keep vigabatrin and all medicines out of the reach of children.

General information about the safe and effective use of vigabatrin.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about vigabatrin that is written for health professionals. Do not use vigabatrin for a condition for which it was not prescribed. Do not give vigabatrin to other people, even if they have the same symptoms that you have. It may harm them.

What are the ingredients in vigabatrin tablets?

Active Ingredient: vigabatrin, USP

Inactive Ingredients: hypromellose 2910, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, polyethylene glycol 8000, polysorbate 80, povidone, sodium starch glycolate and titanium dioxide.

Manufactured in India by: **Watson Pharma Private Limited**, Verna, Salcette Goa 403 722 INDIA
Manufactured for: **Teva Pharmaceuticals USA, Inc.,** North Wales, PA 19454
For more information call Teva Pharmaceuticals USA, Inc. at 1-888-838-2872.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised - 8/2018

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MEDICATION GUIDE
Vigabatrin (vye ga' ba trin) Tablets, USP

What is the most important information I should know about vigabatrin?
Vigabatrin can cause serious side effects, including:

- **Permanent vision loss**
- **Risk of suicidal thoughts or actions**

1. Permanent vision loss:
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- **Vision loss and use of vigabatrin in adults and children 10 years and older:** Because of the risk of vision loss, vigabatrin is used to treat complex partial seizures (CPS) only in people who do not respond well enough to several other medicines.

Tell your healthcare provider right away if you (or your child):
  - might not be seeing as well as before starting vigabatrin
  - start to trip, bump into things, or are more clumsy than usual
  - are surprised by people or things coming in front of you that seem to come out of nowhere
- These changes can mean that you (or your child) have damage to your vision.
- It is recommended that your healthcare provider test your (or your child's) vision (including peripheral vision) and visual acuity (ability to read an eye chart) before you (or your child) start vigabatrin or within 4 weeks after starting vigabatrin, and at least every 3 months after that until vigabatrin is stopped. It is also recommended that you (or your child) have a vision test about 3 to 6 months after vigabatrin is stopped.
- Some people are not able to complete testing of vision. Your healthcare provider will determine if you (or your child) can be tested. If you (or your child) cannot complete vision testing, your healthcare provider may continue prescribing vigabatrin, but your healthcare provider will not be able to watch for any vision loss you (or your child) may get.
- Even if your vision (or your child's vision) seems fine, it is important that you get these regular vision tests because vision damage can happen before you (or your child) notice any changes.
- These vision tests cannot prevent the vision damage that can happen with vigabatrin, but they do allow the healthcare provider to decide if you (or your child) should stop vigabatrin if vision has gotten worse, which usually will lessen further damage.
- If you do not have these vision tests regularly, your healthcare provider may stop prescribing vigabatrin.
- If you drive and your vision is damaged by vigabatrin, driving might be more dangerous, or you may not be able to drive safely at all. Talk about this with your healthcare provider.

All people who take vigabatrin:
- You are at risk for permanent vision loss with any amount of vigabatrin.
- Your risk of vision loss may be higher the more vigabatrin you take daily and the longer you take it.
- It is not possible for your healthcare provider to know when vision loss will happen. It could happen soon after starting vigabatrin or any time during treatment. It may even happen after treatment has stopped.

- Because vigabatrin might cause permanent vision loss, it is available to healthcare providers and patients only under a special program called the Vigabatrin Risk Evaluation and Mitigation Strategy (REMS) Program. Vigabatrin can only be prescribed to people who are enrolled in this program. As part of the Vigabatrin REMS Program, it is recommended that your healthcare provider test your (or your child's) vision from time to time (periodically) while you (or your child) are being treated with vigabatrin, and even

after you (or your child) stop treatment. Your healthcare provider will explain the details of the Vigabatrin REMS Program to you. For more information, go to www.vigabatrinREMS.com or call 1-866-244-8175.

2. Risk of suicidal thoughts or actions:
Like other antiepileptic drugs, vigabatrin may cause suicidal thoughts or actions in a very small number of people, about 1 in 500 people taking it. Call a healthcare provider right away if you or your child have any of these symptoms, especially if they are new, worse, or worry you:

- ○ thoughts about suicide or dying
- ○ new or worse depression
- ○ feeling agitated or restless
- ○ trouble sleeping (insomnia)
- ○ acting aggressive, being angry, or violent
- ○ an extreme increase in activity and talking (mania)
- ○ attempts to commit suicide
- ○ new or worse anxiety
- ○ panic attacks
- ○ new or worse irritability
- ○ acting on dangerous impulses
- ○ other unusual changes in behavior or mood

Suicidal thoughts or actions can be caused by things other than medicines. If you or your child have suicidal thoughts or actions, your healthcare provider may check for other causes.

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.
- Call your healthcare provider between visits as needed, especially if you are worried about symptoms.
- **Do not stop vigabatrin without first talking to a healthcare provider.**
- Stopping vigabatrin suddenly can cause serious problems. Stopping a seizure medicine suddenly can cause seizures that will not stop (status epilepticus) in people who are being treated for seizures.

What is vigabatrin?

- Vigabatrin is a prescription medicine used along with other treatments to treat adults and children 10 years and older with complex partial seizures (CPS) if:
  - The CPS does not respond well enough to several other treatments, and
  - You and your healthcare provider decide the possible benefit of taking vigabatrin is more important than the risk of vision loss.

Vigabatrin should not be the first medicine used to treat CPS.

What should I tell my healthcare provider before starting vigabatrin?
If you or your child has CPS, before taking vigabatrin tell your healthcare provider if you or your child have or had:

- depression, mood problems or suicidal thoughts or behavior
- an allergic reaction to vigabatrin, such as hives, itching, or trouble breathing
- any vision problems
- any kidney problems
- low red blood cell counts (anemia)
- any nervous or mental illnesses, such as depression, thoughts of suicide, or attempts at suicide
- any other medical conditions
- are breastfeeding or planning to breastfeed. Vigabatrin can pass into breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take vigabatrin.
- are pregnant or plan to become pregnant. It is not known if vigabatrin will harm your unborn baby. You and your healthcare provider will have to decide if you should take vigabatrin while you are pregnant.

Pregnancy Registry:
If you become pregnant while taking vigabatrin, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic medicine during pregnancy.

Tell your healthcare provider about all the medicines you or your child take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Vigabatrin and other medicines may affect each other causing side effects.

How should I take vigabatrin?

- Vigabatrin comes as tablets.
- You or your child will receive vigabatrin from a specialty pharmacy.
- Take vigabatrin exactly as your healthcare provider tells you to. Vigabatrin is usually taken 2 times each day.
- Vigabatrin may be taken with or without food.
- Before starting to take vigabatrin, talk to your healthcare provider about what you or your child should do if a vigabatrin dose is missed.
- If you or your child are taking vigabatrin for CPS and the seizures do not improve enough within 3 months, your healthcare provider will stop prescribing vigabatrin.
- **Do not stop taking vigabatrin suddenly.** This can cause serious problems. Stopping vigabatrin or any seizure medicine suddenly can cause seizures that will not stop (status epilepticus) in people who are being treated for seizures. You should follow your healthcare provider's instructions on how to stop taking vigabatrin.
- **Tell your healthcare provider right away about any increase in seizures when vigabatrin treatment is being stopped.** Before your child starts taking vigabatrin, speak to your child's healthcare provider about what to do if your child misses a dose, vomits, spits up, or only takes part of the dose of vigabatrin.
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What should I avoid while taking vigabatrin?

Vigabatrin causes sleepiness and tiredness. Adults taking vigabatrin should not drive, operate machinery, or perform any hazardous task, unless you and your healthcare provider have decided that you can do these things safely.

What are the possible side effects of vigabatrin?

Vigabatrin can cause serious side effects, including:

- **See "What is the most important information I should know about vigabatrin?"**
- **sleepiness and tiredness. See "What should I avoid while taking vigabatrin?"**
- **weight gain that happens without swelling**

The following serious side effects happen in **adults**. It is not known if these side effects also happen in babies who take vigabatrin.

- **low red blood cell counts (anemia)**
- **nerve problems.** Symptoms of a nerve problem can include numbness and tingling in your toes or feet. It is not known if nerve problems will go away after you stop taking vigabatrin.
- **swelling**

If you or your child has CPS, vigabatrin may make certain types of seizures worse. Tell your healthcare provider right away if your (or your child's) seizures get worse.

The most common side effects of vigabatrin in **adults** include:

- problems walking or feeling uncoordinated
- shaking (tremor)
- memory problems and not thinking clearly
- feeling dizzy
- joint pain
- eye problems: blurry vision, double vision and eye movements that you cannot control

The most common side effects of vigabatrin in **children 10 to 16 years of age** include:

- weight gain
- tiredness
- Also expect side effects like those seen in adults
- upper respiratory tract infection
- aggression

Tell your healthcare provider if you or your child have any side effect that bothers you or that does not go away. These are not all the possible side effects of vigabatrin.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store vigabatrin?

- Store vigabatrin tablets at room temperature, between 68°F to 77°F (20°C to 25°C).
- Keep vigabatrin tablets in the container they come in.

Keep vigabatrin and all medicines out of the reach of children.

General information about the safe and effective use of vigabatrin.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about vigabatrin that is written for health professionals. Do not use vigabatrin for a condition for which it was not prescribed. Do not give vigabatrin to other people, even if they have the same symptoms that you have. It may harm them.

What are the ingredients in vigabatrin tablets?

Active Ingredient: vigabatrin, USP

Inactive Ingredients: hypromellose 2910, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, polyethylene glycol 8000, polysorbate 80, povidone, sodium starch glycolate and titanium dioxide.

Manufactured in India by: **Watson Pharma Private Limited**, Verna, Salcette Goa 403 722 INDIA
Manufactured for: **Teva Pharmaceuticals USA, Inc.,** North Wales, PA 19454
For more information call Teva Pharmaceuticals USA, Inc. at 1-888-838-2872.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised - 8/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209822

LABELING REVIEWS

***** This document contains proprietary information that cannot be released to the public.***V.19**

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	December 12, 2018
ANDA Number(s)	209822
Review Number	4
Applicant Name	Teva Pharmaceuticals USA, Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Vigabatrin Tablets USP, 500 mg
Proposed Proprietary Name	None
Submission Received Date	October 19, 2018 (amendment)
Primary Labeling Reviewer	Lily Chua
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☒ ACCEPTABLE – No Comments

☐ ACCEPTABLE – Include Post Approval Comments

☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☒ Yes	☐ No
Acceptable for Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission received October 19, 2018.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
NA

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Review #1 finalized date: March 23, 2017
Review #2 finalized date: September 19, 2017
Review #3 finalized date: July 29, 2018 (Labeling Acceptable)

From Cover Letter, received October 19, 2018:
Enclosed in **Module 1.14**, we provide revised labeling in accordance with the recently approved (August 21, 2018) Reference Listed Drug labeling for Sabril® NDA 022006/S-020.

Reviewer Comments: Acceptable. Firm revise the labeling in accordance with the recently approved (August 21, 2018) Reference Listed Drug labeling for Sabril® NDA 020427/S-018.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments: Not submitted in this amendment. Container label was found acceptable in previous labeling review.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments: NA

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES Generic Name/Dosage Form/Strengths: Multiple AED's: Anti-Epileptic / Anti-Seizure / Anticonvulsant drugs: including, but not limited to; Levetiracetam, carbamazepine, ethosuximide, primidone, topiramate, divalproex, oxcarbazepine No Approval Actions prior to contacting Policy Lead; Disciplines can send CRL, IR/DRL; The Policy Lead: Andrea Bautista Requests the FDA require anti-epileptic [also known as AED's, anti-seizure and anti-convulsant] drug labeling to contain specific language in the warnings and precautions section.
Is the drug product listed on the Susceptibility Test Interpretive Criteria web page? NO

3.2 MODEL LABELING

Table 1: Review Model Labeling (Check the box used as the Model Labeling)
☒ MOST RECENTLY APPROVED NDA MODEL LABELING *(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)* **NDA# /Supplement# (S-000 if original):** NDA 020427/S-018 **Supplement Approval Date:** August 21, 2018 **Proprietary Name:** Sabril® **Established Name:** Vigabatrin Tablets **Description of Supplement:** provide for adding the adverse reaction term, alopecia, to Section 6.2 (Adverse Reactions; Postmarketing Experience) of the Sabril (vigabatrin) prescribing information.
☐ MOST RECENTLY APPROVED ANDA MODEL LABELING **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☐ **OTHER (Describe):** NDA 020427/S-019 is pending REMS supplement - The proposed modification is intended to (b) (4) (b) (4) allow inpatient prescribers to continue admitted patients on vigabatrin therapy for the duration of the inpatient visit, for patients who have already been enrolled in the Vigabatrin REMS Program.

Reviewer Assessment:

Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old), or 201.66 (OTC)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **YES**

Reviewer Comments: Acceptable.

The RLD has combined insert labeling for Vigabatrin Powder for Oral Solution. (b) (4) (b) (4)

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: NDA 020427/S-018 dated 09/04/2018]


Each Tablet Conta
vigabatrin .....
See package insert fo
prescribing informatio
Store at controlled roc
20-25°C (68-77°F).
Dispense in a USP tigl
Manufactured by: Patl
Cincinnati, OH 45237
For: Lundbeck
Deerfield, IL 60015, U
Sabril is a registered t
Lundbeck

3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 12/12/2018.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	YES		Vigabatrin Tablets	(b) (4)
Not Yet Official	NO		NA	

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **YES**

Reviewer Comments: Acceptable.

From Drug Product Review: Dissolution test is USP method. The acceptance criteria is NLT 75% (Q) in 30 minutes.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 12/12/2018.

Table 3 provides Orange Book patents for the Model Labeling NDA 020427 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
N/A						

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments: There are no unexpired patents for this product in the Orange Book database.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
N/A					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments: There is no unexpired exclusivity for this product in the Orange Book database.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Each vigabatrin tablet contains 500 mg of vigabatrin, USP. The inactive ingredients are hypromellose 2910, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, polyethylene glycol 8000, polysorbate 80, povidone, sodium starch glycolate, and titanium dioxide.	Each vigabatrin tablet contains 500 mg of vigabatrin, USP. The inactive ingredients are hypromellose 2910, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, polyethylene glycol 8000, polysorbate 80, povidone, sodium starch glycolate, and titanium dioxide.	No Change

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Vigabatrin tablets, USP are available for oral administration and are supplied as follows: 500 mg — Each white to off-white, film-coated, oval biconvex tablet functionally-scored on one side and debossed with A314 on the other side contains 500 mg of vigabatrin, USP. Tablets are supplied in bottles of 100 (NDC 0591-3851-01). 16.2 Storage and Handling Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature]. Dispense in a tight, light-resistant container that is defined in the USP.	Vigabatrin tablets, USP are available for oral administration and are supplied as follows: 500 mg — Each white to off-white, film-coated, oval biconvex tablet functionally-scored on one side and debossed with A314 on the other side contains 500 mg of vigabatrin, USP. Tablets are supplied in bottles of 100 (NDC 0591-3851-01). 16.2 Storage and Handling Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature]. Dispense in a tight, light-resistant container that is defined in the USP.	No Change

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Manufactured in India by: Watson Pharma Private Limited Verna, Salcette Goa 403 722 INDIA Manufactured for: Teva Pharmaceuticals USA, Inc. North Wales, PA 19454	Manufactured in India by: Watson Pharma Private Limited Verna, Salcette Goa 403 722 INDIA Manufactured for: Teva Pharmaceuticals USA, Inc. North Wales, PA 19454	No Change

5. COMMENTS FOR OTHER DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments: From Drug Product Review dated 11/16/2018:

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No

Is the drug product subject of a USP monograph? ☒ Yes ☐ No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

(b) (4)

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No

If "No," explain.

The drug product is neither OTC Drugs nor Controlled Substance.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	length (mm)	Imprint Code
500 mg	-	White to off-white, film coated, oval, biconvex tablet, functionally scored on one side and debossed with 'A314' on the other side

White to off-white, film coated, oval, biconvex tablet functionally scored on one side and debossed with 'A314' on the other side

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: *None*

List of Deficiencies: *None*

Dissolution: This section is reviewed by Biopharmaceutics reviewer. Dissolution test is USP method. The acceptance criteria is NLT 75% (Q) in 30 minutes.

Vigabatrin Tablet Split Study: Satisfactory (Review Cycle-II)

Split Tablet study was performed on research batch RB693-59 of Vigabatrin Tablets, 500 mg as per protocol El5-49 as per report (b) (4) (in section 3.2.P.2). The research batch RB693-59 formulation and manufacturing process are same as exhibit batches of Vigabatrin tablets, 500 mg.

Reviewer's Assessment: Adequate

Firm performed the tablet split study on research batch RB693-59 as per protocol number E15-49 per report (b) (4). The following tests were performed – appearance, assay, moisture content, content uniformity, dissolution and related compounds.

As per 'Guidance for Industry - Tablet Scoring: Nomenclature, Labeling and Data for Evaluation' – the tablet split study needs to be performed on primary / exhibit stability batches and scale-up.

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container (500 mg)	Draft	(bottles of 100s)	03/12/2018	Satisfactory
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	August 2018	10/19/2018	Satisfactory
Medication Guide	Draft	8/2018	10/19/2018	Satisfactory
SPL Data Elements		8/2018	10/19/2018	Satisfactory

Lily Chua

Digitally signed by Lily Chua
Date: 12/13/2018 07:10:05AM
GUID: 5277fc6700089cebb6783d59b3e106fa

Katherine Won

Digitally signed by Katherine Won
Date: 12/19/2018 02:00:31PM
GUID: 508da6ea00027496d7a9d068086637ee

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	July 18, 2018
ANDA Number(s)	209822
Review Number	3
Applicant Name	Teva Pharmaceuticals USA, Inc.
Established Name & Strength(s)	Vigabatrin Tablets USP, 500 mg
Proposed Proprietary Name	None
Submission Received Date	March 12, 2018 (amendment)
Primary Labeling Reviewer	Lily Chua
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☒ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission dated March 12, 2018.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
NA

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s).

Review #1 finalized date: March 23, 2017
Review #2 finalized date: September 19, 2017

From Response to CR, received March 12, 2018:

PRESCRIBING INFORMATION

A. Please revise your insert labeling to be in accordance with the most recently approved labeling for the reference-listed drug (RLD), Sabril®, NDA 020427/S-016 approved April 27, 2017.

Teva's Response: Teva acknowledges the agency's comment and has revised the insert labeling to be in accordance with the RLD approved on April 27, 2017. In addition, please note, included in this submission is the revised container label reflecting the current corporate design.

B. FULL PRESCRIBING INFORMATION

1) ADVERSE REACTIONS: Please include as the second bullet "• Magnetic Resonance Imaging (MRI) Abnormalities in Infants *[see Warnings and Precautions (5.3)]*"

Teva's Response: Teva acknowledges the agency's comment and has revised the ADVERSE REACTIONS section accordingly.

2) OVERDOSAGE, 10.1 Signs, Symptoms, and Laboratory Findings of Overdosage, second paragraph, second sentence: Please revise "veltigo" to read "vertigo".

Teva's Response: Teva acknowledges the agency's comment and has revised the full prescribing information to correct all noted spelling errors.

3) DESCRIPTION, third paragraph, first sentence: Please revise "vely" to read "very".

Teva's Response: Teva acknowledges the agency's comment and has revised the full prescribing information to correct all noted spelling errors.

4) CLINICAL PHARMACOLOGY, 12.1 Mechanism of Action, first paragraph, first sentence: Please revise "neurotrans1nitter" to read "neurotransmitter".

Teva's Response: Teva acknowledges the agency's comment and has revised the full prescribing information to correct all noted spelling errors.

5) CLINICAL PHARMACOLOGY, 12.2 Pharmacodynamics, first paragraph: Please revise "a." to read "a". [Two instances].

Teva's Response: Teva acknowledges the agency's comment and has revised the CLINICAL PHARMACOLOGY, 12.2 Pharmacodynamics section in the two instances.

CLINICAL STUDIES, 14.1 Complex Partial Seizures, first paragraph after Table 9: Please revise "pa1tial" to read "partial" and "pa1ticular" to read "particular".

Teva's Response: Teva acknowledges the agency's comment and has revised the full prescribing information to correct all noted spelling errors.

2. MEDICATION GUIDE

Please revise your Medication Guide to be in accordance with the most recently approved Medication Guide for the reference listed drug (RLD), Sabril®, NDA 020427/S-016 approved April 27, 2017.

Teva's Response: Teva acknowledges the agency's comment and has revised the Medication Guide to be in accordance with the RLD approved on April 27, 2017.

Reviewer Comments: Responses are acceptable.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?

YES

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments: Acceptable.

Firm included in this submission the revised container label reflecting the current corporate design.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments: NA

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO
If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES

Generic Name/Dosage Form/Strengths: Multiple: Anti-Epileptic / Anti-Seizure / Anticonvulsant drugs (AED's): including, but not limited to; Levetiracetam, carbamazepine, primidone, topiramate, divalproex, oxcarbazepine
No Approval Actions prior to contacting Policy Lead; Disciplines can continue communications (CRL/DRL)
The Policy Lead: Andrea Bautista
Require anti-epileptic [also known as AED's, anti-seizure and anti-convulsant] drug labeling to contain specific language in the warnings and precautions section.

Is the drug product listed on the Susceptibility Test Interpretive Criteria web page? NO

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA020427/S-016

Supplement Approval Date: April 27, 2017

Proprietary Name: Sabril®

Established Name: Vigabatrin Tablets

Description of Supplement: propose modifications to the approved risk evaluation and mitigation strategy (REMS) for Sabril to establish a single, shared system (SSS) REMS for vigabatrin products and updates to the approved Prescribing Information and Medication Guide to incorporate language reflecting the proposed SSS REMS.

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

ANDA#/Supplement# (S-000 if original): Click here to enter text.

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement:

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☐ **OTHER (Describe):** NDA020427/S-017 approved REMS supplement, approved October 23, 2017, propose modifications to the approved Vigabatrin REMS. S-018 is pending labeling supplement.

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **YES**

Reviewer Comments: Acceptable.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: DailyMed Updated April 30, 2017]

3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 7/19/2018.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	YES		Vigabatrin Tablets	(b) (4)
Not Yet Official	NO		Same as above.	

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **YES**

Reviewer Comments: Acceptable.

From Drug Product Review: Dissolution test is USP method. The acceptance criteria is NLT 75% (Q) in 30 minutes.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 7/19/2018.

Table 3 provides Orange Book patents for the Model Labeling NDA 020427 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
N/A						

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments: There are no unexpired patents for this product in the Orange Book database.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
N/A					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments: There is no unexpired exclusivity for this product in the Orange Book database.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **YES**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	Currently Proposed	Assessment
Each vigabatrin tablet contains 500 mg of vigabatrin, USP. The inactive ingredients are hypromellose 2910, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, polyethylene glycol 8000, polysorbate 80, povidone, sodium starch glycolate and titanium dioxide.	Each vigabatrin tablet contains 500 mg of vigabatrin, USP. The inactive ingredients are hypromellose 2910, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, polyethylene glycol 8000, polysorbate 80, povidone, sodium starch glycolate, and titanium dioxide.	No Change

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Vigabatrin tablets, USP are available for oral administration and are supplied as follows: 500 mg — Each white to off-white, film-coated, oval biconvex tablet functionally-scored on one side and debossed with A314 on the other side contains 500 mg of vigabatrin, USP. Tablets are supplied in bottles of 100 (NDC 0591-3851-01). 16.2 Storage and Handling Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature]. Dispense in a tight, light-resistant container that is defined in the USP.	Vigabatrin tablets, USP are available for oral administration and are supplied as follows: 500 mg — Each white to off-white, film-coated, oval biconvex tablet functionally-scored on one side and debossed with A314 on the other side contains 500 mg of vigabatrin, USP. Tablets are supplied in bottles of 100 (NDC 0591-3851-01). 16.2 Storage and Handling Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature]. Dispense in a tight, light-resistant container that is defined in the USP.	No Change

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Manufactured by: Watson Pharma Private Limited Verna, Salcette Goa 403 722 INDIA (b) (4) [redacted]	Manufactured in India by: Watson Pharma Private Limited Verna, Salcette Goa 403 722 INDIA Manufactured for: Teva Pharmaceuticals USA, Inc. North Wales, PA 19454	The Manufactured for statement have been revised to reflect the current facility information.

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline (e.g., OPQ, OB, DCR) reviewer(s):

Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments: From Drug Product Review dated 07/16/2018:

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No
Is the drug product subject of a USP monograph? ☒ Yes ☐ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

(b) (4) [redacted]

[Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer].

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No
ii) Are the storage conditions acceptable? ☒ Yes ☐ No

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No

The drug product is neither OTC Drugs nor Controlled Substance.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	length (mm)	Imprint Code
500 mg	-	White to off-white, film coated, oval, biconvex tablet, functionally scored on one side and debossed with 'A314' on the other side

White to off-white, film coated, oval, biconvex tablet functionally scored on one side and debossed with 'A314' on the other side

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: *None*

List of Deficiencies: *None*

Dissolution: This section is reviewed by Biopharmaceutics reviewer. Dissolution test is USP method. The acceptance criteria is NLT 75% (Q) in 30 minutes.

Reviewer's Assessment: ***Adequate***

Firm performed the tablet split study on research batch RB693-59 as per protocol number E15-49 per report (b) (4). The following tests were performed – appearance, assay, moisture content, content uniformity, dissolution and related compounds.

As per 'Guidance for Industry - Tablet Scoring: Nomenclature, Labeling and Data for Evaluation' – the tablet split study needs to be performed on primary / exhibit stability batches and scale-up.

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container (500 mg)	Draft	(bottles of 100s)	03/12/2018	Satisfactory
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	October 2017	03/12/2018	Satisfactory
Medication Guide	Draft	10/2017	03/12/2018	Satisfactory
SPL Data Elements		10/2017	03/12/2018	Satisfactory

Lily Chua

Digitally signed by Lily Chua
Date: 7/23/2018 08:30:24AM
GUID: 5277fc6700089cebb6783d59b3e106fa

Thuyanh Vu

Digitally signed by Thuyanh Vu
Date: 7/29/2018 09:18:56PM
GUID: 508da70a00028d70c2922eb0a0e2dbbe

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	September 6, 2017
ANDA Number(s)	209822
Review Number	2
Applicant Name	Teva Pharmaceutical USA
Established Name & Strength(s)	Vigabatrin Tablets USP, 500 mg
Proposed Proprietary Name	None
Submission Received Date	April 4, 2017 (amendment)
Labeling Reviewer	Lily Chua
Labeling Team Leader	Adolph Vezza

Review Conclusion

☐ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☒ On Policy Alert List

Generic Name/Dosage Form/Strengths: Multiple AED's: Anti-Epileptic / Anti-Seizure / Anticonvulsant drugs: including, but not limited to; Levetiracetam, carbamazepine, ethosuximide, primidone, topiramate, divalproex, oxcarbazepine
No Approval Actions prior to contacting Policy Lead; Disciplines can send IR/ECD; The Policy Lead: Andrea Bautista

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on September 6, 2017 based on your submission dated April 4, 2017:

1. PRESCRIBING INFORMATION
   A. Please revise your insert labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Sabril®, NDA 020427/S-016 approved April 27, 2017.
   B. FULL PRESCRIBING INFORMATION
      a. ADVERSE REACTIONS: Please include as the second bullet "• Magnetic Resonance Imaging (MRI) Abnormalities in Infants *[see Warnings and Precautions (5.3)]*"
      b. OVERDOSAGE, 10.1 Signs, Symptoms, and Laboratory Findings of Overdosage, second paragraph, second sentence: Please revise "veltigo" to read "vertigo".
      c. DESCRIPTION, third paragraph, first sentence: Please revise "vely" to read "very".
      d. CLINICAL PHARMACOLOGY, 12.1 Mechanism of Action, first paragraph, first sentence: Please revise "neurotrans1nitter" to read "neurotransmitter".
      e. CLINICAL PHARMACOLOGY, 12.2 Pharmacodynamics, first paragraph: Please revise "a." to read "a". [Two instances].
      f. CLINICAL STUDIES, 14.1 Complex Partial Seizures, first paragraph after Table 9: Please revise "pa1tial" to read "partial" and "pa1ticular" to read "particular".

2. MEDICATION GUIDE
   Please revise your Medication Guide to be in accordance with the most recently approved Medication Guide for the reference listed drug (RLD), Sabril®, NDA 020427/S-016 approved April 27, 2017.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) dated (add date)

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).
NA

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s)

Review #1 finalized date: March 23, 2017

From Response to ECD, received April 4, 2017:

1. PRESCRIBING INFORMATION

a. HIGHLIGHTS, WARNINGS AND PRECAUTIONS: Please include as the first bullet "Abnormal MRI signal changes have been reported in some infants with Infantile Spasms receiving vigabatrin (5.3)".

Teva Response: Teva acknowledges the Agency's comment and has revised the labeling accordingly.

b. FULL PRESCRIBING INFORMATION: CONTENTS, WARNINGS AND PRECAUTIONS: Please include "5.3 Magnetic Resonance Imaging (MRI) Abnormalities".

Teva Response: Teva acknowledges the Agency's comment and has revised the labeling accordingly.

c. FULL PRESCRIBING INFORMATION

i. WARNING BOX, last sentence: Please complete the REMS Program website and phone number when available.

Teva Response: Teva acknowledges the Agency's comment. The labeling has been revised to include the REMS Program website and telephone number.

ii. DOSAGE AND ADMINISTRATION, 2.1 Important Dosing and Administration Instructions: Please add as the third paragraph the following: "Vigabatrin tablets and powder for oral solution are bioequivalent. Either tablet or powder can be used for CPS."

Teva Response: Teva acknowledges the Agency's comment and has revised the labeling accordingly.

iii. DOSAGE FORMS AND STRENGTHS: If your drug product complies with the Guidance for Industry Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation, we recommend updating the tablet description to state functionally-scored.

Teva Response: Teva acknowledges the Agency's comment. The tablet description has been revised to state functionally-scored".

iv. WARNINGS AND PRECAUTIONS, 5.2 Vigabatrin REMS Program: Please complete the REMS Program website and phone number when available.

Teva Response: Teva acknowledges the Agency's comment. The labeling has been revised to include the REMS Program website and telephone number.

v. WARNINGS AND PRECAUTIONS: Please include the "5.3 Magnetic Resonance Imaging (MRI) Abnormalities in Infants" section.

Teva Response: Teva acknowledges the Agency's comment and has revised the labeling accordingly.

vi. WARNINGS AND PRECAUTIONS, 5.4 Neurotoxicity, second paragraph, last sentence: Please revise "...clinically in children" to read "…clinically in infants and children".

Teva Response: Teva acknowledges the Agency's comment and has revised the labeling accordingly.

vii. WARNINGS AND PRECAUTIONS, 5.4 Neurotoxicity: Please include as the last paragraph "Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated for Infantile Spasms with vigabatrin. Studies of the effects of vigabatrin on MRI and EP in adult epilepsy patients have demonstrated no clear-cut abnormalities [see Warnings and Precautions (5.3)]."

Teva Response: Teva acknowledges the Agency's comment and has revised the labeling accordingly.

viii. ADVERSE REACTIONS, 6.1 Clinical Trial Experience, Table 6: Please indent "Psychomotor hyperactivity" in the first column to preserve formatting.

Teva Response: Teva acknowledges the Agency's comment and has revised the labeling accordingly

ix. USE IN SPECIFIC POPULATIONS, 8.3 Nursing Mothers: Please revise "[see Warnings and Precautions (5.4)]" to read "[see Warnings and Precautions (5.3, 5.4)]".
Teva Response: Teva acknowledges the Agency's comment and has revised the labeling accordingly.
x. USE IN SPECIFIC POPULATIONS, 8.4 Pediatric Use: Please include as the third paragraph "Abnormal MRI signal changes were observed in infants [see Warnings and Precautions (5.3, 5.4)]."
Teva Response: Teva acknowledges the Agency's comment and has revised the labeling accordingly.
2. MEDICATION GUIDE
We encourage you to include the U.S. contact information (i.e.; telephone number) of your firm in case the patient has questions about this drug product. Please include this information at the end of the "General information" section of the Medication Guide.
Teva Response: Teva acknowledges the Agency's comment and has revised the labeling to include the U.S. contact information.

Reviewer Comments: Responses are acceptable.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments: Not submitted in this amendment.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments: NA

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)* **NDA# /Supplement# (S-000 if original):** NDA 020427/S-016 **Supplement Approval Date:** April 27, 2017 **Proprietary Name:** Sabril® **Established Name:** Vigabatrin Tablets **Description of Supplement:** propose modifications to the approved risk evaluation and mitigation strategy (REMS) for Sabril to establish a single, shared system (SSS) REMS for vigabatrin products and updates to the approved Prescribing Information and Medication Guide to incorporate language reflecting the proposed SSS REMS.
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☐ **OTHER (Describe):** NDA 020427/S-014, approved June 21, 2016, proposed modifications to the approved Sabril (vigabatrin) risk evaluation and mitigation strategy (REMS) and corresponding changes to the Sabril (vigabatrin) Prescribing Information and Medication Guide. S-017 is pending REMS supplement.

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **NO**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **YES**

Reviewer Comments: The firm's submitted insert labeling is based on NDA 020427/S-014 approved June 21, 2016. We will ask firm to revise the insert labeling and Medication Guide to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Sabril®, NDA 020427/S-016 approved April 27, 2017.
We will also ask firm to include as the second bullet "• Magnetic Resonance Imaging (MRI) Abnormalities in Infants [see Warnings and Precautions (5.3)]" in ADVERSE REACTIONS section; revise "veltigo" to read "vertigo" in 10.1 Signs, Symptoms, and Laboratory Findings of Overdosage, second paragraph, second sentence; revise "vely" to read "very" in DESCRIPTION section; revise "neurotrans1nitter" to read "neurotransmitter"; and "a." to read "a" [Two instances] in CLINICAL PHARMACOLOGY section; and revise "pa1tial" to read "partial" and "pa1ticular" to read "particular" in 14.1 Complex Partial Seizures section.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: ANRPT-1 dated 10/20/2010]

3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	9/7/2017	YES	Vigabatrin Tablets	(b) (4)
PF	9/7/2017	YES	Same as above.	

Reviewer Comments: Acceptable.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 9/7/2017.

Table 3 provides Orange Book patents for the Model Labeling NDA 020427 and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter "Carve-out" or "None")
N/A						

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments: There are no unexpired patents for this product in the Orange Book database.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter "Carve-out" or "None")

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
N/A					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments: There is no unexpired exclusivity for this product in the Orange Book database.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **YES**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Each vigabatrin tablet contains 500 mg of vigabatrin, USP. The inactive ingredients are hypromellose 2910, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, polyethylene glycol 8000, polysorbate 80, povidone, sodium starch glycolate and titanium dioxide.	**Each vigabatrin tablet contains 500 mg of vigabatrin, USP. The inactive ingredients are hypromellose 2910, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, polyethylene glycol 8000, polysorbate 80, povidone, sodium starch glycolate and titanium dioxide.**	**No Change**

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Vigabatrin tablets, USP are available for oral administration and are supplied as follows: **500 mg — Each white to off-white, film-coated, oval biconvex tablet scored on one side and debossed with A314 on the other side contains 500 mg of vigabatrin, USP. Tablets are supplied in bottles of 100 (NDC 0591-3851-01).** **16.2 Storage and Handling** **Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature].** **Dispense in a tight, light-resistant container that is defined in the USP.**	**Vigabatrin tablets, USP are available for oral administration and are supplied as follows:** **500 mg — Each white to off-white, film-coated, oval biconvex tablet functionally-scored on one side and debossed with A314 on the other side contains 500 mg of vigabatrin, USP. Tablets are supplied in bottles of 100 (NDC 0591-3851-01).** **16.2 Storage and Handling** **Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature].** **Dispense in a tight, light-resistant container that is defined in the USP.**	**"scored" has been revised to read "functionally-scored". This change is acceptable.** **No change otherwise.**

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Manufactured by: **Watson Pharma Private Limited** **Verna, Salcette Goa 403 722 INDIA** (b) (4) [redacted]	**Manufactured by:** **Watson Pharma Private Limited** **Verna, Salcette Goa 403 722 INDIA** (b) (4) [redacted]	**No Change**

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments: From CMC review dated 07/14/2017:

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No

Is the drug product subject of a USP monograph? ☒ Yes ☐ No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

(b) (4) [redacted]

[Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer].

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	length (mm)	Imprint Code
500 mg	-	White to off-white, film coated, oval, biconvex tablet, functionally scored on one side and debossed with 'A314' on the other side

White to off-white, film coated, oval, biconvex tablet functionally scored on one side and debossed with 'A314' on the other side

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: *None*

List of Deficiencies: *None*

List of Deficiencies from Drug Product:

1. We acknowledge the tablet scoring study, which was performed on research batch (RB693-59) per report (b) (4) [redacted] in section 3.2.P.2. Per FDA guidance for Industry, 'Tablet Scoring: Nomenclature, Labeling and Data for Evaluation' tablet scoring study needs to be performed on Primary / Exhibit stability scale-up batches. Please comment.

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments: NA

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container (500 mg)	Draft	(bottles of 100s)	12/16/2016	Satisfactory
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	March 2017	04/04/2017	Revise
Medication Guide	Draft	March 2017	04/04/2017	Revise
SPL Data Elements		8/2016	12/16/2016	Satisfactory

Lily Chua

Digitally signed by Lily Chua
Date: 9/11/2017 07:27:42AM
GUID: 5277fc6700089cebb6783d59b3e106fa

Adolph Vezza

Digitally signed by Adolph Vezza
Date: 9/19/2017 10:25:10AM
GUID: 508da70600028a9e6a494d73e6454d09

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	February 8, 2017
ANDA Number(s)	209822
Review Number	1
Applicant Name	Teva Pharmaceuticals USA
Established Name & Strength(s)	Vigabatrin Tablets USP, 500 mg
Proposed Proprietary Name	None
Submission Received Date	December 16, 2016
Labeling Reviewer	Lily Chua
Labeling Team Leader	Adolph Vezza

Review Conclusion

☐ ACCEPTABLE – No Comments

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☒ On Policy Alert List

Generic Name/Dosage Form/Strengths: Multiple AED's: Anti-Epileptic / Anti-Seizure / Anticonvulsant drugs: including, but not limited to; Levetiracetam, carbamazepine, ethosuximide, primidone, topiramate, divalproex, oxcarbazepine
No Actions prior to contacting Policy Lead; No IR/ECD/CC for: Labeling
Notes: If changes are approved to RLD, will effect ANDA labeling
The Policy Lead: Andrea Bautista

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1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on February 8, 2017 based on your submission dated December 16, 2016:

1. PRESCRIBING INFORMATION
   a. HIGHLIGHTS, WARNINGS AND PRECAUTIONS: Please include as the first bullet "Abnormal MRI signal changes have been reported in some infants with Infantile Spasms receiving vigabatrin (5.3)".
   b. FULL PRESCRIBING INFORMATION: CONTENTS, WARNINGS AND PRECAUTIONS: Please include "5.3 Magnetic Resonance Imaging (MRI) Abnormalities".
   c. FULL PRESCRIBING INFORMATION
      i. WARNING BOX, last sentence: Please complete the REMS Program website and phone number when available.
      ii. DOSAGE AND ADMINISTRATION, 2.1 Important Dosing and Administration Instructions: Please add as the third paragraph the following: "Vigabatrin tablets and powder for oral solution are bioequivalent. Either tablet or powder can be used for CPS."
      iii. DOSAGE FORMS AND STRENGTHS: If your drug product complies with the Guidance for Industry Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation, we recommend updating the tablet description to state functionally-scored.
      iv. WARNINGS AND PRECAUTIONS, 5.2 Vigabatrin REMS Program: Please complete the REMS Program website and phone number when available.
      v. WARNINGS AND PRECAUTIONS: Please include the "5.3 Magnetic Resonance Imaging (MRI) Abnormalities in Infants" section.
      vi. WARNINGS AND PRECAUTIONS, 5.4 Neurotoxicity, second paragraph, last sentence: Please revise "...clinically in children" to read "…clinically in infants and children".
      vii. WARNINGS AND PRECAUTIONS, 5.4 Neurotoxicity: Please include as the last paragraph "Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated for Infantile Spasms with vigabatrin. Studies of the effects of vigabatrin on MRI and EP in adult epilepsy patients have demonstrated no clear-cut abnormalities [see Warnings and Precautions (5.3)]."
      viii. ADVERSE REACTIONS, 6.1 Clinical Trial Experience, Table 6: Please indent "Psychomotor hyperactivity" in the first column to preserve formatting.
      ix. USE IN SPECIFIC POPULATIONS, 8.3 Nursing Mothers: Please revise "[see Warnings and Precautions (5.4)]" to read "[see Warnings and Precautions (5.3, 5.4)]"
      x. USE IN SPECIFIC POPULATIONS, 8.4 Pediatric Use: Please include as the third paragraph "Abnormal MRI signal changes were observed in infants [see Warnings and Precautions (5.3, 5.4)]."

2. MEDICATION GUIDE

   We encourage you to include the U.S. contact information (i.e.; telephone number) of your firm in case the patient has questions about this drug product. Please include this information at the end of the "General information" section of the Medication Guide.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission(s) dated (add date).

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).
NA

2. LABELING REVIEW INFORMATION

2.1 REGULATORY INFORMATION

Has the ANDA been accepted for filing? YES
Are there any pending issues in DLR's SharePoint Drug Facts? YES Potential pediatric template required- please check patents and exclusivities. None in need of template as of 12/20/2015
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO

2.2 MODEL LABELING

2.2.1 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA RLD information.)* **NDA#/Supplement# (S-000 if original):** NDA 020427/S-014 **Supplement Approval Date:** June 21, 2016 **Proprietary Name:** Sabril® **Established Name:** Vigabatrin Tablets **Description of Supplement:** proposed modifications to the approved Sabril (vigabatrin) risk evaluation and mitigation strategy (REMS) and corresponding changes to the Sabril (vigabatrin) Prescribing Information and Medication Guide.
☐ **MOST RECENTLY APPROVED ANDA RLD LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:** Click here to enter text.
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☒ **OTHER (Describe):** NDA 020427/S-015, approved September 18, 2015 proposes changes to the following sections of labeling: Section 5.3, Magnetic Resonance Imaging (MRI) Abnormalities in Infants; Section 5.4, Neurotoxicity; and Section 8.4, Pediatric Use. S-012, approved October 26, 2013, combining the separate, previously approved package insert for Sabril tablet and Sabril powder for oral solution into a single package insert. S-016 is pending labeling supplement.

2.2.2 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: ANRPT-1 dated 10/20/2010**)**

2.3 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	2/7/2017	YES	Vigabatrin Tablets	(b) (4)
PF	2/7/2017	YES	Same as above.	

2.4 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 2/7/2017.

Table 3 provides Orange Book patents for the Model Labeling (NDA 020427) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
N/A			There are no unexpired patents for this product in the Orange Book database.			

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
NPP	Oct 26, 2016	NEW PATIENT POPULATION	Expired		None
PED	Apr 26, 2017	PEDIATRIC EXCLUSIVITY	Wait until exclusivity expires	12/16/2016	None

Teva Pharmaceuticals USA does not intend to market the proposed product prior to the expiration of the exclusivity on Apr 26, 2017.

2.5 MANUFACTURING FACILITY

Table 5 provides a description of the drug product manufacturing facility.

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements		
Name and Address of ANDA Manufacturer/Distributor/Packer (3.2.P.3.1 MANUFACTURER)	**Name and Address on ANDA Container/Carton**	**Name and Address on ANDA Prescribing Information**
Watson Pharma Private Limited [redacted (b) (4)] Verna, Salcette, Goa - 403722, India.	Manufactured by: Watson Pharma Private Limited Verna, Salcette Goa 403 722 INDIA [redacted (b) (4)]	Manufactured by: Watson Pharma Private Limited Verna, Salcette Goa 403 722 INDIA [redacted (b) (4)]

3. ASSESSMENT OF ANDA LABELING AND LABELS

The results for each material reviewed in this section provide the basis for the labeling comments to the applicant.

Is this product Rx or OTC? Please check one.

☒ Rx Product (If Rx, skip 3.2 OTC DRUG PRODUCT and go to 3.3 CONTAINER/CLOSURE.)
☐ OTC Product (If OTC, skip 3.1 RX DRUG PRODUCT and go to 3.3 CONTAINER/CLOSURE)

3.1 RX (PRESCRIPTION) DRUG PRODUCT

3.1.1 RX: PRESCRIBING INFORMATION

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Is the established name for this ANDA acceptable? **YES**
Does the Model Labeling have combined insert labeling for multiple NDAs or dosage forms? **YES**
Are the required USP recommendations reflected in the labeling? **YES**
Is the applicant's "patent carve out" acceptable? **NA**
Is the applicant's "exclusivity carve out" acceptable? **NA**
Is the Manufacturer statement acceptable? **YES**

Reviewer Comments: The most recently approved reference listed drug labeling, NDA 020427/S-014 is a combined inert with oral solution-approved for Infantile Spasms, we will ask firm to revise the labeling as follow based on NDA 020427/S-005, approved December 11, 2012, labeling for the oral tablets only:

a. HIGHLIGHTS, WARNINGS AND PRECAUTIONS: Please include as the first bullet "Abnormal MRI signal changes have been reported in some infants with Infantile Spasms receiving vigabatrin (5.3)".
b. FULL PRESCRIBING INFORMATION: CONTENTS, WARNINGS AND PRECAUTIONS: Please include "5.3 Magnetic Resonance Imaging (MRI) Abnormalities".
c. FULL PRESCRIBING INFORMATION
   i. WARNING BOX, last sentence: Please complete the REMS Program website and phone number when available.
   ii. DOSAGE AND ADMINISTRATION, 2.1 Important Dosing and Administration Instructions: Please add as the third paragraph the following: "Vigabatrin tablets and powder for oral solution are bioequivalent. Either tablet or powder can be used for CPS."
   iii. DOSAGE FORMS AND STRENGTHS: If your drug product complies with the Guidance for Industry Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation, we recommend updating the tablet description to state functionally-scored.
   iv. WARNINGS AND PRECAUTIONS, 5.2 Vigabatrin REMS Program: Please complete the REMS Program website and phone number when available.
   v. WARNINGS AND PRECAUTIONS: Please include the "5.3 Magnetic Resonance Imaging (MRI) Abnormalities in Infants" section.
   vi. WARNINGS AND PRECAUTIONS, 5.4 Neurotoxicity, second paragraph, last sentence: Please revise "...clinically in children" to

read "…clinically in infants and children".

vii. WARNINGS AND PRECAUTIONS, 5.4 Neurotoxicity: Please include as the last paragraph "Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated for Infantile Spasms with vigabatrin. Studies of the effects of vigabatrin on MRI and EP in adult epilepsy patients have demonstrated no clear-cut abnormalities [see Warnings and Precautions (5.3)]."

viii. ADVERSE REACTIONS, 6.1 Clinical Trial Experience, Table 6: Please indent "Psychomotor hyperactivity" in the first column to preserve formatting.

ix. USE IN SPECIFIC POPULATIONS, 8.3 Nursing Mothers: Please revise "[see Warnings and Precautions (5.4)]" to read "[see Warnings and Precautions (5.3, 5.4)]"

x. USE IN SPECIFIC POPULATIONS, 8.4 Pediatric Use: Please include as the third paragraph "Abnormal MRI signal changes were observed in infants [see Warnings and Precautions (5.3, 5.4)]."

The decision was made to retain most of the information relating to the MRI changes observed in infants with IS (infantile spasms) treated with vigabatrin powder for oral solution since this information was present in the last labeling for Sabril (RLD) tablets before the RLD insert was combined with the insert for Sabril Powder for Oral Solution. (2 separate NDAs).

3.1.1.1 RX: DESCRIPTION

We reviewed the DESCRIPTION section for accuracy (with input from the chemistry review, if appropriate) and acceptability from Labeling perspective. We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

Table 6: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling Inactive Ingredients	ANDA Labeling Inactive Ingredients
Each SABRIL tablet contains 500 mg of vigabatrin. The inactive ingredients are hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycols, povidone, sodium starch glycolate, and titanium dioxide.	Each vigabatrin tablet contains 500 mg of vigabatrin, USP. The inactive ingredients are hypromellose 2910, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, polyethylene glycol 8000, polysorbate 80, povidone, sodium starch glycolate and titanium dioxide.

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling Memorandum of Understanding (MOU)?
YES, chemistry review pending as of 02/27/2017
(Note: The MOU became effective on November 1, 2014. MOU does not apply to amendment reviews for ANDAs originally reviewed before November 1, 2014.)

If the chemistry review follows the MOU, labeling reviewer is not responsible for reviewing for accuracy of the DESCRIPTION section for chemical properties, system components of the drug product, etc. Please refer to the MOU, Appendix A, DESCRIPTION section for delineation of responsibilities. If chemistry review does NOT follow the MOU, labeling reviewer will follow the traditional review approach of reviewing the entire DESCRIPTION section.)

Are the inactive ingredients information consistent with "Components and Composition" information as provided in Module 3.2.P.1? (If Chemistry follows the MOU, refer to the Labeling section of Chemistry review.) **YES**
For products required to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **NA**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **NA** Has the statement been verified by chemistry? **NA**

Reviewer Comments:
From 3.2.P.1.5 From 3.2.P.1.4

(b) (4)

3.1.1.2 RX: HOW SUPPLIED/STORAGE AND HANDLING

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 7 and will be referred to the appropriate review discipline for evaluation.

Table 7: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	SABRIL 500 mg tablets are white, film-coated, oval, biconvex, scored on one side, and debossed with OV 111 on the other. They are supplied as bottles of 100 (NDC 67386-111-01). SABRIL 500 mg packets contain a white to off-white granular powder. They are supplied in packages of 50 (NDC 67386-211-65). 16.2 Storage and Handling Store at 20 to 25°C (68 to 77°F). See USP controlled room temperature.
ANDA Labeling	Vigabatrin tablets, USP are available for oral administration and are supplied as follows: 500 mg — Each white to off-white, film-coated, oval biconvex tablet scored on one side and debossed with A314 on the other side contains 500 mg of vigabatrin, USP. Tablets are supplied in bottles of 100 (NDC 0591-3851-01). 16.2 Storage and Handling Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature]. Dispense in a tight, light-resistant container that is defined in the USP.

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling MOU? **YES, chemistry review pending as of 02/27/2017**
If the chemistry review does NOT follow the MOU, is the description (scoring, color and imprint) of the finished product in the HOW SUPPLIED section consistent with the information in Module 3.2.P.5.1 for Drug Product Specification? **YES**
Does the ANDA require the same color coding as the Model Labeling? **NO**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NO**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **YES**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **NA**
Is the storage or dispensing statement acceptable as compared to the Model Labeling? **YES**
Is the storage or dispensing statement acceptable as compared to the USP? **YES**

Reviewer Comments: From 3.2.P.1.1 Dosage Form Description:
White to off-white, film coated, oval, biconvex tablet scored on one side and debossed with 'A314' on the other side.

3.1.2 RX: MEDICATION GUIDE

Is Medication Guide required? **YES**
If YES go to Reviewer Assessment below, if NO go to section 3.1.3.

Reviewer Assessment:

Was Medication Guide submitted? **YES**
Is the Medication Guide same as the model labeling, except for allowable differences? **YES**

Does the Medication Guide meet the requirements of 21 CFR 208.20? **YES**
Has the Applicant committed to provide a sufficient number of medication guides? **YES**
Is the phonetic spelling of the proprietary or established name present? **YES**
Is FDA 1-800-FDA-1088 phone number included? **YES**

Reviewer Comments: We will encourage firm to include the U.S. contact information (i.e.; telephone number) of the firm at the end of the "General information" section of the Medication Guide.

(b) (4)

3.1.3 RX: OTHER PATIENT LABELING

Are other patient labeling required? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.

Reviewer Assessment:

Was other patient labeling submitted? **NA**
Is the patient labeling the same as the model labeling, except for allowable differences? **NA**

Reviewer Comments:

3.1.4 RX: CONTAINER LABEL

Was container label (other than Blisters) submitted? **YES**
(For BLISTER labels go to section 3.1.5.)

We evaluated the container labels for the inclusion of all required statements and safety considerations.

Reviewer Assessment:

Is the established name acceptable? **YES**
Is title case used in expressing the established name? **YES**
Does labeling comply with Tall Man lettering recommendations found on FDA webpage? **NA**
Is container label too small to contain all required information? **NO** If yes, does the container meet the "too small" exemption found in 21 CFR 201.10(i)? **NO**
Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **YES**
Is the following information properly displayed?

- Net quantity statement: **YES**
- Route(s) of administration (other than oral): **NA**
- Warnings (if any) or cautionary statements (if any): **NA**
- Medication Guide Pharmacist instructions per 21 CFR 208.24(d): **YES**
- Controlled substance symbol: **NA**
- Usual Dosage statement: **YES**
- Product strength equivalency statement: **NA**
- NDC: **YES**
- Bar code per 21 CFR 201.25(c)(2): **YES**

Is the Manufacturer/Distributor/Packager statement acceptable? **YES**
For foreign manufacturers, does the labeling have the country of origin? **YES**
Are the required USP recommendations reflected on the label(s)? **YES**
Is the storage or dispensing statement consistent with the How Supplied section of the insert? **YES**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**
Are multiple strengths differentiated by use of different color or other acceptable means? **NA**
Are the labels of related products differentiated to avoid selection errors? **YES**
Does the ANDA require the same color coding as the Model Labeling? **NO**

Are the requirements of 21 CFR 201.15 met for all required label statements? **YES**
Are the requirements of 21 CFR 201.100 met for all required label statements? **YES**

Reviewer Comments: Acceptable.

ANDA 209824:

3.1.4.1 RX: CONTAINER LABEL FOR PARENTERAL SOLUTIONS

Is container for parenteral solution? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.2.

Reviewer Assessment:

Is the product strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP, General Chapter <1> Injection? **NA**
If volume is less than 1 mL, is strength per fraction of a milliliter the only expression of strength? **NA**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **NA**

Reviewer Comments:

3.1.4.2 RX: CONTAINER LABEL FOR SOLID INJECTABLE

Is container for solid injectable (other than Pharmacy Bulk Package)? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.3.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **NA**
Are instructions for reconstitution and resultant concentration provided, if space permits? **NA**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **NA**

Reviewer Comments:

3.1.4.3 RX: CONTAINER LABEL FOR PHARMACY BULK PACKAGE

Is container a Pharmacy Bulk Package (parenteral preparations for admixtures)? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.5.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **NA**
Is there a prominent, boxed declaration reading "Pharmacy Bulk Package – Not for Direct Infusion" on the principal display panel following the expression of strength? **NA**
Does the container label include graduation marks? **NA**
Are instructions for reconstitution and resultant concentration provided, if space permits? **NA**
Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **NA**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **NA**

Reviewer Comments:

3.1.5 RX: UNIT DOSE BLISTER LABEL

Is container a Unit Dose Blister Pack? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.1.6.

Reviewer Assessment:

Does each blister include only one dosage unit (e.g., one tablet, one capsule)? **NA**
Do proprietary name, established name, strength, bar code, and manufacturer appear accurately on each blister cell? **NA**

Reviewer Comments:

3.1.6 RX: CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Was carton labeling submitted? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Are the answers to the Container Label questions the same for the Carton Labeling? **NA** If no, please explain the differences in the Reviewer Comments section.
If container is too small or otherwise unable to accommodate a label with enough space to include all required information, is all required information present on the carton labeling? **NA**
If country of origin is not on Container, does it appear on outer packaging labeling? **NA**

Reviewer Comments:

3.2 OTC (OVER THE COUNTER) DRUG PRODUCT

3.2.1 OTC: LABELING THAT INCLUDES DRUGS FACTS INFORMATION

Reviewer Assessment:

Is Drug Facts Labeling format acceptable per 21 CFR 201.66? **NA**
Does "Questions?" have a toll-free number no less than 6 pt. font size per 21 CFR 201.66(c)(9) or "1-800-FDA-1088" per 21 CFR 201.66 (c)(5)(vii)? **NA**
Did firm submit a Labeling Format Information Table to evaluate the font size? **NA**
Is the applicant's "patent carve out" acceptable? **NA**
Is the applicant's "exclusivity carve out" acceptable? **NA**
Is the established name for this ANDA acceptable? **NA**
Is title case used in expressing the established name? **NA**
Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **NA**
Is the following information properly displayed?
- Pharmacological category: **NA**
- Net quantity statement: **NA**
- Route(s) of administration (other than oral): **NA**
- Warnings (if any) or cautionary statements (if any): **NA**
- NDC: **NA**
- Bar code per 21 CFR 201.25(c)(2): **NA**

Is the Manufacturer/Distributor/Packager statement acceptable? **NA**
For foreign manufacturers, does the labeling have the country of origin? **NA**
Are the required USP recommendations reflected in the labeling? **NA**
Is the storage statement acceptable? **NA**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**
Are multiple strengths differentiated by use of different color or other acceptable means? **NA**
Are the labels of related products differentiated to avoid selection errors? **NA**

Reviewer Comments:

3.2.1.1 OTC: INACTIVE INGREDIENTS COMPARISON

We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

Table 8: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling Inactive Ingredients	**ANDA Inactive Ingredients**
Click here to enter text.	Click here to enter text.

Reviewer Assessment:

Are the inactive ingredients information consistent with "Components and Composition" information as provided in Module 3.2.P.1? **NA**
Are the inactive ingredients listed in alphabetical order? **NA**
For products required/recommended to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **NA**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **NA** Has the statement been verified by chemistry? **NA**

Reviewer Comments:

3.2.1.2 OTC: HOW SUPPLIED AND STORAGE INFORMATION

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 9 and will be referred to the appropriate review discipline for evaluation.

Table 9 Comparison of Model Labeling to ANDA finished product	
Model Labeling	**Description of Finished Product** (Source: Click here to enter text.) Click here to enter text. **Package Configurations** (Source: Click here to enter text.) Click here to enter text. **Storage Conditions** (Source: Click here to enter text.) Click here to enter text.
ANDA	**Description of Finished Product** (Source: Click here to enter text.) Click here to enter text. **Package Configurations** (Source: Click here to enter text.) Click here to enter text. **Storage Conditions** (Source: Click here to enter text.) Click here to enter text.

Reviewer Assessment:

Is the description (scoring, color and imprint) of the finished product consistent with the Drug Product Quality submission? **NA**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NA**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **NA**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **NA**
Is the storage statement acceptable as compared to the Model Labeling? **NA**
Is the storage statement acceptable as compared to USP? **NA**

Reviewer Comments:

3.2.2 OTC: PATIENT LABELING

Is patient labeling required? **NA**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Was patient labeling submitted? **NA**
Is the patient labeling the same as the model labeling, except for allowable differences? **NA**

Reviewer Comments:

3.3 CONTAINER/CLOSURE

We evaluated the container/closure system of this product to determine if special child-resistant packaging is required based on packaging configuration. Additionally, we evaluated other aspects of the container closure that relate to the dosage form, product formulation, and product class. Below is a description of the container/closure for the ANDA product.

Reviewer Assessment:

Describe container closure (e.g., 30s CRC, 100s non-CRC) and cite source of information in **Reviewer Comments** text box.
Does the container require a child-resistant closure (CRC) as described in the Poison Prevention Act and regulations? **YES**
Are the tamper evident requirements met for OTC and Controlled Substances? (If quality review follows the chemistry-labeling MOU, obtain answer from Appendix D of chemistry review; if quality review does not follow the MOU, labeling reviewer is responsible for assessing for tamper evidence) **NA**

For ophthalmic products:

Does this ophthalmic product cap color match the American Academy of Ophthalmology (AAO) packaging color-coding scheme? **NA**

For parenteral products:

Is there text on the cap/ferrule overseal of this injectable product? **NA**
If YES, does text comply with the recommendations in USP General Chapter <1>? **NA**
What is the cap color? NA

NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Reviewer Comments: From 3.2.P.7.1: 100s CRC

3.4 CALCULATIONS FOR CONTENTS IN LABELING

Is calculation of ingredient(s) required? **NO**
If YES, go to Table 10 and Reviewer Assessment below, if NO go to section 3.5.

We verified the calculation on the following content.

Table 10: Ingredients

Ingredient	Stated Content	Location of the Information
Click here to enter text.	Click here to enter text.	Click here to enter text.

(Note: For Rx products, if chemistry review follows the MOU, chemistry reviewer will verify the accuracy of the active and inactive ingredient amount(s) if information is in the DESCRIPTION and HOW SUPPLIED sections for all products, and additionally, DOSAGE AND ADMINISTRATION section for parenteral products. See Chemistry-Labeling MOU, Appendix A, Miscellaneous section for discussion on calculations.)

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling MOU? **NA**
Are the stated contents in the table above acceptable? **NA**

Aluminum content in small volume parenterals, large volume parenterals, and pharmacy bulk packages, which are used in TPNs, need to be in the labeling per 21 CFR 201.323.

Did the chemistry reviewer verify the aluminum content? **NA**

Are the labeling requirements met per 21 CFR 201.323? **NA**

Reviewer Comments:

3.5 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

Was SPL submitted? **YES**

We evaluated the SPL data elements to ensure they are consistent with the information submitted in the ANDA.

	(b) (4)
Tablet/Capsule Strength	
500 mg	

Reviewer Assessment:

For solid oral dosage forms: Do size and imprint code from the SPL data elements match the information provided in the quality submission? **YES**

Are all the other data elements (strength, inactive ingredients, product characteristics, packaging etc.) consistent with the information submitted in the ANDA labeling? **YES**

Reviewer Comments: From 3.2.P.1.2 Comparative evaluation of generic drug product and reference listed drug product:

(b) (4)

4. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments: Issues for Drug Product Reviewer: Does the drug product complies with the Guidance for Industry Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation, to state functionally-scored in the labeling?

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other review discipline reviewer(s):

Reviewer Comments: NA

6. SPECIAL CONSIDERATIONS

NA

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 12 and 13 provide a summary of recommendations for each labeling piece analyzed in this review.

Table 12: Review Summary of Container Label and Carton Labeling

	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container (500 mg)	**Draft**	(bottles of 100s)	12/16/2016	Satisfactory
Table 13 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	July 2016	12/16/2016	Revise
Medication Guide	Draft	July 2016	12/16/2016	Revise
SPL Data Elements		8/2016	12/16/2016	Satisfactory

Adolph Vezza

Digitally signed by Adolph Vezza
Date: 3/23/2017 11:10:56AM
GUID: 508da70600028a9e6a494d73e6454d09

Lily Chua

Digitally signed by Lily Chua
Date: 2/28/2017 08:42:54AM
GUID: 5277fc6700089cebb6783d59b3e106fa

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209822

CHEMISTRY REVIEWS

QUALITY ASSESSMENT

Recommendation: *Approvable*

ANDA 209822
Review # 03

Drug Name/Dosage Form	Vigabatrin Tablets, USP	
Strength	500 mg	
Route of Administration	Oral	
Rx/OTC Dispensed	Rx	
Applicant	***Name and Address of Applicant***	***DP Manufacturing facility***
	Teva Pharmaceuticals USA 200 Elmora Ave. Elizabeth NJ 07207 USA regulatoryaffairsUS@actavis.com	Watson Pharma Private Limited (b) (4) Verna Salcette, Goa 403722 India (b) (4)
US agent, if applicable	NA	

Submission(s) Reviewed	Document Date	Disciplines Affected
Original submission	12/16/2016	All
Response to CR Major	03/12/2018	All
Response to CR letter	*10/19/2018*	*All*

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance		
Drug Product	Ravi Erukulla	OLDP/Branch I/DIRP1
Process		
Microbiology		
Facility		
Biopharmaceutics		
Regulatory Business Process Manager		
Application Technical Lead	Yuping Niu	OLDP/Branch I/DIRP1
Laboratory (OTR)		
ORA Lead		
Environmental Analysis (EA)		

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	Reviewer
Type II					
[redacted]	[redacted]	[redacted] (b) (4)	***Adequate***	*09/24/2018*	*Sun X. (Amendment 13)*
Type III					
[redacted] (b) (4)			N/A		
			N/A		
			N/A		
			N/A		
			N/A		
			N/A		
			N/A		
			N/A		
Type IV					

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed).

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	020427	RLD

2. CONSULTS: ***None***

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

Executive Summary

I. Recommendations

A. Recommendations and Conclusion on Approvability

CMC is ***Approvable***.

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

N/A

II. Summary of Quality Assessments

A. Product Overview

<table>
<tr><td>Proposed Indication(s) including Intended Patient Population</td><td>Vigabatrin tablets, USP are indicated for the treatment of:
• Refractory Complex Partial Seizures in patients ≥10 years of age

Dosage and Administration
<table>
<tr><th>Indication</th><th>Adult</th><th>Pediatric</th></tr>
<tr><td>Seizures</td><td>1000 mg/day (500 mg twice daily)
Increase to 3000 mg/day (1500 twice daily)</td><td>500 mg/day (250 mg twice)
Increase to 2000 mg/day (1000 twice daily)</td></tr>
</table></td></tr>
<tr><td>Duration of Treatment</td><td>NA</td></tr>
<tr><td>Maximum Daily Dose</td><td>3000 mg</td></tr>
<tr><td>Alternative Methods of Administration</td><td>Per physician recommendation</td></tr>
</table>

B. Quality Assessment Overview

Drug Substance:

Vigabatrin is a white or almost white powder and manufactured by (b) (4) (b) (4) The Drug Substance Vigabatrin is freely soluble in water, slightly soluble in Methanol and (b) (4)

Vigabatrin has an official USP monograph.

Drug Product:

(i) Description of Drug Product

The Vigabatrin tablets description is listed in below table.

500 mg	White to off-white, film coated, oval, biconvex tablet functionally scored on one side and debossed with 'A314' on the other side

The drug product is an Immediate Release formulation has an active ingredient Vigabatrin. The active ingredient concentration is equal to RLD tablet. The excipients used in proposed generic drug is fairly described and listed in FDA's Inactive Ingredients Database.

(b) (4)

[redacted]

C. Biopharmaceutics Considerations

1. BCS Classification

- Drug Substance: Firm stated that the product is BCS Class I with high solubility and high permeability (under DBE review).
- Drug Product:

2. Biowaiver/Biostudies

- Biowaiver Request: Firm requested BE waiver based on their proposed BCS classification of the DS. As per GDRP information Bioequivalence review is *adequate*.
- PK Studies:

- Dissolution: Biopharmaceutics review *adequate*.

D. Special Product Quality Labeling Recommendations (N/A)

E. Final Risk Assessment (see Attachment)

ATTACHMENT I: Final Risk Assessments

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LABELING

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☒ Yes ☐ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

(b) (4)

[Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer].

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No

If "No," explain.

The drug product is neither OTC Drugs nor Controlled Substance.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	length (mm)	Imprint Code
500 mg	-	White to off-white, film coated, oval, biconvex tablet, functionally scored on one side and debossed with 'A314' on the other side

White to off-white, film coated, oval, biconvex tablet functionally scored on one side and debossed with 'A314' on the other side

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: *None*

List of Deficiencies: *None*

Primary Drug Product Reviewer: *Ravi Erukulla/04-28-2017, 07/11/2018(v3)*
Secondary Reviewer: Yuping Niu / 7-6-2018(v2), 7-16-2018

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Yuping Niu

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Date: 11/16/2018 02:07:27PM
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Ravi Erukulla

Digitally signed by Ravi Erukulla
Date: 11/16/2018 02:14:04PM
GUID: 57224b6b009387827442458c6b28325d

QUALITY ASSESSMENT

Recommendation: *Not Approvable – IR Minor*

ANDA 209822
Review # 02

Drug Name/Dosage Form	Vigabatrin Tablets, USP	
Strength	500 mg	
Route of Administration	Oral	
Rx/OTC Dispensed	Rx	
Applicant	***Name and Address of Applicant***	***DP Manufacturing facility***
	Teva Pharmaceuticals USA 200 Elmora Ave. Elizabeth NJ 07207 USA regulatoryaffairsUS@actavis.com	Watson Pharma Private Limited (b) (4) Verna Salcette, Goa 403722 India (b) (4)
US agent, if applicable	NA	

Submission(s) Reviewed	Document Date	Disciplines Affected
Original submission	12/16/2016	All
Response to CR Major	*03/12/2018*	*All*

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance		
Drug Product	Ravi Erukulla	OLDP/Branch I/DIRP1
Process		
Microbiology		
Facility		
Biopharmaceutics		
Regulatory Business Process Manager		
Application Technical Lead	Yuping Niu	OLDP/Branch I/DIRP1
Laboratory (OTR)		
ORA Lead		
Environmental Analysis (EA)		

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	Reviewer
Type II					
[redacted] (b) (4)			*Adequate*	10/03/2017 per GDRP	Dai W. (Amendment 11)
Type III					
[redacted] (b) (4)			N/A		
			N/A		
			N/A		
			N/A		
			N/A		
			N/A		
			N/A		
			N/A		
Type IV					

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed).

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	020427	RLD

2. CONSULTS: ***None***

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

Executive Summary

I. Recommendations

A. Recommendations and Conclusion on Approvability

CMC is ***Not Approvable***. It is recommended that ***Minor*** deficiency letter to be sent to the sponsor.

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

N/A

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	***Vigabatrin tablets, USP are indicated for the treatment of:*** • Refractory Complex Partial Seizures in patients ≥10 years of age ***Dosage and Administration*** **Indication** / **Adult** / **Pediatric** Seizures / 1000 mg/day (500 mg twice daily) Increase to 3000 mg/day (1500 twice daily) / 500 mg/day (250 mg twice) Increase to 2000 mg/day (1000 twice daily)
Duration of Treatment	NA
Maximum Daily Dose	3000 mg
Alternative Methods of Administration	Per physician recommendation

B. Quality Assessment Overview

Drug Substance:

Vigabatrin is a white or almost white powder and manufactured by (b) (4) (b) (4) The Drug Substance Vigabatrin is freely soluble in water, slightly soluble in Methanol and (b) (4)

Vigabatrin has an official USP monograph.

Drug Product:

(i) Description of Drug Product

The Vigabatrin tablets description is listed in below table.

500 mg	White to off-white, film coated, oval, biconvex tablet functionally scored on one side and debossed with 'A314' on the other side

The drug product is an Immediate Release formulation has an active ingredient Vigabatrin. The active ingredient concentration is equal to RLD tablet. The excipients used in proposed generic drug is fairly described and listed in FDA's Inactive Ingredients Database.

(b) (4)

[redacted]

C. Biopharmaceutics Considerations

1. BCS Classification

- Drug Substance: Firm stated that the product is BCS Class I with high solubility and high permeability (under DBE review).
- Drug Product:

2. Biowaiver/Biostudies

- Biowaiver Request: Firm requested BE waiver based on their proposed BCS classification of the DS. As per GDRP information Bioequivalence review is Inadequate - Major
- PK Studies:
- Dissolution: Biopharmaceutics review pending

D. Special Product Quality Labeling Recommendations (N/A)

E. Final Risk Assessment (see Attachment)

ATTACHMENT I: Final Risk Assessments

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LABELING

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☒ Yes ☐ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

(b) (4)

[Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer].

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No

If "No," explain.

The drug product is neither OTC Drugs nor Controlled Substance.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	length (mm)	Imprint Code
500 mg	-	White to off-white, film coated, oval, biconvex tablet, functionally scored on one side and debossed with 'A314' on the other side

White to off-white, film coated, oval, biconvex tablet functionally scored on one side and debossed with 'A314' on the other side

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: *None*

List of Deficiencies: *None*

Primary Drug Product Reviewer: *Ravi Erukulla/04-28-2017, 07/11/2018(v3)*
Secondary Reviewer: Yuping Niu / 7-6-2018(v2), 7-16-2018

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PROCESS

Product Background Vigabatrin Tablets, USP 500 mg, are indicated for the adjunctive treatment of Refractory Complex Partial with expanded use in children 10-16 years of age with refractory complex partial seizures . Sabril ® 500 mg is the Brand name which were approved on August 21st 2009 as Immediate Release Tablet for USA market. The drug product needs to be stored at 20 ºC to 25 ºC (68 ºF to 77 ºF) [see USP Controlled Room Temperature]

Related NDAs
ANDA 209822 references Sabril (vigabatrin) Tablets NDA 020427 owned by Lundbeck Pharmaceuticals LLC.

Drug Product Name / Strength:
The proposed drug product has (b) (4) 500 mg in a tablet (b) (4) (b) (4) (b) (4) The formulation ingredients include Microcrystalline (b) (4) (b) (4) povidone (b) (4) (b) (4), Sodium Starch Glycolate (b) (4) and magnesium stearate. (b) (4) (b) (4)

Route of Administration:
Oral administration

Applicant Name:
Teva US Generics

Review Summary: Adequate
The manufacturing process of Vigabatrin tablets is a (b) (4) (b) (4)

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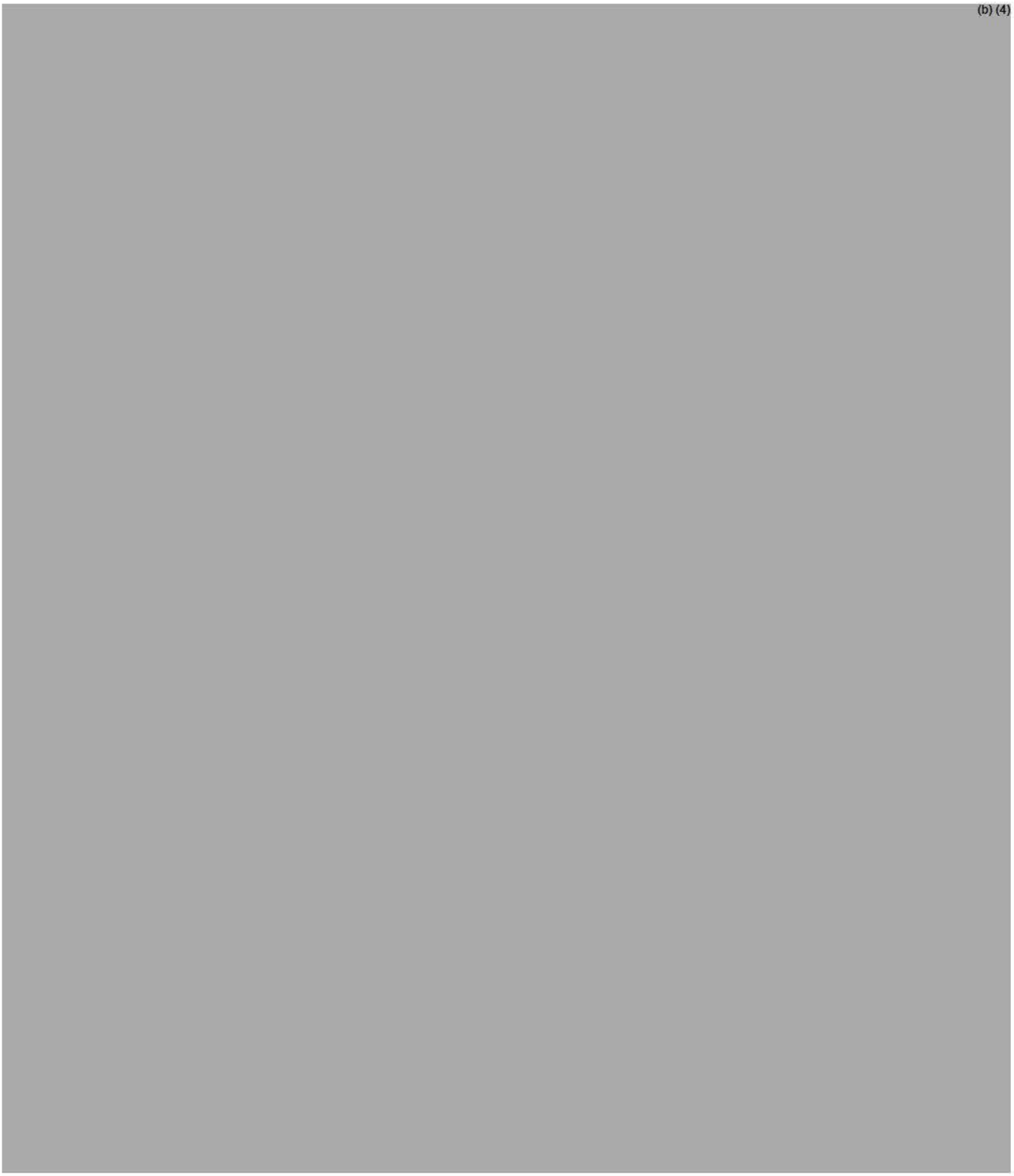
(b) (4)



Comparability Protocols

Reviewer's Assessment: N/A

N/A

Post-Approval Commitments

Reviewer's Assessment: Adequate

No Validation study or plan was submitted in current application.

Lifecycle Management Considerations

N/A

List of Deficiencies:

None

Primary Process Reviewer Name and Date:

Tianhong Tim Zhou, Ph. D. June 26nd, 2017, July 6th, 2017; August 8th, 2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Minor revisions/questions are noted.

N. Chidambaram, Ph.D., 07/06/2017

I concur

N. Chidambaram, Ph.D., 07/06/2017, 08/09/2018

QUALITY ASSESSMENT

Recommendation: ***Not Approvable – Minor (CR due to BE major)***

ANDA 209822
Review # 01

Drug Name/Dosage Form	Vigabatrin Tablets, USP	
Strength	500 mg	
Route of Administration	Oral	
Rx/OTC Dispensed	Rx	
Applicant	***Name and Address of Applicant***	***DP Manufacturing facility***
	Teva Pharmaceuticals USA 200 Elmora Ave. Elizabeth NJ 07207 USA regulatoryaffairsUS@actavis.com	Watson Pharma Private Limited (b) (4) Verna Salcette, Goa 403722 India (b) (4)
US agent, if applicable	NA	

Submission(s) Reviewed	**Document Date**
Original submission (Multiple Categories/Subcategories)	12/16/2016
General Correspondance	01/13/2017
Multiple Categories / Subcategories	03/29/2017
Multiple Categories / Subcategories	04/04/2017
REMS / Amendment	04/26/2017
Multiple Categories / Subcategories	04/27/2017
Multiple Categories / Subcategories	05/24/2017
Multiple Categories / Subcategories	06/22/2017
Multiple Categories / Subcategories	08/23/2017
Multiple Categories / Subcategories	09/26/2017

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance		
Drug Product	Ravi Erukulla	OLDP/Branch I/DIRP1
Process		
Microbiology		
Facility		
Biopharmaceutics		
Regulatory Business Process Manager		
Application Technical Lead	Yuping Niu	OLDP/Branch I/DIRP1
Laboratory (OTR)		
ORA Lead		
Environmental Analysis (EA)		

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	Reviewer
Type II					
		(b) (4)	*Adequate*	10/03/2017 per GDRP	Dai W. (Amedment 11)
Type III					
		(b) (4)	N/A		
			N/A		
			N/A		
			N/A		
			N/A		
			N/A		
			N/A		
			N/A		
Type IV					

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed).

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	020427	RLD

2. CONSULTS: ***None***

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

Executive Summary

I. Recommendations

A. Recommendations and Conclusion on Approvability

CMC is ***Not Approvable***. It is recommended that ***Minor*** deficiency letter to be sent to the sponsor.

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

N/A

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	***Vigabatrin tablets, USP are indicated for the treatment of:*** • Refractory Complex Partial Seizures in patients ≥10 years of age ***Dosage and Administration*** **Indication** / **Adult** / **Pediatric** Seizures / 1000 mg/day (500 mg twice daily) Increase to 3000 mg/day (1500 twice daily) / 500 mg/day (250 mg twice) Increase to 2000 mg/day (1000 twice daily)
Duration of Treatment	NA
Maximum Daily Dose	3000 mg
Alternative Methods of Administration	Per physician recommendation

B. Quality Assessment Overview

Drug Substance:

Vigabatrin is a white or almost white powder and manufactured by (b) (4) (b) (4) The Drug Substance Vigabatrin is freely soluble in water, slightly soluble in Methanol and (b) (4)

Vigabatrin has an official USP monograph.

Drug Product:

(i) Description of Drug Product

The Vigabatrin tablets description is listed in below table.

500 mg	White to off-white, film coated, oval, biconvex tablet functionally scored on one side and debossed with 'A314' on the other side

The drug product is an Immediate Release formulation has an active ingredient Vigabatrin. The active ingredient concentration is equal to RLD tablet. The excipients used in proposed generic drug is fairly described and listed in FDA's Inactive Ingredients Database.

(b) (4)

C. Biopharmaceutics Considerations

1. BCS Classification

- Drug Substance: Firm stated that the product is BCS Class I with high solubility and high permeability (under DBE review).
- Drug Product:

2. Biowaiver/Biostudies

- Biowaiver Request: Firm requested BE waiver based on their proposed BCS classification of the DS . As per GDRP information Bioequivalence review is Inadequate - Major
- PK Studies:
- Dissolution: Biopharmaceutics review inadequate

D. Special Product Quality Labeling Recommendations (N/A)

E. Final Risk Assessment (see Attachment)

ATTACHMENT I: Final Risk Assessments

Following this page, 66 Pages Withheld in Full as (b)(4)

(b) (4)

R. Regional Information

Environmental Analysis:

Reviewer's Assessment:
EA certificate is provided in module 1.12.14 to claim categorical exclusion under 21 CFR 25.31 and 25.15(d). This is acceptable.

Methods Validation Package: 3.2.R.3.S & 3.2.R.3.P

Comparability Protocols: No protocols provided

Post-Approval Commitments: N/A

Lifecycle Management Considerations: N/A

List of Deficiencies from Drug Product:

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.

9. (b) (4)

10

Section B:

1. (b) (4)

2. Please provide all available long term stability data in your next amendment.

Primary Drug Product Reviewer: *Ravi Erukulla/04-28-2017, 07/11/2017, 10/03/2017, 10/04/2017*
Secondary Reviewer: Yuping Niu */07-07-2017, 07/14/2017, 10/05/2017*

LABELING

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☒ Yes ☐ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

(b) (4)

[Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer].

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No

If "No," explain.

The drug product is neither OTC Drugs nor Controlled Substance.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	length (mm)	Imprint Code
500 mg	-	White to off-white, film coated, oval, biconvex tablet, functionally scored on one side and debossed with 'A314' on the other side

White to off-white, film coated, oval, biconvex tablet functionally scored on one side and debossed with 'A314' on the other side

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer: *None*

List of Deficiencies: *None*

Primary Drug Product Reviewer: *Ravi Erukulla/04-28-2017, 07/11/2017*

Secondary Drug Product Reviewer: *Yuping Niu/07-07-2017, 07/14/2017*

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Yuping Niu

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Ravi Erukulla

Digitally signed by Ravi Erukulla
Date: 10/05/2017 09:06:25AM
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PROCESS

Product Background Vigabatrin Tablets, USP 500 mg, are indicated for the adjunctive treatment of Refractory Complex Partial with expanded use in children 10-16 years of age with refractory complex partial seizures . Sabril ® 500 mg is the Brand name which were approved on August 21st 2009 as Immediate Release Tablet for USA market. The drug product needs to be stored at 20 °C to 25 °C (68 °F to 77 °F) [see USP Controlled Room Temperature]

Related NDAs
ANDA 209822 references Sabril (vigabatrin) Tablets NDA 020427 owned by Lundbeck Pharmaceuticals LLC.

Drug Product Name / Strength:
The proposed drug product has (b) (4) 500 mg in a tablet (b) (4)

The formulation ingredients include Microcrystalline Cellulose (b) (4) povidone (b) (4), Sodium Starch Glycolate (b) (4) and magnesium stearate. (b) (4)

Route of Administration:
Oral administration

Applicant Name:
Teva US Generics

Review Summary:
The manufacturing process of Vigabatrin tablets is a (b) (4)

Following this page, 34 Pages Withheld in Full as (b)(4)

(b) (4)

[redacted]

Comparability Protocols

Reviewer's Assessment: N/A

N/A

Post-Approval Commitments

Reviewer's Assessment: Adequate

No Validation study or plan was submitted in current application.

Lifecycle Management Considerations

N/A

List of Deficiencies:

(b) (4)

[redacted]

Primary Process Reviewer Name and Date:

Tianhong Tim Zhou, Ph. D. June 26nd, 2017, July 6th, 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Minor revisions/questions are noted.

N. Chidambaram, Ph.D., 07/06/2017

I concur

N. Chidambaram, Ph.D., 07/06/2017

Tianhong Tim Zhou

Digitally signed by Tianhong Tim Zhou
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Nallaperumal Chidambaram

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FACILITIES

Product Background

ANDA/NDA: ANDA 209822-ORIG-1

Drug Product Name / Strength: Vigabatrin Tablets USP 500 mg

Route of Administration: Oral

Applicant Name: Teva Pharmaceuticals USA

Review Recommendation: Submission is recommended for approval from a facilities assessment standpoint.

Review Summary: All facilities are acceptable for the operations listed in ANDA 209822.

List Submissions being reviewed: ANDA 209822-ORIG-1

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None.

List Number of Comparability Protocols (ANDA only): N/A

3.2.S.2 Manufacture

Summary of Facility Information:

(b) (4)

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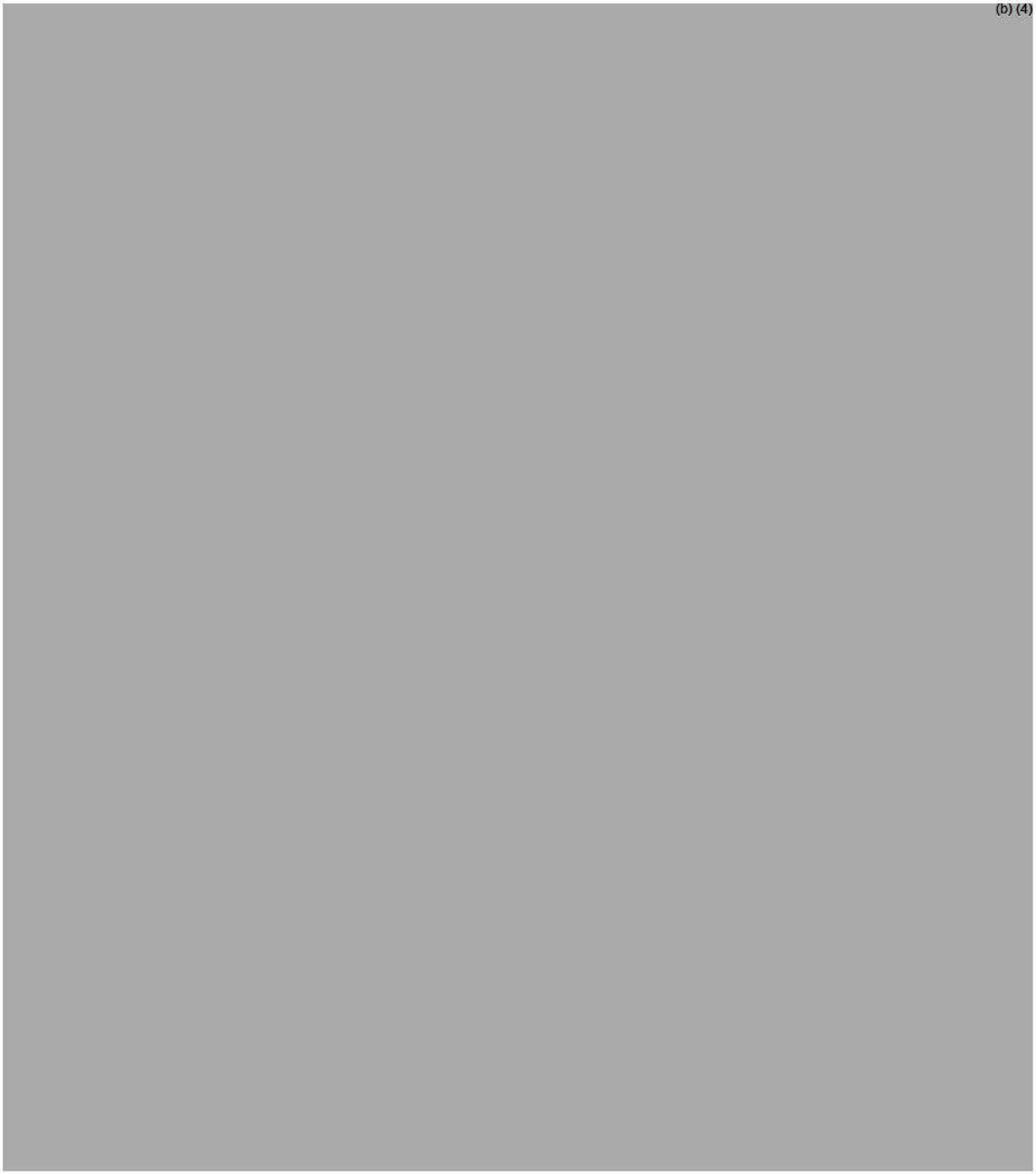
(b) (4)



Comparability Protocols

Reviewer's Assessment: N/A

Post-Approval Commitments (For NDA only)

Reviewer's Assessment: N/A

Lifecycle Management Considerations

None

List of Deficiencies:

No facilities deficiencies identified. Subject ANDA is recommended for approval from a facilities assessment standpoint.

Primary Facilities Reviewer Name and Date:

Steven Fong, Ph.D., Microbiologist OPQ/OPF/DIA Branch I, 09/11/2017

Secondary Reviewer Name and Date:

Zhihao Peter Qiu, Branch Chief, CDER/OPQ/OPF/DIA, Branch 1, 09/11/2017

Steven Fong

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Zhihao Peter Qiu

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209822

BIOEQUIVALENCE REVIEWS

BIOPHARMACEUTICS REVIEW FOR ANDA SUBMISSION	
Application No.:	ANDA-209822-ORIG-1
Applicant/Sponsor:	Teva Pharmaceuticals USA
Product Name:	Vigabatrin Oral Tablets
Dosage Form/Strength:	Tablets/500 mg
Intended Use:	Treatment of Refractory Complex Partial Seizures as adjunctive therapy in patients greater than or equal to 10 years of age who have responded inadequately to several alternative treatments
Reference Listed Drug:	NDA-20427 [Sabril® (Vigabatrin) Tablets, 500 mg]
Submission Dates:	12/16/2016 3/12/2018 (Response to Information Request dated 10/17/2017)
Review Date:	8/7/2018
Primary Reviewer:	Yang Zhao, Ph.D.
Secondary Reviewers:	Ta-Chen Wu, Ph.D.
Recommendation:	**ADEQUATE**

1. EXECUTIVE SUMMARY:

Submission: Teva Pharmaceuticals USA submitted ANDA-209822 seeking approval for the proposed Vigabatrin Tablets 500 mg under section of 505(j) of the Federal Food, Drug, and Cosmetic Act.

Review: The focus of the Biopharmaceutics Review is the evaluation of data supporting the adequacy of the proposed dissolution method and acceptance criterion for the dissolution test for the proposed drug products.

Reviewer's Assessment: The proposed dissolution method and revised dissolution acceptance criterion are acceptable.

Acceptable dissolution method and dissolution acceptance criterion				
USP Apparatus	**Speed (rpm)**	**Medium**	**Volume (mL)**	**Acceptance criterion**
II (paddle)	50	water@37 °C	900	Q= (b) (4) % dissolved in 15 minutes

Recommendation: From a Biopharmaceutics perspective, ANDA 209822 for Vigabatrin Tablets 500 mg is recommended for **APPROVAL**.

2. SUBMISSION CONTENT CHECKLIST:

	INFORMATION	YES	NO	N/A
1	Is there a USP dissolution method?	☐	☒	☐
2	Did the Applicant use the USP dissolution method?	☐	☐	☒
3	Is there an FDA database dissolution method?	☒	☐	☐
4	Did the Applicant use the FDA database dissolution method?	☒	☐	☐
5	Did the Applicant conduct dissolution testing with an in-house method?	☐	☒	☐
6	Did the Applicant use 12 units of the test drug products in the dissolution testing?	☒	☐	☐
7	Did the Applicant provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)?	☒	☐	☐
8	Was the dissolution method SOP effective at the time of testing?	☒	☐	☐
9	Is the validation of the analytical method used for dissolution testing acceptable?	☒	☐	☐
10	Was the dissolution/release testing conducted using an unexpired product?	☒	☐	☐
11	Do any of the proposed product strengths have functional scoring?	☒	☐	☐
12	Was the dissolution/release testing conducted using split tablets?	☒	☐	☐

3. REVIEW SUMMARY:

a) Proposed dissolution method and acceptance criterion:

USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance criterion
II (paddle)	50	water@37 °C	900	Q=75% dissolved in 30 minutes

The Applicant reported that vigabatrin is a very highly soluble molecule (Table 1).

Table 1. Solubility of vigabatrin in different pH media measured at 25 °C

Solvent Media	Solubility (mg/ml)
pH 1.2 Solution	300 mg/1 mL
pH 3.0 Solution	300 mg/1 mL
pH 4.5 Solution	300 mg/1 mL
pH 6.8 Solution	300 mg/1 mL
pH 7.2 Solution	300 mg/1 mL
pH 8.0 Solution	300 mg/1 mL

b) In vitro dissolution data for Vigabatrin Tablets 500 mg:

The whole Vigabatrin Tablets were less than 4 months old at the time of the dissolution testing. The Applicant provided dissolution data at 30 minutes for the stability samples. There are no apparent changes in the Applicant's provided dissolution data at 30 minutes of the stability samples in various storage conditions (long-term condition up to 24 months).

(b) (4)

The proposed Vigabatrin Tablets 500 mg are functionally-scored on one side and debossed with A314 on the other side. The similarity factor (f_2) between the whole and the split Vigabatrin Tablets is not calculated because all dissolution profiles showed more than (b) (4)% dissolved in 15 minutes.

(b) (4)

The similarity in dissolution profiles between the whole and the split tablets support the tablet scoring on the proposed Vigabatrin Tablets, 500 mg.

The originally proposed dissolution acceptance criterion of "Q=75% dissolved in 30 minutes" is permissive and NOT acceptable. Based on the dissolution profile data, in the Complete Response Letter issued on 10/17/2017, the Agency recommended the following dissolution acceptance criterion for the proposed drug product: Q= (b)(4)% in 15 minutes. In the Response dated 3/12/2018, the Applicant accepted the Agency's recommendation and revised the dissolution acceptance criterion to Q= (b)(4)% in 15 minutes. The revised dissolution acceptance criterion is acceptable.

4. RECOMMENDATION:

From the Biopharmaceutics perspective, ANDA 209822 for the proposed Vigabatrin Tablets 500 mg is recommended for **APPROVAL**.

5. SIGNATURE BLOCK

Primary Biopharmaceutics Reviewer:
Yang Zhao, Ph.D., 8/7/2018
Division of Biopharmaceutics
Office of New Drug Products/OPQ

Secondary Biopharmaceutics Reviewer:
I concur with Dr. Yang Zhao's assessment.

Ta-Chen Wu, Ph.D., 8/7/2018
Acting Biopharmaceutics Lead
Division of Biopharmaceutics, ONDP/OPQ

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APPENDIX

CR comments: In the Complete Response Letter issued on 10/17/2017, the following Biopharmaceutics comments were conveyed to the Applicant:

1. The proposed acceptance criterion of "Q=75% dissolved in 30 minutes" is permissive and NOT acceptable. Based on the provided dissolution data, we recommend a dissolution acceptance criterion of "Q= (b)(4)% in 15 minutes" for your proposed drug products. Note that sometimes dissolution Stage 2 testing, and occasionally Stage 3 testing may be needed, which is acceptable.

2. Submit a copy of the updated drug product specification table with the revised acceptance criterion for the dissolution test and update other section of your submission as appropriate.

CR Response: In the Response dated 3/12/2018, the Applicant accepted the Agency's recommended dissolution acceptance criterion of Q= (b)(4)% in 15 minutes and revised the Finished Product and Stability specifications in Module 3.2.P.5.1.

Yang Zhao

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Ta-Chen Wu

Digitally signed by Ta-Chen Wu
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DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	209822	
Drug Product Name	Vigabatrin Tablets, USP	
Strength(s)	500 mg	
Applicant Name	Teva Pharmaceuticals USA, Inc.	
Applicant Address	200 Elmora Avenue Elizabeth, NJ 07207	
US Contact Name and US Mailing Address	Janak Jadeja, R.Ph., Director, Regulatory Affairs 200 Elmora Avenue Elizabeth, NJ 07207 RegulatoryAffairsUS@actavis.com	
US Contact Telephone Number	908-659-2595	
US Contact Fax Number	908-659-2250	
Original Submission Date(s)	Dec 16, 2016	
Submission Date(s) of Amendment(s) Under Review	Mar 12, 2018 (Complete Response Amendment)	
Primary Reviewer	Brittany Avaritt, Ph.D.	
Secondary Reviewer	Kuldeep Dhariwal, Ph.D.	
Study Number(s)	ACT-17201	ACT-17202
Study Type(s)	Fasting	Fed
Strength(s)	500 mg	500 mg
Clinical Site	Watson Therapeutics Inc.	
Clinical Site Address	3400 Enterprise Way Miramar, FL 33025, USA	
Analytical Site	(b) (4)	
Analytical Site Address		
Office of Study Integrity and Surveillance (OSIS) status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)** [1]	**Post October 1, 2014 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☒ **Complete** ☐ **N/A (Waiver/Deem Bioequivalent)** [1]

[1] Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

Waiver/Deem Bioequivalent	☐ Granted ☐ Tentatively granted ☐ Not granted ☒ N/A		
QC Dissolution	☒ Pending ☐ Adequate ☐ Inadequate		
Formulation	☒ Adequate ☐ Inadequate		
Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A		
Deficiency Classification	☐ Major ☐ Minor/IR ☒ N/A (Review is Adequate)		
Major Deficiency Theme	N/A		
Justification for Major Designation	N/A		
Overall Review Result	☒ Adequate ☐ Inadequate		
Product Specific Guidance (PSG) Referenced in Review	*Reminder: Check PSG in development spreadsheet on V:drive (if PSG is under development, wait for PSG to post to finalize the review)* ☒ Recommended/Latest Revision Date: Mar 2015 RLD Number: 020427 ☐ N/A (no PSG available at time of review)		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
11	Fasting	500 mg	☒ Adequate ☐ Inadequate
11	Fed	500 mg	☒ Adequate ☐ Inadequate

1 EXECUTIVE SUMMARY

This is a review of a **study amendment**.

The original application submitted Dec 16, 2016 contained solubility, permeability (in situ perfusion), and multimedia dissolution studies to support a BCS waiver request. The application was inadequate with multiple deficiencies. Additionally, the test product did not meet the BCS guidance criteria for classification as BCS class 1 because the test and reference product dissolution profiles were not similar.

This amendment contains the results of fasting and fed bioequivalence (BE) studies comparing a test product, Teva Pharmaceuticals USA's Vigabatrin Tablets, USP, 500 mg to the corresponding reference product, Lundbeck Pharmaceuticals LLC's SABRIL® (vigabatrin) Tablets, 500 mg. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male subjects. The applicant's fasting and fed BE studies are acceptable. The reviewer-calculated results are summarized in the tables below.

Vigabatrin Tablets, 500 mg Fasting Bioequivalence Study No. ACT-17201, N=24 (Male=24 and Female=0) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (µg·hr/mL)	55.69	55.02	1.01	98.96	103.53
AUC∞ (µg·hr/mL)	59.50	58.65	1.01	99.35	103.60
Cmax (µg/mL)	15.61	15.27	1.02	94.32	110.70

Vigabatrin Tablets, 500 mg Fed Bioequivalence Study No. ACT-17202, N=23 (Male=23 and Female=0) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (µg·hr/mL)	55.58	54.35	1.02	100.90	103.62
AUC∞ (µg·hr/mL)	59.91	58.64	1.02	100.33	104.04
Cmax (µg/mL)	11.34	11.96	0.95	86.34	104.12

Per GDRP, OSIS recommends accepting data without on-site inspections for the clinical[2] and analytical[3] sites. In addition, the studies submitted in the current ANDA do not indicate any conduct issues and no data integrity deficiencies were identified by the reviewer. The OSIS inspection status of the current ANDA is complete.

The application is adequate.

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[2] GDRP: ANDA-209822-ORIG-1-AMEND-11 Clinical PK/PD Sites Site: WATSON THERAPEUTICS, INC. Decline to Inspection_A209822_WatsonMiramar_Clin.pdf last updated by Nicola Fenty-Stewart on Mar 30, 2018

[3] GDRP: (b) (4) Bioanalytical Sites Site: (b) (4) Decline to Inspection_(b) (4)_A209822_(b) (4).pdf last updated by Nicola Fenty-Stewart on Mar 30, 2018

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3 REVIEW OF SUBMISSION

The applicant's responses to the deficiency comments provided in the Complete Response Letter issued Oct 12, 2017 are located in the cover letter to the Mar 12, 2018 submission. The applicant provided information for deficiencies related to the BCS waiver request in Module 1.11.3. Clinical Information Amendment. Because the applicant submitted fasting and fed in vivo BE studies and is seeking approval to market Teva Pharmaceuticals USA's Vigabatrin Tablets, USP, 500 mg based on the results of these BE studies the response to the deficiency comments will not be reviewed.

4 SUBMISSION SUMMARY

4.1 Drug Product Information

Test Drug Product and Strength(s)	Vigabatrin Tablets, USP, 500 mg
Reference Standard (RS) and Strength(s)	SABRIL® (vigabatrin) Tablets, 500 mg
RS Holder; NDA/ANDA Number; Approval Date[4]	Lundbeck Pharmaceuticals LLC; N020427; Aug 21, 2009
Reference Listed Drug (RLD) and Strength(s)	SABRIL® (vigabatrin) Tablets, 500 mg
RLD Holder; NDA/ANDA Number; Approval Date[4]	Lundbeck Pharmaceuticals LLC; N020427; Aug 21, 2009

4.2 PK/PD Information [5]

Most recent RLD label Please check if an NG/G/J tube study is needed.	Sabril Label 27Apr2017.pdf
Indication	SABRIL is indicated for the treatment of: • Refractory Complex Partial Seizures as adjunctive therapy in patients ≥10 years of age who have responded inadequately to several alternative treatments; SABRIL is not indicated as a first line agent • Infantile Spasms - monotherapy in infants 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss
Boxed warning	**WARNING: PERMANENT VISION LOSS** • SABRIL can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some

[4] Electronic Orange Book, updated through Mar 2018, last accessed May 2, 2018
[5] Drugs@FDA, NDA 020427 Label, updated Apr 27, 2017, last assessed May 2, 2018

cases, SABRIL also can damage the central retina and may decrease visual acuity *[see Warnings and Precautions (5.1)]*.

- The onset of vision loss from SABRIL is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time after starting treatment, even after months or years.
- Symptoms of vision loss from SABRIL are unlikely to be recognized by patients or caregivers before vision loss is severe. Vision loss of milder severity, while often unrecognized by the patient or caregiver, can still adversely affect function.
- The risk of vision loss increases with increasing dose and cumulative exposure, but there is no dose or exposure known to be free of risk of vision loss.
- Vision assessment is recommended at baseline (no later than 4 weeks after starting SABRIL), at least every 3 months during therapy, and about 3 to 6 months after the discontinuation of therapy.
- Once detected, vision loss due to SABRIL is not reversible. It is expected that, even with frequent monitoring, some patients will develop severe vision loss.
- Consider drug discontinuation, balancing benefit and risk, if vision loss is documented.
- Risk of new or worsening vision loss continues as long as SABRIL is used. It is possible that vision loss can worsen despite discontinuation of SABRIL.
- Because of the risk of vision loss, SABRIL should be withdrawn from patients with refractory complex partial seizures who fail to show substantial clinical benefit within 3 months of initiation and within 2-4 weeks of initiation for patients with infantile spasms, or sooner if treatment failure becomes obvious. Patient response to and continued need for SABRIL should be periodically reassessed.
- SABRIL should not be used in patients with, or at high risk of, other types of irreversible vision loss unless the benefits of treatment clearly outweigh the risks.
- SABRIL should not be used with other drugs associated with serious adverse ophthalmic effects such as retinopathy or glaucoma unless the benefits clearly outweigh the risks.
- Use the lowest dosage and shortest exposure to SABRIL consistent with clinical objectives *[see Dosage and Administration (2.1)]*.

Because of the risk of permanent vision loss, SABRIL is available only through a restricted program under a Risk Evaluation and Mitigation

	Strategy (REMS) called the Vigabatrin REMS Program *[see Warnings and Precautions (5.2)]*.
Bioavailability	Following oral administration, vigabatrin is essentially completely absorbed. Bioequivalence has been established between the oral solution and tablet formulations.
Food Effect	A food effect study involving administration of vigabatrin to healthy volunteers under fasting and fed conditions indicated that the Cmax was decreased by 33%, Tmax was increased to 2 hours, and AUC was unchanged under fed conditions.
Tmax	The time to maximum concentration (Tmax) is approximately 1 hour for children (10 years – 16 years) and adults, and approximately 2.5 hours for infants (5 months – 2 years).
Metabolism	Vigabatrin is not significantly metabolized; it is eliminated primarily through renal excretion. Vigabatrin induces CYP2C9, but does not induce other hepatic cytochrome P450 enzyme systems.
Excretion	Following administration of [14]C-vigabatrin to healthy male volunteers, about 95% of total radioactivity was recovered in the urine over 72 hours with the parent drug representing about 80% of this.
Half-life	The terminal half-life of vigabatrin is about 5.7 hours for infants (5 months – 2 years), 9.5 hours for children (10 years – 16 years), and 10.5 hours for adults.
Maximum Daily Dose	3000 mg

4.3 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance	Product-specific guidance for Vigabatrin Tablets, recommended Mar 2015  Vigabatrin Tablet Guidance.pdf Control #24501 BE Guidance Review  Vigabatrin Tablet N20427 BE Guidance F	
Summary of OGD or DB History	Approved ANDAs:	No
	Pending ANDAs:	(b) (4) A209822 (Teva) (b) (4)
	Controls:	None from current applicant

	Protocols:	None from current applicant
	Pending Citizen Petitions and other legal and regulatory issues:[6] If yes, please comment.	☒ Yes ☐ No CP FDA-2006-P-0461

4.4 Pre-Study Bioanalytical Method Validation

Information Requested	Analyte 1
Bioanalytical method validation report location	Module 5.3.1.4, analyt-validation.pdf Method Validation Report (b) (4), Page nos. 15, 77-80, 82, 83 and 84 of 87 Addendum I to (b) (4) Page nos. 16-20 and 23 of 25
Analyte	Vigabatrin
Internal standard (IS)	Vigabatrin 13CD2
Method description	LCMS/MS method, Solid phase extraction
Limit of quantitation	0.199
Recovery of drug at each QC (% CV)	AVG: 64.26 (8.14) HQC: 70.19 MQC: 62.30 LQC: 60.29
Average recovery of IS (%)	64.23
Standard curve concentrations (µg/mL)	0.199 to 50.501
QC concentrations (µg/mL)	LLOQQC: 0.203 LQC: 0.589 AQC: 2.031 MQC: 20.310 HQC: 38.686 DQC-2T: 77.930 DQC-4T: 155.859
QC Intraday precision range (%)	0.55 to 5.57
QC Intraday accuracy range (%)	88.08 to 112.37
QC Interday precision range (%)	4.49 to 8.30
QC Interday accuracy range (%)	93.60 to 99.39
Bench-top stability (hrs)	6 hr 30 min in ice water bath
Stock stability (days)	Short term working solution stability: 70.00 hr 30 min for analyte and 71.00 hr for IS at room temperature Short term stock solution stability: 71.00 hr at room temperature Long term stock solution stability: 28 days in cooling cabinet at 2°C to 8°C
Processed stability (hrs)	Wet extract: 4.00 hr at room temperature Dry extract: 31.00 hr in cooling cabinet at 2°C to 8°C 50 hr 55 min in autosampler at 5°C
Freeze-thaw stability (cycles)	4 cycles at -70°C (-60°C to -85°C) on ice water bath

[6] Please check DLRS policy updates in the link http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/DLRS/SitePages/Home.aspx

Long-term storage stability (days)	27 days at about -70°C (-60°C to -80°C) and below -20°C (-20°C to -35°C)
Dilution integrity	Concentration diluted 2 fold and 4 fold
Selectivity	No interfering peaks noted in blank plasma samples

SOP for bioanalytical method validation submitted?	☒ Yes ☐ No
Is the same anticoagulant used in the pre-method validation study and BE sample analysis? **If not, was cross validation study conducted?**	☒ Yes ☐ No K_2EDTA
Does the duration of the each of the LTSS stability parameters support the sample preparation/assay duration and clinical study sample storage temperature?	☒ Yes ☐ No
Was the % recovery consistent across QC concentrations?	☒ Yes ☐ No
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	☒ Yes ☐ No

Comments on the Pre-Study Method Validation: Adequate

Per the method validation report samples were thawed in an ice water bath, and the entire sample processing was carried out under yellow monochromatic light.

4.5 In Vivo Studies

Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (µg/mL)	*T_{max} (hr)	AUC_{0-t} (µg.hr/mL)	AUC_{0-inf} (µg hr/mL)	T ½ (hr)	K_{el} (hr^{-1})	
ACT-17201	The primary objective of the study was to assess the bioequivalence of Vigabatrin Tablets, 500 mg compared to that of Sabril® (vigabatrin) Tablets, 500 mg following a single oral dose (1 x 500 mg tablet) in healthy human, adult male subjects when administered under fasting conditions The secondary objective of the study was to assess the safety and tolerability of the test product and reference product in healthy human, adult male subjects	This was an open label, randomized, single dose, two treatment, two period, two sequence, crossover bioequivalence study under fasting conditions.	**Test Product (T):** Vigabatrin Tablets, 500 mg Batch No.: 1115900127 Per oral **Reference Product (R):** Sabril® (Vigabatrin) Tablets 500 mg Lot No.: 3150748 Per oral	24 subjects participated in this study and all of 24 participated subjects completed both the periods of the study and were analyzed for measurement of concentrations Vigabatrin (N=24) were considered for Pharmacokinetic and statistical analysis Mean age: 37.5 (Range: 22 – 53 years)	**Vigabatrin**						Module 5.3.1.2 Page nos 26, 27,37, 58, 59, & 61 of report-body.pdf
					Test Product (T)						
					16.08 ± 4.06 (25.25)	0.750 (0.500 - 2.000)	55.90 ± 8.00 (14.31)	59.82 ± 9.11 (15.23)	7.577 ± 1.028 (13.56)	0.0929 ± 0.0111 (11.92)	
					Reference Product (R)						
					15.49 ± 2.76 (17.83)	1.000 (0.750 - 1.750)	55.11 ± 6.84 (12.42)	58.82 ± 7.81 (13.28)	7.322 ± 1.025 (13.99)	0.0966 ± 0.0145 (14.99)	

Note: *For all parameters mean ± SD (%CV) values are reported except T_{max} for which median (min-max) values are reported.

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (µg/mL)	*T_{max} (hr)	AUC_{0-t} (µg hr/mL)	AUC_{0-inf} (µg hr/mL)	$T_{½}$ (hr)	K_{el} (hr^{-1})	
ACT-17202	The primary objective of the study is to assess the bioequivalence of Vigabatrin Tablets, 500 mg compared to that of Sabril® (vigabatrin) Tablets, 500 mg following a single oral dose (1 x 500 mg tablet) in healthy human, adult male subjects when administered under fed conditions. The secondary objective of the study is to assess the safety and tolerability of the test product and reference product in healthy human, adult male subjects	This was an open label, randomized, single dose, two treatment, two period, two sequence, crossover bioequivalence study under fed conditions.	**Test Product (T):** Vigabatrin Tablets, 500 mg Batch No.: 1115900127 Per oral **Reference Product (R):** Sabril® (Vigabatrin) Tablets 500 mg Lot No.: 3150748 Per oral	24 male subjects participated in this study and out of 24 participated subjects, 23 subjects completed the study and were analyzed for measurement of concentrations Vigabatrin (N=23) were considered for Pharmacokinetic and statistical analysis Mean age: 36.7 (Range: 25 - 48 years)	**Vigabatrin**						Module 5.3.1.2 Page nos. 26, 27, 37, 58, 59 & 61 of report-body.pdf
					Test Product (T)						
					11.58 ± 2.55 (22.02)	1.667 (1.000 - 5.000)	55.73 ± 9.56 (17.16)	60.15 ± 10.84 (18.02)	7.471 ± 1.135 (15.19)	0.0948 ± 0.0145 (15.24)	
					Reference Product (R)						
					12.30 ± 3.12 (25.39)	1.667 (1.000 - 5.000)	54.52 ± 9.85 (18.07)	59.03 ± 12.02 (20.36)	7.492 ± 1.487 (19.85)	0.0952 ± 0.0149 (15.67)	

Note: *For all parameters mean ± SD (%CV) values are reported except T_{max} for which median (min-max) values are reported.

5 APPENDIX

5.1 Individual Study Reviews

5.1.1 Single-dose Fasting Bioequivalence Study

5.1.1.1 Study Design

5.1.1.1.1 Study Information

Study Number	Study No. ACT-17201
Study Title	An open label, randomized, single dose, two way crossover bioequivalence study of Vigabatrin Tablets, 500 mg in healthy human, adult male subjects under fasting conditions.
Clinical Site (Name & Address)	Watson Therapeutics Inc. 3400 Enterprise Way Miramar, FL 33025, USA Phone: 954-266-1000 Ext. 1441100 Fax: 954-266-1012
Principal Clinical Investigator	Dr. Maria J. Gutierrez, M.D. Maria.Gutierrez@actavis.com
Dosing Dates	Period 1: Dec 16, 2017 Period 2: Dec 21, 2017
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	Jan 3-8, 2018
Principal Analytical Investigator	(b) (4)
Sample Storage: **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)** **(b) Temperature Range (e.g., -20°C to -80°C)**	(a) 24 days (b) -70°C (-60°C to -80°C) in deep freezer
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	27 days at about -70°C (-60°C to -80°C) and below -20°C (-20°C to -35°C)

5.1.1.1.2 Product (Bio-batch) Information

Product	Test	RLD
Treatment ID	T	R
Product Name	Vigabatrin Tablets, 500 mg	Sabril® (Vigabatrin) Tablets 500 mg
Manufacturer	Watson Pharma Pvt Ltd., Plot A-3 to A-6 Phase-I-A, Verna, Goa, India 403722	Manufactured by: Patheon Cincinnati, OH 45237, U.S.A for Lundbeck Deerfield, IL 60015, U.S.A
Batch/Lot No.	1115900127	3150748
Manufacture Date	10/31/2015	N/A
Expiration Date		May/2019
Strength	500 mg	500 mg
Dosage Form	Tablet	Tablet
Bio-Batch Size	(b) (4) Tablets	N/A
Production Batch Size	Tablets	N/A
Potency (Assay)	98.4%	97.2%
Content Uniformity (expressed as mean, % CV or per USP)	Mean: 98.3%, AV: 1.2	Mean: 96.7%, AV: 4.3
Dose Administered	1 x 500 mg	1 x 500 mg
Route of Administration	Oral	Oral

Are the test and reference products expired at the time of study? **If Yes, please comment.**	☒ Yes ☐ No The proposed shelf-life for Vigabatrin Tablets is 24 months. The test product (batch# 1115900127) was manufactured Oct 31, 2015, and the fasting and fed BE studies were conducted Dec 16-22, 2017. The 24-month stability testing for the test product (batch# 1115900127) was conducted on Jan 25, 2018 and conforms to all stability specifications per the Drug Product Quality review.
Is same bio-batch used in the dissolution and all BE studies? **If No, please comment.**	☒ Yes ☐ No
Is the bio-batch size at least the recommended minimum of 100K or 10% of the production batch (whichever is greater) for oral solid dosage form? **If No, please comment.**	☒ Yes ☐ No The bio-batch size is (b) (4) of the production batch size, which is (b) (4) tablets. DBII reviewed the applicant's reasoning for manufacturing this batch and batch size (see below) and accepts the batch size used in BE studies.
Is difference of the potency values for the Test and RLD within 5%? **If No, please comment.**	☒ Yes ☐ No

Comments on bio-batch size

Per the Product Development Report Section 2.3.8.7. Film Coating Parameters (Exhibit Batches)[7]:

(b) (4)

(b) (4)

(b) (4). The applicant submitted sufficient stability data on the bio-batch, and both the BE studies and dissolution testing were conducted using the same batch. Therefore, the bio-batch size is adequate.

5.1.1.1.3 Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 24 Dosed: 24 Completed: 24 Samples Analyzed: 24 Statistically Analyzed: 24
No. of Sequences	2 (1=TR; 2=RT)
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	5 days
Randomization	☒ Yes ☐ No
Blood Sampling Times	Prior to dosing (0.000 hour) and after dosing at 0.250, 0.500, 0.750, 1.000, 1.250, 1.500, 1.750, 2.000, 2.500, 3.000, 3.500, 4.000, 5.000, 6.000, 8.000, 10.000, 12.000, 16.000, 18.000, and 24.000 hours (±2 minutes window for all post dose blood draws)
IRB Approval	☒ Yes Date: Dec 4, 2017 (V 1.0); Dec 15, 2017 (V 2.0) ☐ No
Informed Consent	☒ Yes Date: Dec 4, 2017 (English); Dec 5, 2017 (Spanish) ☐ No
Length of Fasting	At least 10 hours before dosing and 4 hours after dosing

[7] GS Review: ANDA 209822 0000 (1) 12/16/2016 ORIG-1 Module 3.2.P.2. Pharmaceutical Development (Pharmaceutical Development Report p.77)

Length of Confinement	At least 11 hours prior to dosing until at least 24 hours after dosing in each study period
Was the drug product administered per labeling for specialized dosage forms (e.g. ODT)?	☐ Yes ☐ No ☒ N/A
Safety Monitoring	☒ Yes ☐ No

Comments on Study Design: Adequate

The product-specific guidance for Vigabatrin Tablets recommends a multiple-dose, two-treatment, two-way, steady-state crossover in vivo pharmacokinetic BE study in adult refractory complex partial-seizure patients. The applicant conducted a single-dose, two-way crossover study in healthy subjects under fasting and fed conditions. In the Clinical Summary (Module 2.7.1.) The applicant stated that:

> *Teva believes dosing Vigabatrin Tablets, 500 mg in healthy male subjects is justifiable. In addition the study protocols (fasting study # ACT-17201 and fed study # ACT-17202) were IRB reviewed and approved prior to the conduct of the studies to ensure the rights and welfare of human subjects were protected during their participation and safety measures were incorporated in the studies in compliance with GCP. During the conduct of both studies, in fasting and fed conditions, no adverse events, no serious adverse events or other significant adverse events were reported. Both formulations (i.e. test and reference products) were found to be safe and equally well tolerated based on the clinical data obtained from the subjects who completed the study under fasting and fed conditions.*

5.1.1.2 Clinical Results

5.1.1.2.1 Demographic Profile of Subjects

Category		Study No. ACT-17201 Treatment Groups	
		Test Product N = 24	**Reference Product N = 24**
Age (years)	**Mean ± SD**	37.5 ± 9.2	37.5 ± 9.2
	Range	22 - 53	22 - 53
Age Groups	**< 18**	0 (0.0%)	0 (0.0%)
	18 – 40	12 (50.0%)	12 (50.0%)
	41 – 64	12 (50.0%)	12 (50.0%)
	65-75	0 (0.0%)	0 (0.0%)
	> 75	0 (0.0%)	0 (0.0%)
Sex	**Male**	24 (100.0%)	24 (100.0%)
	Female	0 (0.0%)	0 (0.0%)
Race	**Asian**	0 (0.0%)	0 (0.0%)
	Black	5 (20.8%)	5 (20.8%)
	Caucasian	19 (79.2%)	19 (79.2%)
	Other	0 (0.0%)	0 (0.0%)
BMI	**Mean ± SD**	26.73 ± 2.02	26.73 ± 2.02
	Range	23.08 – 29.81	23.08 – 29.81

Other Factors: Ethnicity	**Hispanic or Latino**	24 (100.0%)	24 (100.0%)
	Non-Hispanic or Latino	0 (0.0%)	0 (0.0%)

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No

5.1.1.2.2 Dropout Information

Subject No.	Reason	Period	Replaced?
None of the subjects were withdrawn or dropped out from the study.			

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No

5.1.1.2.3 Study Adverse Events

Body System / Adverse Event	**Reported Incidence by Treatment Groups**	
	Fasting Bioequivalence Study No. ACT-17201	
	Test	**Reference**
There were no adverse events reported in the study.		

Test Product (T) = 24 subjects dosed; Reference product (R) = 24 subjects dosed.

Were subjects who experienced vomiting included in statistical analysis?	☐ Yes ☐ No ☒ N/A
If yes, does the time of emesis exceed two times the median Tmax value (IR products) or the labeled dosing interval (MR products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No
Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

5.1.1.2.4 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
Sampling time point deviations in period-1		(b) (6)
Sampling time point deviations in period-2		
Deviation 01:		

Description of Deviation: Period 1 doses were not prepared under yellow monochromatic light/low intensity light		

If the applicant used nominal time points, the sampling time deviations (if any) are > 5%, and 90% CI of any PK parameters are border line, please reanalyze data using actual sampling time.	☒ Actual ☐ Nominal

Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Comments on Clinical Results: Adequate

Per the study protocol drug accountability, drug dispensing, drug administration, archival, blood sampling, sample processing, segregation, and sample analysis were to be done under yellow monochromatic light/low intensity light. The applicant reported that drug doses in Period 1 were prepared under regular fluorescent light by the pharmacy staff. This protocol deviation is unlikely to impact the outcome of the fasting BE study because the applicant demonstrated that <0.5% impurities are formed when the drug product is under UV light for two days or visible light for seven days.[8]

5.1.1.3 Bioanalytical Results

5.1.1.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Repeat Analysis of Samples
		Mass spectrometric method for the determination of Vigabatrin in human plasma
		Preparation of calibration curve standards and quality control samples and defining analytical batch acceptance criteria
		Chromatography acceptance criteria
		Incurred sample reanalysis
		Reinjection of samples during analysis
		Bioanalytical method validation
		System Suitability Test
		Procedure for recording, rounding off, and reporting the data

[8] GS Review: ANDA 209822 0000 (1) 12/16/2016 ORIG-1 Module 3.2.P.5.3. Validation of Analytical Procedures (b) (4) pp.67-76)

All necessary SOPs submitted?	☒ Yes ☐ No

5.1.1.3.2 Sample Analysis Calibration and Quality Control

Bioequivalence Study No. ACT-17201 Vigabatrin								
Parameter	**Standard Curve Samples**							
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**
Concentration (µg/mL)	0.199	0.397	2.545	5.090	12.120	24.240	40.401	50.501
Inter day Precision (CV%)	1.41	2.68	2.97	2.49	1.92	1.64	3.34	3.01
Inter day Accuracy (%Actual)	100.35	99.27	100.17	99.85	100.13	100.33	100.19	99.70
Linearity	0.9950 to 0.9999 (range of r values)							
Linearity Range (µg/mL)	0.199 to 50.501							
Sensitivity/LOQ (µg/mL)	0.199							

Bioequivalence Study No. ACT-17201 Vigabatrin				
Parameter	**Quality Control Samples**			
	LQC	**AQC**	**MQC**	**HQC**
Concentration (µg/mL)	0.589	2.031	20.310	38.686
Inter day Precision (CV%)	4.64	4.68	5.01	5.63
Inter day Accuracy (%Actual)	97.72	98.40	99.72	99.90

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☐ Yes ☒ No
Were 20% of chromatograms included?	☒ Yes ☐ No 100% included
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly
Any interfering peaks in chromatogram?	☐ Yes ☒ No
Were the chromatograms submitted by the applicant acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

5.1.1.3.3 Reanalysis of Study Samples

Study No. ACT-17201 Vigabatrin Additional information in Module 5.3.1.4, bioanalytical-study-report.pdf, Bio-analytical report, Page no. 39-40 of 48								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Code RB	21	21	2.08	2.08	21	21	2.08	2.08
Total	21	21	2.08	2.08	21	21	2.08	2.08

Code RB = Rejected Bioanalytical Batch
T = Test Product
R = Reference Product

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	☒ Yes ☐ No The entire batch for subject (b) (6) was repeated.
If no, is recalculation of PK parameters necessary?	☐ Yes ☐ No ☒ N/A
Did recalculation of PK parameters change the study outcome?	☐ Yes ☐ No ☒ N/A
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	☐ Yes ☐ No ☒ N/A

Comments on Bioanalytical Results: Adequate

The applicant noted that samples were thawed on ice water bath and entire sample processing was carried out under yellow monochromatic light.

5.1.1.4 Pharmacokinetic Results

5.1.1.4.1 Arithmetic Mean Pharmacokinetic Parameters – Applicant Calculated

Fasting Bioequivalence Study No. ACT-17201									
Parameter (units)	Test				Reference				T/R
	Mean	% CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *µg/ml)	55.9050	14.3136	45.3900	75.5700	55.1054	12.4189	43.3000	69.05000	1.01
AUC∞ (hr *µg/ml)	59.8167	15.2333	48.0400	84.6700	58.8171	13.2766	45.2700	76.6500	1.02
Cmax (µg/ml)	16.0783	25.2493	10.5800	23.7900	15.4929	17.8331	11.7700	21.5900	1.04
Tmax* (hr)	0.75	-	0.50	2.00	1.00	-	0.75	1.75	0.75
Kel (hr^{-1})	0.0929	11.9080	0.0686	0.1081	0.0966	14.9854	0.0758	0.1355	0.96
T1/2 (hr)	7.5765	13.5614	6.4110	10.1030	7.3225	13.9911	5.1150	9.1450	1.03

* Tmax values are presented as median, range

5.1.1.4.2 Arithmetic Mean Pharmacokinetic Parameters – Reviewer Calculated

Fasting Bioequivalence Study No. ACT-17201									
Parameter (units)	Test				Reference				T/R
	Mean	% CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *µg/ml)	56.214	14.29	45.65	75.89	55.422	12.45	43.54	69.48	1.01
AUC∞ (hr *µg/ml)	60.125	15.20	48.30	84.99	59.134	13.30	45.51	77.09	1.02
Cmax (µg/ml)	16.078	25.25	10.58	23.79	15.492	17.83	11.77	21.59	1.04
Tmax* (hr)	0.750	.	0.50	2.00	1.000	.	0.75	1.75	0.75
Kel (hr^{-1})	0.093	11.92	0.07	0.11	0.097	14.99	0.08	0.14	0.96
T1/2 (hr)	7.577	13.56	6.41	10.10	7.322	13.99	5.12	9.15	1.03

* Tmax values are presented as median, range

5.1.1.4.3 Geometric Means and 90% Confidence Intervals - Applicant Calculated

Vigabatrin Tablets, 500 mg (No. of subjects completed = 24) Dose (1 x 500 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasted Bioequivalence Study (Study No.: ACT-17201)							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC0-t (hr *µg/ml)	55.38	24	54.70	24	101.24	98.96	103.56
AUC∞ (hr *µg/ml)	59.19	24	58.34	24	101.47	99.36	103.63
Cmax (µg/ml)	15.61	24	15.27	24	102.18	94.32	110.69

5.1.1.4.4 Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Vigabatrin Tablets, 500 mg (No. of subjects completed = 24) Dose (1 x 500 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasted Bioequivalence Study (Study No.: ACT-17201)							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *µg/ml)	55.69	24	55.02	24	1.01	98.96	103.53
AUC∞ (hr *µg/ml)	59.50	24	58.65	24	1.01	99.35	103.60
Cmax (µg/ml)	15.61	24	15.27	24	1.02	94.32	110.70

5.1.1.4.5 Additional Information for the Study

Root Mean Square Error	AUCt: 0.0456 AUCi: 0.0422 Cmax: 0.1615
Is there a Tmax difference between Test and Reference? **If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference).**	☒ Yes ☐ No Test=0.75 (0.50-2.00) h (mean=0.95 h) Ref=1.00 (0.75-1.75) h (mean=1.00 h) The T/R ratio for the median Tmax is 0.75; however, the mean Tmax of the test and reference products are similar (T/R=0.95).
Were the subjects dosed in groups? **If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?**	☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? **If yes, please comment (and take necessary action, if needed).**	☐ Yes ☒ No
Are there first measurable drug concentrations as Cmax? **If yes, please comment.**	☐ Yes ☒ No
Are there Cmax at the first time point? **If yes, is the study (sample) design adequate?**	☐ Yes ☒ No

Ratio of AUC0-t/AUC∞[9]				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	24	0.94	0.88	0.95
Reference	24	0.94	0.90	0.97
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.				N/A

[9] See individual test to reference ratios of PK Parameters in SAS Output

Comments on PK results: Adequate

The 90% confidence intervals of the ln-transformed AUC0-t, AUC0-∞, and Cmax geometric mean test/reference ratios are within the acceptable limits of 80-125%.

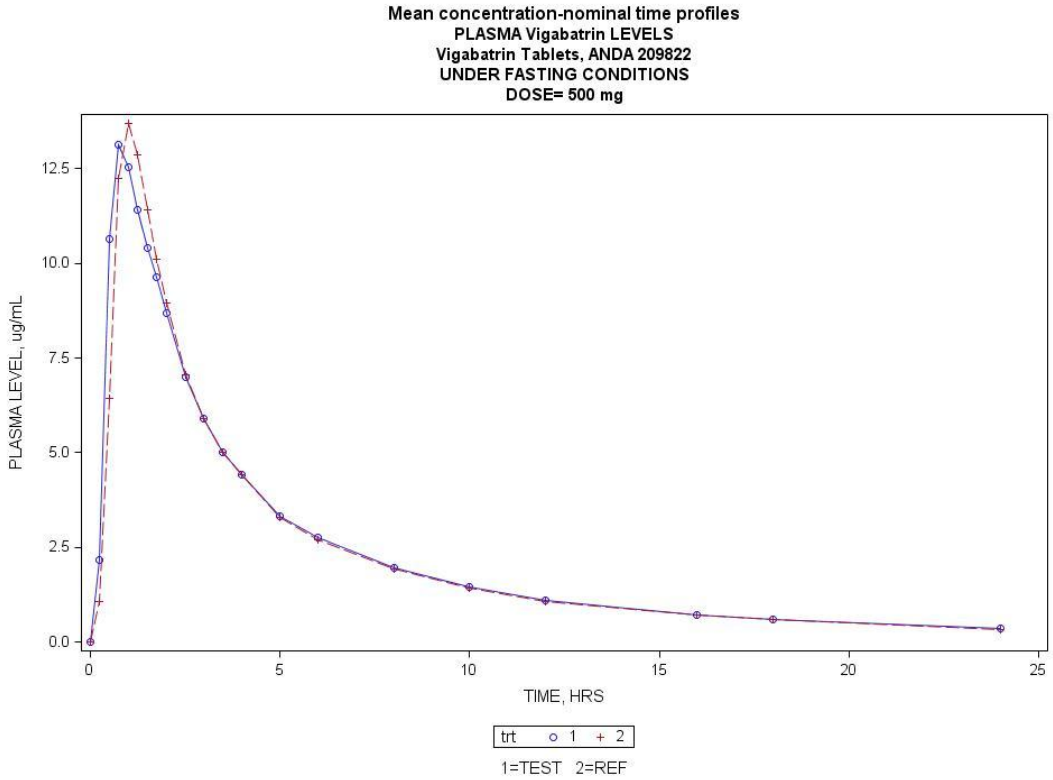
5.1.1.5 Overall Comment

Was the fasting bioequivalence study acceptable? Acceptable

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Vigabatrin					
Time (hr)	Test (n=24)		Reference (n=24)		T/R Ratio
	Mean (µg/mL)	% CV	Mean (µg/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.25	2.17	170.72	1.08	115.73	2.01
0.50	10.64	67.83	6.43	63.99	1.66
0.75	13.14	46.86	12.24	41.66	1.07
1.00	12.53	34.22	13.70	24.16	0.91
1.25	11.42	20.66	12.85	15.79	0.89
1.50	10.39	16.40	11.41	15.55	0.91
1.75	9.63	16.12	10.12	16.92	0.95
2.00	8.68	18.04	8.96	16.04	0.97
2.50	7.01	20.34	7.06	13.92	0.99
3.00	5.90	18.66	5.90	13.70	1.00
3.50	5.02	19.80	5.00	12.94	1.00
4.00	4.41	20.00	4.41	14.10	1.00
5.00	3.33	18.36	3.29	14.05	1.01
6.00	2.77	19.45	2.69	14.58	1.03
8.00	1.95	20.30	1.94	15.07	1.00
10.00	1.45	21.05	1.43	18.18	1.01
12.00	1.10	21.50	1.07	17.34	1.03
16.00	0.73	26.05	0.72	21.48	1.01
18.00	0.60	25.43	0.59	23.97	1.03
24.00	0.35	30.55	0.35	27.28	1.02

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



5.1.2 Single-Dose Fed Bioequivalence Study

5.1.2.1 Study Design

5.1.2.1.1 Study Information

Study Number	Study No. ACT-17202
Study Title	An open label, randomized, single dose, two way crossover bioequivalence study of Vigabatrin Tablets, 500 mg in healthy human, adult male subjects under fed conditions.
Clinical Site (Name & Address)	Watson Therapeutics Inc. 3400 Enterprise Way Miramar, FL 33025, USA Phone: 954-266-1000 Ext. 1441100 Fax: 954-266-1012
Principal Clinical Investigator	Maria J. Gutierrez, M.D. Email: Maria.Gutierrez@actavis.com
Dosing Dates	Period 1: Dec 16, 2017 Period 2: Dec 21, 2017
Analytical Site (Name & Address)	(b) (4)
Analysis Dates	Jan 3-9, 2018
Principal Analytical Investigator	(b) (4)
Sample Storage: **(a) Duration (no. of days from the first day of sample collection to the last day of sample analysis)** **(b) Temperature Range (e.g., -20°C to -80°C)**	24 days -70°C (-60°C to -80°C) in deep freezer
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	27 days at -20°C (-20°C to -35°C) and at about -70°C (-60°C to -80°C)

5.1.2.1.2 Product Information

See Section 0.

5.1.2.1.3 Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	Enrolled: 24 Dosed: Period 1: 24; Period 2: 23 Completed: 23 Samples Analyzed: 24 Statistically Analyzed: 23
No. of Sequences	2 (1=TR; 2=RT)
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	5 days
Randomization	☒ Yes ☐ No
Blood Sampling Times	Prior to dosing (0.000 hour) and after dosing at 0.333, 0.667, 1.000, 1.333, 1.667, 2.000, 2.333, 2.667, 3.000, 3.333, 3.667, 4.000, 4.500, 5.000, 6.000, 8.000, 10.000, 12.000, 16.000, 18.000, and 24.000 hours (±2 minutes for post dose blood draws)
IRB Approval	☒ Yes Date: Dec 4, 2017 (V 1.0); Dec 15, 2017 (V 2.0) ☐ No
Informed Consent	☒ Yes Date: Dec 4, 2017 (English); Dec 5, 2017 (Spanish) ☐ No
Length of Fasting	At least 10 hours before consumption of high-fat, high-calorie breakfast and 4 hours after dosing
Length of Confinement	At least 11 hours prior to dosing and until 24 hours after dosing in each period
Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?	☐ Yes ☐ No ☒ N/A
Safety Monitoring	☒ Yes ☐ No

Standard FDA Meal Used?	☒ Yes ☐ No

Per the study protocol:
The contents of standardized high calorie, high fat breakfast may be as follows:

- two fried eggs,
- two strips of bacon,
- two slices of toast with butter,
- four ounces of hash brown potatoes, and
- eight ounces of whole milk

(Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity.)
The study report states, "subjects were served standard test meal (standardized high calorie, high fat breakfast) 30 minutes prior to scheduled administration of the investigational product."

Comments on Study Design: Adequate

The product-specific guidance for Vigabatrin Tablets recommends a multiple-dose, two-treatment, two-way, steady-state crossover in vivo pharmacokinetic BE study in adult refractory complex partial-seizure patients. The applicant conducted a single-dose, two-way crossover study in healthy subjects. See comments in Section 5.1.1.1.

5.1.2.2 Clinical Results

5.1.2.2.1 Demographic Profile of Subjects

Category		Study No. ACT-17202 Treatment Groups	
		Test Product N = 23	Reference Product N = 23
Age (years)	Mean ± SD	36.7 ± 6.9	36.7 ± 6.9
	Range	25 - 48	25 - 48
Age Groups	< 18	0 (0.0%)	0 (0.0%)
	18 – 40	14 (60.9%)	14 (60.9%)
	41 – 64	9 (39.1%)	9 (39.1%)
	65-75	0 (0.0%)	0 (0.0%)
	> 75	0 (0.0%)	0 (0.0%)
Sex	Male	23 (100.0%)	23 (100.0%)
	Female	0 (0.0%)	0 (0.0%)
Race	Asian	0 (0.0%)	0 (0.0%)
	Black	2 (8.7%)	2 (8.7%)
	Caucasian	21 (91.3%)	21 (91.3%)
	Other	0 (0.0%)	0 (0.0%)
BMI	Mean ± SD	26.45 ± 2.38	26.45 ± 2.38
	Range	22.14 – 29.93	22.14 – 29.93
Other Factors: Ethnicity	Hispanic or Latino	23 (100.0%)	23 (100.0%)
	Non-Hispanic or Latino	0 (0.0%)	0 (0.0%)

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation?	☒ Yes ☐ No

5.1.2.2.2 Dropout Information

Subject No.	Reason	Period	Replaced?
(b) (6)	Subject withdrawn on (b) (6) due to unable to consume required breakfast. Last treatment received by the subject "test".	2	No

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No

5.1.2.2.3 Study Adverse Events

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study No.	
	Test	Reference
There were no adverse events reported in the study.		

Test Product (T) = 24 subjects dosed; Reference product (R) = 23 subjects dosed.

Were subjects who experienced vomiting included in statistical analysis?	☐ Yes ☐ No ☒ N/A
If yes, does the time of emesis exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No
Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

5.1.2.2.4 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
Sampling time point deviations in period-1		(b) (6)
Sampling time point deviations in period-2		
Missing samples in period 1		
Missing samples in period 2		

If the applicant used nominal time points, the sampling time deviations (if any) are > 5%, and 90% CI of any PK parameters are border line, please reanalyze data using actual sampling time.	☒ Actual ☐ Nominal

Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Comments on Clinical Results: Adequate

5.1.2.3 Bioanalytical Results

5.1.2.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

See Section 5.1.1.3.1.

5.1.2.3.2 Sample Analysis Calibration and Quality Control

Bioequivalence Study No. ACT-17202 Vigabatrin								
Parameter	**Standard Curve Samples**							
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**
Concentration (µg/mL)	0.199	0.397	2.545	5.090	12.120	24.240	40.401	50.501
Inter day Precision (CV%)	1.31	2.64	2.98	1.87	1.40	1.83	2.27	1.77
Inter day Accuracy (%Actual)	100.30	99.47	99.23	100.49	99.51	100.25	100.62	100.11
Linearity	0.9986 to 0.9999 (range of r values)							
Linearity Range (µg/mL)	0.199 to 50.501							
Sensitivity/LOQ (µg/mL)	0.199							

Bioequivalence Study No. ACT-17202 Vigabatrin				
Parameter	**Quality Control Samples**			
	LQC	**AQC**	**MQC**	**HQC**
Concentration (µg/mL)	0.589	2.031	20.310	38.686
Inter day Precision (CV%)	5.32	3.80	6.17	3.89
Inter day Accuracy (%Actual)	97.83	98.76	99.84	98.76

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions.	☐ Yes ☒ No
Were 20% of chromatograms included?	☒ Yes ☐ No 100% included
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly
Any interfering peaks in chromatogram?	☐ Yes ☒ No
Were the chromatograms submitted by the applicant acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

5.1.2.3.3 Reanalysis of Study Samples

Study No. ACT-17202 Vigabatrin Additional information in bioanalytical-study-report.pdf, Bio-analytical report, Page no. 39-41 of 49								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Code PE	2	0	0.19	0.00	2	0	0.19	0.00
Code RB	22	22	2.13	2.13	22	22	2.13	2.13
Total	24	22	2.32	2.13	24	22	2.32	2.13

Code PE = Processing error
Code RB = Rejected Bioanalytical Batch,
T = Test Product
R = Reference Product
Note: **Number of samples reanalyzed** contains samples reanalyzed for the first time (Repeat I)

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	☒ Yes ☐ No The entire batch for subject (b) (6) was repeated. Two samples for subject (b) (6) were repeated because no analyte or internal standard were in the original samples.
If no, is recalculation of PK parameters necessary?	☐ Yes ☐ No ☒ N/A
Did recalculation of PK parameters change the study outcome?	☐ Yes ☐ No ☒ N/A
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	☐ Yes ☐ No ☒ N/A

Comments on Bioanalytical Results: Adequate

The applicant noted that samples were thawed on ice water bath and entire sample processing was carried out under yellow monochromatic light.

5.1.2.4 Pharmacokinetic Results

5.1.2.4.1 Arithmetic Mean Pharmacokinetic Parameters – Applicant Calculated

Fed Bioequivalence Study No. ACT-17202									
Parameter (units)	Test				Reference				T/R
	Mean	% CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *µg/mL)	55.7252	17.1574	41.3600	83.5900	54.5243	18.0737	40.8200	83.5000	1.02
AUC∞ (hr *µg/mL)	60.1496	18.0160	44.1400	89.4600	59.0309	20.3585	42.9300	90.7600	1.02
Cmax (µg/mL)	11.5848	22.0123	7.6400	17.5400	12.2991	25.3911	7.6500	19.8500	0.94
Tmax* (hr)	1.667	-	1.00	5.00	1.667	-	1.00	5.00	1.00
Kel (hr^{-1})	0.0948	15.2274	0.0708	0.1312	0.0952	15.6731	0.0544	0.1236	1.00
T1/2 (hr)	7.4706	15.1887	5.2820	9.7890	7.4924	19.8502	5.6060	12.7450	1.00

* Tmax values are presented as median, range

5.1.2.4.2 Arithmetic Mean Pharmacokinetic Parameters – Reviewer Calculated

Fed Bioequivalence Study No. ACT-17202									
Parameter (units)	Test				Reference				T/R
	Mean	% CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *µg/mL)	56.083	17.15	41.57	84.04	54.896	18.07	41.05	83.96	1.02
AUC∞ (hr *µg/mL)	60.507	18.00	44.35	89.91	59.404	20.34	43.16	91.22	1.02
Cmax (µg/mL)	11.584	22.02	7.64	17.54	12.297	25.39	7.65	19.85	0.94
Tmax* (hr)	1.667	.	1.00	5.00	1.667	.	1.00	5.00	1.00
Kel (hr^{-1})	0.095	15.24	0.07	0.13	0.095	15.67	0.05	0.12	1.00
T1/2 (hr)	7.471	15.19	5.28	9.79	7.492	19.85	5.61	12.74	1.00

* Tmax values are presented as median, range

5.1.2.4.3 Geometric Means and 90% Confidence Intervals - Applicant Calculated

Vigabatrin Tablets, 500 mg (No. of subjects completed = 23) Dose (1 x 500 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study (Study No.: ACT-17202)							
Parameter (units)	Test	N	RLD	N	Ratio	90% C.I.	
AUC0-t (hr *µg/mL)	55.22	23	53.99	23	102.29	100.94	103.65
AUC∞ (hr *µg/mL)	59.56	23	58.27	23	102.21	100.36	104.09
Cmax (µg/mL)	11.34	23	11.96	23	94.80	86.33	104.11

5.1.2.4.4 Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Vigabatrin Tablets, 500 mg (No. of subjects completed = 23) Dose (1 x 500 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study (Study No.: ACT-17202)							
Parameter (units)	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC0-t (hr *µg/mL)	55.58	23	54.35	23	1.02	100.90	103.62
AUC∞ (hr *µg/mL)	59.91	23	58.64	23	1.02	100.33	104.04
Cmax (µg/mL)	11.34	23	11.96	23	0.95	86.34	104.12

5.1.2.4.5 Additional Information for the Study

Root Mean Square Error	AUCt: 0.0262 AUCi: 0.0358 Cmax: 0.1844
Is there a Tmax difference between Test and Reference? **If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference)**	☐ Yes ☒ No
Were the subjects dosed in groups? **If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?**	☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? **If yes, please comment (and take necessary action, if needed).**	☐ Yes ☒ No
Are there first measurable drug concentrations as Cmax? **If yes, please comment.**	☐ Yes ☒ No
Are there Cmax at the first time point? **If yes, is the study (sample) design adequate?**	☐ Yes ☒ No

Ratio of AUC0-t/AUC∞[10]				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	23	0.93	0.88	0.96
Reference	23	0.93	0.80	0.96
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.			Subject (b) (6) had a ratio of 0.8 for the reference product and 0.91 for the test product. The sampling schedule was adequate.	

[10] See individual test to reference ratios of PK Parameters in SAS Output.

Comments on PK results: Adequate

The 90% confidence intervals of the ln-transformed AUC0-t, AUC0-∞, and Cmax geometric mean test/reference ratios are within the acceptable limits of 80-125%.

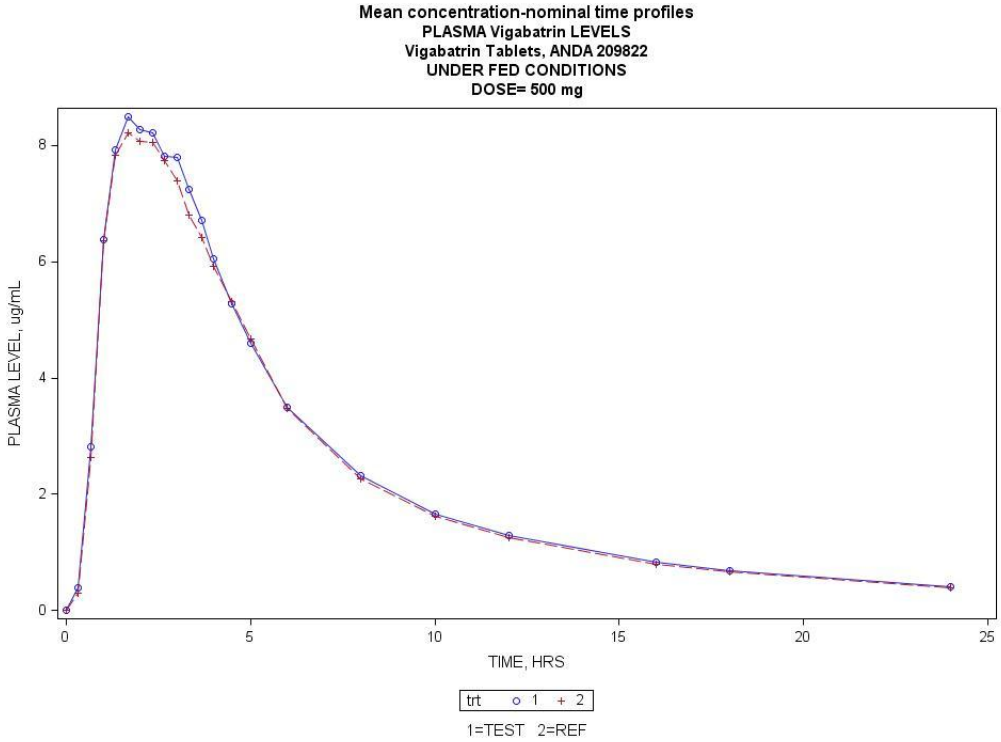
5.1.2.5 Overall Comment

Was the Fed bioequivalence study acceptable? Acceptable

Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Vigabatrin					
Time (hr)	Test (n=23)		Reference (n=23)		T/R Ratio
	Mean (µg/mL)	% CV	Mean (µg/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.33	0.39	389.55	0.30	167.93	1.28
0.67	2.81	109.24	2.63	116.87	1.07
1.00	6.38	86.75	6.36	99.72	1.00
1.33	7.93	61.49	7.83	70.93	1.01
1.67	8.50	47.83	8.22	53.87	1.03
2.00	8.28	34.34	8.08	43.63	1.02
2.33	8.22	25.73	8.04	35.29	1.02
2.67	7.82	23.06	7.75	30.64	1.01
3.00	7.80	23.86	7.39	25.73	1.05
3.33	7.25	28.18	6.81	26.13	1.06
3.67	6.71	28.24	6.42	27.22	1.05
4.00	6.04	28.78	5.93	29.70	1.02
4.50	5.28	30.39	5.31	36.22	1.00
5.00	4.60	35.15	4.67	41.66	0.99
6.00	3.49	33.58	3.48	31.80	1.00
8.00	2.32	26.54	2.26	28.48	1.03
10.00	1.66	26.59	1.62	25.82	1.02
12.00	1.29	25.94	1.25	26.20	1.03
16.00	0.82	25.67	0.80	27.61	1.03
18.00	0.68	24.72	0.67	32.02	1.01
24.00	0.40	28.63	0.39	38.22	1.02

Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



5.2 Formulation Data

5.2.1 Test Formulation

Ingredient	Amount (mg) / Tablet	Amount (%) / Tablet
Cores		
Vigabatrin, USP	500	(b) (4)
Povidone, USP (b) (4) (b) (4)		(b) (4)
(b) (4)		
Microcrystalline cellulose (b) (4) NF		
Sodium starch glycolate		
Magnesium Stearate, NF (b) (4)		
(b) (4)		
Total	**708**	**NA**

(b) (4) .

(b) (4)

5.2.2 Inactive Ingredients (IIG Table)

Components	mg/unit	Maximum amount (mg)/MDD	IIG limit (mg/day)
Povidone (b) (4)			
Microcrystalline Cellulose (b) (4)			
Sodium Starch Glycolate			
Magnesium Stearate			
Titanium dioxide			
HPMC 2910/ (b) (4) (b) (4)			
(b) (4)/ Polyethylene Glycol (PEG) MW 400			
(b) (4) Polyethylene Glycol (PEG) MW 8000			
Polysorbate 80			

Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	☐ Yes ☐ No ☒ N/A
Are the amounts of all inactive ingredients, based on Maximum Daily Dose (MDD), within IIG (per unit) limits?	☐ Yes ☒ No
If no, are they all within IIG (per day) limits?	☒ Yes ☐ No ☐ N/A
If no, are additional data or Pharm/Tox consult necessary?	☐ Yes ☐ No ☒ N/A
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	☐ Yes ☐ No ☒ N/A
Are all strengths of the test formulation acceptable?	☒ Yes ☐ No

Comments on Formulation:
The maximum daily intake of inactive ingredients was calculated based on a maximum daily dose of 3000 mg (6 x 500 mg tablets) for Vigabatrin Tablets. All inactive ingredients are within the IIG limits. The test and reference products are qualitatively and quantitatively the same except for the tablet coating.

The formulation is acceptable.

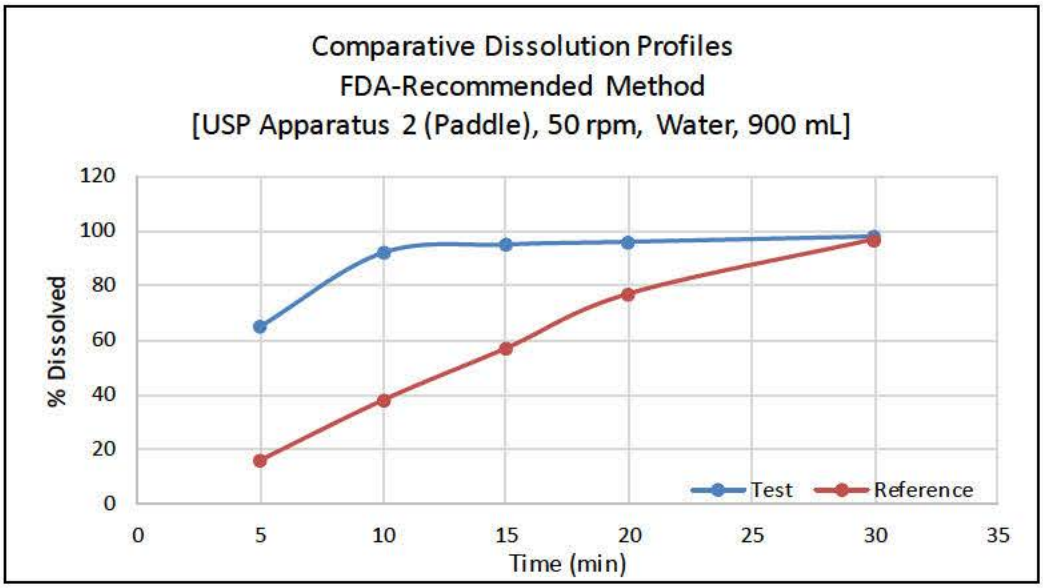
5.3 Dissolution Testing

5.3.1 Dissolution Data

Dissolution Conditions	**Apparatus:**	USP Apparatus II (Paddle)
	Sinker:	N/A
	Speed of Rotation:	50 rpm
	Medium:	Water
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Applicant's Proposed Specifications	NLT (b) (4)% (Q) of the labeled amount of Vigabatrin is dissolved in 15 minutes.	
Dissolution Testing Site (Name, Address)	Teva Phamaceuticals USA, Inc. 200 Elmora Avenue Elizabeth, NJ 07207	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times					Study Report Location
						5 min	10 min	15 min	20 min	30 min	
N/A	11/29/17	Vigabatrin Tablets, Batch # 1115900127 Manufacture Date: 10/2015	500 mg Tablet	12	Mean	65	92	95	96	98	Module 2.7
					Range	(b) (4)					
					%RSD	14.1	4.3	3.2	2.7	2.7	
N/A	11/28/17	Sabril Tablets, Lot# 3150748 Expiration Date: 05/2019	500 mg Tablet	12	Mean	16	38	57	77	97	Module 2.7
					Range	(b) (4)					
					%RSD	13.4	8.2	7.4	10.4	0.7	

5.3.2 Dissolution Profiles



5.3.3 F2 Metric

F2 metric calculated?	☐ Yes ☒ No
If no, reason why F2 not calculated	The test and reference products are rapidly dissolving (>85% in 30 min)

Please comment on whether dissolution data are adequate to support requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).	N/A

The quality control dissolution method and specification were reviewed by OPQ and determined to be inadequate pending acceptance of a tighter specification. In the current amendment, the applicant has accepted the recommended specification of Q= (b)(4)% in 15 min.

The applicant used the USP method for quality control and product release dissolution testing.

USP Apparatus	II (Paddle)
Rotational Speed (rpm)	50
Temperature (°C)	37 ± 0.5
Medium	Water
Volume (mL)	900
Specification	NLT (b)(4)% (Q) in 15 min

Overall Comments: Adequate

5.4 Attachments

5.4.1 SAS Output

Study	SAS Data	SAS Code	SAS Stat	SAS Output/Table
Fasting	209822_Fasting_ConcPK.xls	Fast 209822_CONTINU2.sa	209822_FASTING_stat_Vigabatrin.doc	209822_FASTING_table_Vigabatrin.doc
Fed	209822_Fed_ConcPK.xls	Fed 209822_CONTINU2.sa	209822_FED_stat_Vigabatrin.doc	209822_FED_table_Vigabatrin.doc

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	209822
APPLICANT:	Teva Pharmaceuticals USA, Inc.
DRUG PRODUCT:	Vigabatrin Tablets, USP, 500 mg

The Division of Bioequivalence II (DBII) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if chemistry, manufacturing and controls, microbiology, labeling, or other scientific, regulatory or inspectional issues or concerns arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Ethan M. Stier, Ph.D., R. Ph.
Director, Division of Bioequivalence II
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5.5 Outcome Page

ANDA: 209822

Reviewer:	Avaritt, Brittany	**Date Completed:**	
Verifier:	,	**Date Verified:**	
Division:	Division of Bioequivalence		
Description:	Vigabatrin Tablets, 500 mg		

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*		
35579	3/12/2018	BIO	ANDA Amendment [1]	1	1	Edit	Delete
35579	3/12/2018	Parallel	Fasting Study (Full template) [1]	1	1	Edit	Delete
35579	3/12/2018	Parallel	Fed Study (Full Template) [1]	1	1	Edit	Delete
35579	3/12/2018	Parallel	Pre-Screening [0.25]	0.25	0.25	Edit	Delete
				Total:	3.25		

BIOPHARMACEUTICS REVIEW	
Application No.:	ANDA-209822-ORIG-1
Applicant/Sponsor:	Teva Pharmaceuticals USA
Product Name:	Vigabatrin Tablets
Dosage Form/Strength	Tablets/500 mg
Route of Administration:	Oral
Intended Use:	Treatment of Refractory Complex Partial Seizures as adjunctive therapy in patients greater than or equal to 10 years of age who have responded inadequately to several alternative treatments
Reference listed drug:	NDA-020427 [Sabril® (Vigabatrin) Tablets, 500 mg]
Submission Date:	December 16, 2016
Review Date:	June 30, 2017
Primary Reviewer:	Yang Zhao, Ph.D.
Secondary Reviewer:	Elsbeth Chikhale Ph.D. for Ta-Chen Wu, Ph.D.
Recommendation:	**PENDING (Inadequate)**

1. EXECUTIVE SUMMARY:

Submission: Teva Pharmaceuticals USA submitted ANDA-209822 seeking approval for the proposed Vigabatrin Tablets 500 mg under section of 505 (j) of the Federal Food, Drug, and Cosmetic Act.

Review: The focus of the Biopharmaceutics Review is the evaluation of data supporting the adequacy of the proposed dissolution method and acceptance criterion for the dissolution test for the proposed drug products.

Reviewer's Assessment: The dissolution testing was conducted with the FDA database dissolution method (*USP Apparatus 2 at 50 rpm; 900 mL of water at 37 °C*). The proposed dissolution method is acceptable; however, the proposed acceptance criterion is permissive and NOT acceptable. The Applicant will be requested to revise the dissolution acceptance criterion.

Recommendation: From a Biopharmaceutics perspective, the recommendation on the approvability of ANDA 209822 for Vigabatrin Tablets 500 mg is **PENDING** due to outstanding Information Request Comments. The comments described under the List of Biopharmaceutics Information Request Comments Section 5, should be sent to the Applicant.

2. SUBMISSION CONTENT CHECKLIST:

	INFORMATION	YES	NO	N/A
1	Is there a USP dissolution method?	☐	☒	☐
2	Did the Applicant use the USP dissolution method?	☐	☐	☒
3	Is there an FDA database dissolution method?	☒	☐	☐
4	Did the Applicant use the FDA database dissolution method?	☒	☐	☐
5	Did the Applicant conduct dissolution testing with an in-house method?	☐	☒	☐
6	Did the Applicant use 12 units of the test drug products in the dissolution testing?	☒	☐	☐
7	Did the Applicant provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)?	☒	☐	☐
8	Was the dissolution method SOP effective at the time of testing?	☒	☐	☐
9	Is the validation of the analytical method used for dissolution testing acceptable?	☒	☐	☐
10	Was the dissolution/release testing conducted using an unexpired product?	☒	☐	☐
11	Do any of the proposed product strengths have functional scoring?	☒	☐	☐
12	Was the dissolution/release testing conducted using split tablets?	☒	☐	☐

3. REVIEW SUMMARY:

a) List of Submissions being reviewed:

Original submission dated December 16, 2016.

b) Highlight of Key Outstanding Issues from Last Cycle:

None.

c) Concise Description of Outstanding Issues:

The proposed acceptance criterion for the dissolution test is NOT acceptable. The Applicant will be requested to revise the dissolution acceptance criterion.

d) Proposed dissolution method and acceptance criterion:

USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance criterion
II (paddle)	50	water@37 ± 0.5 °C	900	Q=75% dissolved in 30 minutes

The Applicant reported that vigabatrin is a very highly soluble molecule (Table 1).

Table 1. Solubility of vigabatrin in various different pH media measured at 25 °C

Solvent Media	Solubility (mg/ml)
pH 1.2 Solution	300 mg/1 mL
pH 3.0 Solution	300 mg/1 mL
pH 4.5 Solution	300 mg/1 mL
pH 6.8 Solution	300 mg/1 mL
pH 7.2 Solution	300 mg/1 mL
pH 8.0 Solution	300 mg/1 mL

Reviewer's Assessment: The proposed dissolution method, an FDA database dissolution method for Vigabatrin Tablets, is acceptable for the proposed drug products.

(b) (4)

The proposed Vigabatrin Tablets 500 mg are functionally-scored on one side and debossed with A314 on the other side. The similarity factor (f_2) between the whole and the split Vigabatrin Tablets is not calculated because all dissolution profiles showed (b) (4)% dissolved in (b) (4) minutes.

(b) (4)

Reviewer's Assessment: The originally proposed dissolution acceptance criterion of "Q=75% dissolved in 30 minutes" is permissive and NOT acceptable. Based on the dissolution profile data, the Agency recommends the following dissolution acceptance criterion for the proposed drug products:
Q= (b) (4)% in 15 minutes.

The similarity in dissolution profiles between the whole and the split tablets support the tablet scoring on the proposed Vigabatrin Tablets, 500 mg.

g) What was the age of the test product at the time of dissolution testing?

The tested whole Vigabatrin Tablets were less than 4 months old at the time of the dissolution testing.

h) Is there significant change in the dissolution of stability samples?

The Applicant provided dissolution data at 30 minutes for the stability samples. There are no apparent changes in the Applicant's provided dissolution data of the stability samples in various storage conditions.

i) Analytical procedures and validation

The amount of drug dissolved was determined using an HPLC method (see validation report in Module 3.2.P.5.2). The analytical method was validated for system suitability, specificity, precision, accuracy, linearity, solution stability, filter compatibility.

4. REVIEWER'S OVERALL ASSESSMENT:

- *Dissolution Method:* The dissolution testing for the proposed drug products was conducted with the FDA database dissolution method (*USP Apparatus 2 at 50 rpm; 900 ml of water at 37 °C*). The proposed dissolution method is acceptable for QC purposes.
- *Dissolution Acceptance Criterion:* The proposed dissolution acceptance criterion of "Q=75% dissolved in 30 minutes" is NOT acceptable. The Applicant will be requested to revise the acceptance criterion for the proposed products as follow:
  Q= (b) (4)% in 15 minutes.

5. BIOPHARMACEUTICS INFORMATION REQUESTS:

The following Biopharmaceutics Information Request comments should be conveyed to the Applicant:

1. The proposed acceptance criterion of "Q=75% dissolved in 30 minutes" is permissive and NOT acceptable. Based on the provided dissolution data, we recommend a dissolution acceptance criterion of "Q= (b) (4)% in 15 minutes" for your proposed drug products. Note that sometimes dissolution Stage 2 testing, and occasionally Stage 3 testing may be needed, which is acceptable.

2. Submit a copy of the updated drug product specification table with the revised acceptance criterion for the dissolution test and update other section of your submission as appropriate.

6. RECOMMENDATION:

From the Biopharmaceutics perspective, the recommendation on the approvability of ANDA 209822 for the proposed Vigabatrin Tablets 500 mg is **PENDING** due to Applicant's outstanding response to the above Biopharmaceutics Information Requests.

7. SIGNATURE BLOCK

Primary Biopharmaceutics Reviewer Name and Date:

Yang Zhao, Ph.D., 6/28/2017
Division of Biopharmaceutics
Office of New Drug Products/OPQ

Secondary Biopharmaceutics Reviewer Name and Date:

I concur with Dr. Yang Zhao's assessment and Biopharmaceutics Information Requests.

Elsbeth Chikhale, Ph.D. for Ta-Chen Wu, Ph.D., 6/30/2017
Acting Biopharmaceutics Lead
Division of Biopharmaceutics, ONDP/OPQ

(b) (4)

Ta-Chen Wu

Digitally signed by Ta-Chen Wu
Date: 10/02/2017 12:34:28PM
GUID: 508da6df000269e151ff37cd8f4e13a1

Yang Zhao

Digitally signed by Yang Zhao
Date: 9/29/2017 01:31:44PM
GUID: 56f958740001a1f9707b4476d760e12f

DIVISION OF BIOEQUIVALENCE REVIEW OF AN OSIS INSPECTION REPORT

ANDA No.	209822	
Drug Product Name	Vigabatrin Tablets, USP	
Strength(s)	500 mg	
Applicant Name	Teva Pharmaceuticals USA	
Applicant Address	200 Elmora Avenue Attention: Regulatory Affairs Department Elizabeth, NJ 07207	
U.S. Agent's Point of Contact	Janak Jadeja, R.Ph Director, Regulatory Affairs RegulatoryAffairsUS@actavis.com	
U.S. Agent's Telephone Number	908-659-2595	
U.S. Agent's Fax Number	908-659-2250	
Original Submission Date(s)	Dec 16, 2016	
Submission Date(s) of OSIS Inspection Report	(b) (4)	
OSIS Inspection Dates		
First Generic	Yes	
Reviewer	Brittany Avaritt, Ph.D.	
Study Number (s)	TR15-209A	TR15-215
Study Type (s)	Solubility	Dissolution
Strength (s)	API	500 mg
In Vitro Site #1/OSIS Status	Biopharmaceutical Sciences Laboratory, Actavis Elizabeth LLC	Complete (Declined to Inspect)
In Vitro Site #1 Address	200 Elmora Ave. Elizabeth, NJ 07202	
Study Number (s)	15ACTAP6R1GLPS305	
Study Type (s)	In Situ Permeability	
Strength (s)	API	
Analytical Site #1/OSIS Status	(b) (4)	Complete (VAI)
Analytical Site #1 Address		
Site(s) Inspected (e.g. analytical, clinical)	Analytical	
Reason for OSIS Inspection Request (e.g. New Sites, Three Years Routine, For Cause)	Routine	
Current ANDA	**Parent ANDA**	
OSIS Report Review Outcome (Current ANDA)	**ADEQUATE (see deficiencies in original review)**	
Nature of OSIS Findings	**SYSTEMIC**	

Review of an OSIS Inspection Report

1 EXECUTIVE SUMMARY

This is a review of the Office of Study Integrity and Surveillance (OSIS) inspection report for [redacted] (b) (4) [1].

The inspection report references the in situ permeability study 15ACTAP6R1GLPS305 that was submitted in the original application dated Dec 16, 2016, comparing the test product, Teva Pharmaceuticals USA's Vigabatrin Tablets, USP, 500 mg to the reference listed drug (RLD), Lundbeck Pharmaceuticals LLC's SABRIL® (vigabatrin) Tablets, 500 mg.[2]

OSIS conducted an inspection of the analytical site at [redacted] (b) (4) on Jun 5-9, 2017 and Form FDA 483 was issued for the analytical portion of the in situ permeability study. The inspection included a thorough examination of study records, facilities, laboratory equipment, method validations, sample analysis, and interviews with the firm's management and staff. In addition, relevant SOPs, training records, and in-house data management systems were also reviewed.

The firm's response to Form FDA 483 was received on Jun 30, 2017.

The OSIS outcome was voluntary action indicated (VAI) for the analytical portion of the in situ permeability study.

In the Electronic Inspection Report dated Jul 20, 2017, OSIS provided the Division of Bioequivalence II (DBII) with its findings. Based on the inspection and the firm's response, OSIS provided the following conclusion:

After reviewing the inspectional findings and the firm's response to Form FDA 483, the objectionable findings do not likely impact the reliability of data from the audited studies. We recommend accepting the analytical data for further Agency review. However, this conclusion will be re-assessed upon receipt and evaluation of expected additional data from the firm. If the assessment of these studies changes, we will update this review accordingly.

Due to significant documentation issues, and concerns regarding the handling of precision and accuracy data in the audited method validations, the overall performance of the site was not adequate. The impact on other studies that were not reviewed during this inspection is unknown. We were able to assess likelihood of study impact from these observations on the current studies due to access to source study data and the firm's responses.

---

[1] [redacted] (b) (4) (b) (4)

[2] GDRP: ANDA-209822-ORIG-1 Bioequivalence Review submitted by Brittany Avaritt on Jul 6, 2017

Thus, studies using similar methods conducted prior to 2016 should be carefully evaluated during Agency review, and future inspections will be required to verify that proposed changes were implemented and that current observations do not affect other studies.

DBII reviewed the inspection report and concurs with OSIS's evaluation. The in situ permeability study submitted in ANDA 209822 was previously found to be inadequate with multiple deficiencies.[2]

DBII's recommendations for the OSIS report review are adequate for the current ANDA, but the issues identified in OSIS's report are systemic and may affect other studies conducted at (b) (4) due to documentation issues and data reporting. The PM will assign all related ANDAs for review to determine the acceptability of other studies conducted at the same analytical laboratory.

The in situ permeability study in ANDA 209822 is inadequate. Therefore, the application is **inadequate**.

The deficiencies listed in the original bioequivalence (BE) review completed on Jul 6, 2017 should be communicated to the firm.[2]

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3 REVIEW OF OSIS INSPECTION REPORT

3.1 Analytical Site Inspectional Observations

Form FDA 483 was issued to (b) (4) on Jun 9, 2017 with the following observations:

(b) (4)

Following this page, 5 Pages Withheld in Full as (b)(4)

☐ **Isolated** ☒ **Systemic**

3.1.4 OSIS Overall Comments and Conclusions

Objectionable findings were observed during this inspection and Form FDA 483 was issued. The final inspection classification is Voluntary Action Indicated (VAI).

After reviewing the inspectional findings and the firm's response to Form FDA 483, the objectionable findings do not likely impact the reliability of data from the audited studies. We recommend accepting the analytical data for further Agency review. However, this conclusion will be re-assessed upon receipt and evaluation of expected additional data from the firm. If the assessment of these studies changes, we will update this review accordingly.

Due to significant documentation issues, and concerns regarding the handling of precision and accuracy data in the audited method validations, the overall performance of the site was not adequate. The impact on other studies that were not reviewed during this inspection is unknown. We were able to assess likelihood of study impact from these observations on the current studies due to access to source study data and the firm's responses.

Thus, studies using similar methods conducted prior to 2016 should be carefully evaluated during Agency review (see Attachment 1 below), and future inspections will be required to verify that proposed changes were implemented and that current observations do not affect other studies.

3.1.5 DB Reviewer Overall Comments and Conclusions

The reviewer agrees with the OSIS statement that the inspection observations reflect a general weakness in documentation and data reporting. However, the OSIS observations are not likely to impact the outcome of the in situ permeability study submitted in ANDA 209822. Therefore, the OSIS inspection report review for the (b) (4) analytical site for the current ANDA is adequate.

Study 15ACTAP6R1GLPS305 was already determined to be inadequate in the BE review due to many deficiencies identified in the study conduct and analysis.[2]

The OSIS findings are considered systemic. Reviewers of related ANDAs should evaluate the impact of these findings on his/her own respective ANDA.

☐ **Isolated** ☒ **Systemic**

4 DEFICIENCY COMMENTS

None

5 RECOMMENDATIONS

Based on DBII's evaluation of the OSIS inspection report, the inspected site (b) (4) (b) (4) is adequate for ANDA 209822.

6 RECOMMENDATIONS FOR RELATED ANDAS

Should the OSIS report be reviewed separately for the impact on the related ANDAs?	**Yes**

7 APPENDIX

7.1 Attachment I: OSIS Inspection Report for Analytical Site— (b) (4)

(b) (4)

NOTE TO REGULATORY PROJECT MANAGER (RPM): The firm should receive the deficiencies listed in the original BE review archived in Panorama on Jul 6, 2017.Error! Bookmark not defined.

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 209822

APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Vigabatrin Tablets, USP, 500 mg

SEE PANORAMA: ANDA-209822-ORIG-1 Bioequivalence Discipline Review archived by Eva Chan on Jul 6, 2017

8 OUTCOME PAGE

ANDA: 209822

Reviewer: Avaritt, Brittany **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Vigabatrin Tablets, USP, 500 mg

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*		
32264	7/21/2017	BIO	OSIS Inspection Report Review [1]	1	1	Edit	Delete
32264	7/21/2017	Parallel	OSIS Inspection Report: Review of Parent (Per application) [1]	1	1	Edit	Delete
				Total:	2		

DIVISION OF BIOEQUIVALENCE REVIEW

BCS Waiver

ANDA No.	209822	
Drug Product Name	Vigabatrin Tablets, USP	
Strength(s)	500 mg	
Applicant Name	Teva Pharmaceuticals USA	
Applicant Address	200 Elmora Avenue Attention: Regulatory Affairs Department Elizabeth, NJ 07207	
US Agent Name	Janak Jadeja, R.Ph Director, Regulatory Affairs RegulatoryAffairsUS@actavis.com	
US Agent's Telephone Number	908-659-2595	
US Agent's Fax Number	908-659-2250	
Original Submission Date(s)	Dec 16, 2016	
Submission Date(s) of Amendment(s) Under Review	N/A	
First Generic (Yes or No)	Yes	
Reviewer	Brittany Avaritt, Ph.D.	
Study No.	TR15-209A	TR15-215
Study Type (s)	Solubility	Dissolution
Strength (s)	API	500 mg
Testing Site	Biopharmaceutical Sciences Laboratory, Actavis Elizabeth LLC	
Testing Site Address	200 Elmora Ave. Elizabeth, NJ 07202	
Analytical Site	Biopharmaceutical Sciences Laboratory, Actavis Elizabeth LLC	
Analytical Site Address	200 Elmora Ave. Elizabeth, NJ 07202	
Study No.	15ACTAP6R1GLPS305	
Study Type (s)	In Situ Permeability	
Strength (s)	API	
Testing Site	(b) (4)	
Testing Site Address		
Analytical Site		
Analytical Site Address		
OSIS Status	**Backlog, Year 1 and Year 2 ANDAs**	**Post October 1, 2014 ANDAs**

	☐ Pending ☐ Complete ☐ N/A (Waiver)	☒ Pending ☐ For Cause Inspection ☐ Complete
Waiver	☐ Granted ☐ Tentatively granted ☒ Not granted ☐ N/A	
QC Dissolution	☐ Pending ☐ Adequate ☒ Inadequate	
Formulation	☒ Adequate ☐ Inadequate	
Will Response to CR Result in A Reformulation?	☒ Possibly ☐ No ☐ N/A	
Overall Review Result	☐ Adequate ☒ Inadequate	
Revised/New Draft Guidance Generated as Part of Current Review	☐ Yes ☒ No	
Deficiency Classification	☒ Major ☐ Minor IR Eligible? ☐ Yes ☐ No ☐ Not Applicable	

Bioequivalence Study Tracking/ Supporting Document #	Study/Test Type	Strength	Review Result
1, 3	Solubility	API	☐ Adequate ☒ Inadequate
1, 3	Permeability	API	☐ Adequate ☒ Inadequate
1, 3	Dissolution (Multi-pH media)	500 mg	☐ Adequate ☒ Inadequate
1, 3	BCS Waiver	500 mg	☐ Adequate ☒ Inadequate

1 EXECUTIVE SUMMARY

This is a review of a waiver request of in vivo bioequivalence study requirements for Teva Pharmaceuticals USA's test product Vigabatrin Tablets, USP, 500 mg, based on the Biopharmaceutics Classification System (BCS)[1] for highly soluble and highly permeable drug substances (Class I) in immediate release solid oral dosage forms that exhibit rapid in vitro dissolution. The corresponding reference product is Lundbeck Pharmaceuticals LLC's SABRIL® (vigabatrin) Tablets, 500 mg (NDA 020427) approved on Aug 21, 2009.

The firm's submission contains the results of solubility testing, in situ rat intestinal perfusion studies, and multimedia dissolution testing.

The solubility testing is inadequate due to analytical method validation deficiencies.

The in situ rat intestinal perfusion studies are inadequate due to method suitability and sample exclusion deficiencies.

The multimedia dissolution testing demonstrates that the test product meets the BCS guidance definition of rapidly dissolving (≥85% in 30 minutes) in 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer; however, the reference product does not. Additionally, the dissolution profiles for the test and reference products are not similar (f2<50). The firm's dissolution testing with the USP method for quality control was reviewed by the Office of Pharmaceutical Quality (OPQ) and determined to be inadequate. The dissolution testing is inadequate.

The Division of Bioequivalence II does not grant Teva Pharmaceuticals USA's BCS waiver request due to multiple deficiencies.

The application is inadequate.

[1] Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System Guidance for Industry; issued May 5, 2015

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Vigabatrin Tablets, USP, 500 mg
Reference Product[2]	SABRIL® (vigabatrin) Tablets, 500 mg
RLD Manufacturer	Lundbeck Pharmaceuticals LLC
NDA No.	N020427
RLD Approval Date	Aug 21, 2009
Indication[3]	SABRIL is indicated for the treatment of: • Refractory Complex Partial Seizures as adjunctive therapy in patients ≥10 years of age who have responded inadequately to several alternative treatments; SABRIL is not indicated as a first line agent • Infantile Spasms - monotherapy in infants 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss

3.2 PK/PD Information [3]

Has this drug been classified as a BCS Class I Drug?	No
If Yes, Basis of Classification?	N/A
Bioavailability	Following oral administration, vigabatrin is essentially completely absorbed. Bioequivalence has been established between the oral solution and tablet formulations.
Intestinal Perfusion Studies	**Did the firm or innovator conduct Intestinal Perfusion Studies?** Yes; current firm
Food Effect	A food effect study involving administration of vigabatrin to healthy volunteers under fasting and fed conditions indicated that the Cmax was decreased by 33%, Tmax was increased to 2 hours, and AUC was unchanged under fed conditions.
Tmax	The time to maximum concentration (Tmax) is approximately 1 hour for children (10 years – 16 years) and adults, and approximately 2.5 hours for infants (5 months – 2 years).
Metabolism	Vigabatrin is not significantly metabolized; it is eliminated primarily through renal excretion. Vigabatrin induces CYP2C9, but does not induce other hepatic cytochrome P450 enzyme systems.
Excretion	**Did the firm or innovator conduct any Mass Balance studies?** Yes; Innovator: the firm conducted a mass balance study using 1.5 g of 14C-Vigabatrin administered as a single oral dose in six healthy male subjects. (**See Appendix 4.3**) Following administration of $^{[14]}$C-vigabatrin to healthy male volunteers, about 95% of total radioactivity was recovered in the urine over 72 hours with the parent drug representing about 80% of this.

[2] Electronic Orange Book, current through Mar 2017, last accessed Apr 27, 2017
[3] Drugs@FDA NDA 020427 Label, updated Jun 21, 2016

Half-life	The terminal half-life of vigabatrin is about 5.7 hours for infants (5 months – 2 years), 9.5 hours for children (10 years – 16 years), and 10.5 hours for adults.
Maximum Daily Dose	Adults (17 years of age or older): 3000 mg (1500 mg twice daily) Pediatric (10 to 16 years of age): 2000 mg (1000 mg twice daily) Infants 1 month to 2 years of age: 150 mg/kg Dose adjustment recommended for renal impairment
Drug Specific Issues (if any)	WARNING: PERMANENT VISION LOSS • SABRIL can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, SABRIL may also decrease visual acuity. • Risk increases with increasing dose and cumulative exposure, but there is no dose or exposure to SABRIL known to be free of risk of vision loss. • Risk of new and worsening vision loss continues as long as SABRIL is used, and possibly after discontinuing SABRIL. • Baseline and periodic vision assessment is recommended for patients on SABRIL. However, this assessment cannot always prevent vision damage. • SABRIL is available only through a restricted program called the SABRIL REMS Program.

Is this a Prodrug? (Refer to Page 9 in Guidance)	No
If Yes, does Prodrug drug conversion take place before or after intestinal membrane permeation?	N/A
Is this a narrow therapeutic range drug? (Page 9 in Guidance)	No
Is this dosage form intended to be absorbed in the oral cavity (i.e. sublingual or buccal tablets)? (Page 9 in Guidance)	No

3.3 OGD Recommendations for Drug Product

3.3.1 In Vivo Bioequivalence Studies

Number of studies recommended:	1

1.	**Type of study:**	A multiple-dose, two-treatment, two-way, steady-state pharmacokinetic bioequivalence (BE) study
	Design:	Two-way crossover in vivo
	Strength:	500 mg
	Subjects:	Adult refractory complex partial-seizure adult patients who are already on established vigabatrin adjunctive therapy
	Additional Comments:	1. The study drug should not be given with other drugs associated with serious adverse ophthalmic effects, such as retinopathy. 2. Females should not be pregnant or lactating, and, if applicable, should practice abstention or contraception during the study. 3. The study design (e.g., inclusion/exclusion criteria) and procedures (e.g., safety monitoring) should address all of the elements related to patient safety specified in the reference listed drug (RLD) label. Vigabatrin was approved with a risk evaluation and mitigation strategy (REMS), which restricts its

		use. All pertinent elements of the REMS must be incorporated into the protocol and informed consent. 4. Patients who are receiving a stable dosage of vigabatrin twice daily would be eligible to participate in the study by continuing their established maintenance dose. FDA recommends that studies not be conducted using healthy subjects. 5. According to the randomization schedule, an equal number of patients should receive either the generic formulation (Treatment A) or the reference formulation (Treatment B) in the same dose as administered prior to the study every 12 hours until the steady state is achieved. Patients are then switched to the other product for a second period of the same duration. No washout period is necessary between the two treatment periods. After the study is completed, patients can continue on their current dose of vigabatrin using an approved vigabatrin product, as prescribed by their clinicians. 6. Attainment of steady state should be confirmed with at least three consecutive trough levels. 7. Blood sampling for BE should consist of appropriate sampling times over a 12-hour period following attainment of steady state. 8. Investigators should refer to the Warnings, Precautions, Contraindications, and Adverse Reactions in the FDA-approved labeling and follow the directions closely.

3.3.2 In Vitro Bioequivalence Studies

Number of studies recommended:	**Note:** There are currently no in vitro bioequivalence studies recommended. The firm is requesting a waiver of in vivo bioequivalence requirements based on the BCS Class I classification of Vigabatrin. The recommendations below are from FDA's Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System Guidance for Industry (May 2015)[1] 3; Solubility, Permeability, and Dissolution

1.	**Type of study:**	Solubility
	Design:	The pH-solubility profile of the test drug substance should be determined at 37 ± 1°C in aqueous media with a pH in the range of 1-6.8. A sufficient number of pH conditions should be evaluated to accurately define the pH-solubility profile within the pH range of 1-6.8.
	Strength:	N/A
	Additional Comments:	A drug substance should be classified as highly soluble when the highest strength is soluble in < 250 mL of aqueous media over the pH range of 1-6.8.

2.	**Type of study:**	Permeability
	Design:	1. Pharmacokinetic Studies in Humans a. Mass balance studies b. Absolute bioavailability studies

		2. Intestinal Permeability Methods a. In vivo intestinal perfusion studies in humans b. In vivo or in situ intestinal perfusion studies using suitable animal models c. In vitro permeation studies using excised human or animal intestinal tissues d. In vitro permeation studies across a monolayer of cultured epithelial cells 3. Instability in the Gastrointestinal Tract
	Strength:	N/A
	Additional Comments:	In many cases, a single method may be sufficient: (i) when the absolute BA is 85 percent or more, or (ii) when 85 percent or more of the administered drug is excreted unchanged in urine, or (iii) when 85 percent or more of the administered drug is recovered in urine as parent and metabolites with evidence indicating stability in the GI tract. When a single method fails to conclusively demonstrate a permeability classification, two different methods may be advisable. In case of conflicting information from different types of studies, it is important to note that human data supersede in vitro or animal data.

3.	**Type of study:**	Dissolution
	Design:	USP Apparatus I at 100 rpm or Apparatus II at 50 rpm (or at 75 rpm when appropriately justified) using 500 mL of the following dissolution media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.
	Strength:	All strengths
	Additional Comments:	An IR drug product is considered rapidly dissolving when 85 percent or more of the labeled amount of the drug substance dissolves within 30 minutes using the method above.

Analytes to measure (in plasma/serum/blood):	Vigabatrin in plasma
Bioequivalence based on:	90% CI of Vigabatrin
Waiver request of in-vivo testing:	N/A
Source of most recent recommendations:	Draft Guidance on Vigabatrin Tablets Recommended Mar 2015  Vigabatrin Tablet Guidance.pdf Control #24501 BE Guidance Review  Vigabatrin Tablet N20427 BE Guidance R

Summary of OGD or DBE History:	There are currently (b) (4) pending ANDAs for Vigabatrin Tablets: ANDA 209822 (Teva Pharmaceuticals USA) (b) (4) All (b) (4) applicants are requesting a BCS waiver. Actavis Elizabeth LLC (a wholly owned subsidiary of Teva Pharmaceuticals USA) previously submitted controlled correspondences 48651 (received Feb 6, 2015) and 1349925 (received Sep 1, 2015) to request a letter from FDA stating that their bioequivalence study protocols contain safety protections comparable to applicable REMS for the RLD.

3.4 Contents of Submission

Study Types	Yes/No?	How many?
BE Studies	No	--
Solubility	Yes	1 (pH 1.0, 2.0, 3.0, 4.0, 5.0 and 6.8)
Permeability	Yes	1 pivotal 2 pilot
In vitro dissolution	Yes	1 (Water, pH 1.2, pH 4.5, and pH 6.8)
Waiver requests	No	--
BCS Waivers	Yes	1
Failed Studies	No	--
Amendments	No	--

3.5 Data Supporting Classification of Vigabatrin Tablets, USP as a BCS Class I Drug

Table 1. Product Information

Product	Test	RLD
Treatment ID	N/A	N/A
Product Name	Vigabatrin Tablets, USP	Sabril® (vigabatrin) Tablets
Manufacturer	Watson Pharma Pvt. Ltd.	Patheon
Batch/Lot No.	1115900057 (used for multi-media dissolution) 1115900058 1115900060 1115900127	3132857
Manufacture Date	1115900057-06/2015 1115900058-06/2015 1115900060-06/2015	[redacted]

	1115900127-10/2015	[redacted]
Expiration Date	[redacted]	05/2018
Strength	500 mg	500 mg
Dosage Form	Tablet	Tablet
Bio-Batch Size	(b) (4) tablets ablets ablets ablets	[redacted]
Production Batch Size	(b) (4) tablets	
Potency (Assay)	1115900057-97.3% 1115900058-99.6% 1115900060-98.6% 1115900127-98.8%	98.9%
Content Uniformity (per USP <905>)	1115900057-AV=2.7 1115900058-AV=1.0 1115900060-AV=1.2 1115900127-AV=1.2	[redacted]
Dose Administered	N/A	N/A
Route of Administration	Oral	Oral

3.5.1 Solubility Testing Study

A drug substance is considered highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH ranges of 1-6.8.[1]

The highest marketed dose strength of Vigabatrin Tablets, USP is 500 mg. Therefore, the minimum concentration which will satisfy these BCS criteria for Vigabatrin Tablets, USP is 500 mg/250 mL or 2 mg/mL.

Table 2. Method Validation for Solubility Testing

Information Requested	Analyte 1
Bioanalytical method validation report location	Analytical method: (b) (4), in house method adapted from USP.
Study Report Number	(b) (4)
Analyte	Vigabatrin
Internal standard (IS) (if applicable)	N/A
Method description	(b) (4)

(b) (4)

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(b) (4)

Were the standard operating procedures (SOP) submitted? (Y/N)	Solubility studies: No Analytical method: Yes (b) (4)
Did the firm include the details of the Buffer Preparation? Y/N	Yes
Were the specific experimental testing conditions included? Y/N	Yes

Table 4. Solubility Data for Vigabatrin in Different Buffered Media at pH 1.0-6.8

Sr. No.	Buffer	Volume	Mean Drug solubility	Initial Drug Concentration used for solubility	pH after Solubilization	Number of Replicates (n=)	SD	%RSD
1	pH 1.0	15 mL	>4mg/mL	5 mg/mL	pH 1.1	3	0.9	0.9
2	pH 2.0	15 mL	>4mg/mL	5 mg/mL	pH 2.0	3	1.4	1.4
3	pH 3.0	15 mL	>4mg/mL	5 mg/mL	pH 3.1	3	1.7	1.7
4	pH 4.0	15 mL	>4mg/mL	5 mg/mL	pH 4.0	3	1.2	1.2
5	pH 5.0	15 mL	>4mg/mL	5 mg/mL	pH 5.0	3	1.5	1.5
6	pH 6.8	15 mL	>4mg/mL	5 mg/mL	pH 6.8	3	2.1	2.0

Note: Due to extremely high solubility of this drug, saturation was not reached therefore the concentration of 5 mg/mL was selected as the target concentration for this study, which is higher than twice the concentration reached when dissolving the dose of 500 mg in 250 mL aqueous media (2 mg/mL). The SD and % RSD values correspond to the % recovery values.

(b) (4)

(b) (4)

[redacted]

Reviewer's Comments on Solubility Testing:

- The firm conducted solubility testing for the drug substance, Vigabatrin, at 37°C in six different media with pH ranging from 1.0 to 6.8. Per FDA recommendation, the number of pH conditions should include pH=pKa, pH=pKa+1, pH=pKa-1, pH=1, and pH=6.8. The pKa of Vigabatrin is 4; therefore, the firm's use of pH 1.0 solution, pH 2.0 solution, pH 3.0 solution, pH 4.0 biphthalate buffer, pH 5.0 biphthalate buffer, and pH 6.8 phosphate buffer is acceptable.

- The pH of all solutions and buffers was checked and adjusted after addition of the drug substance. The pH was also checked after 2 and 24 hours of incubation, and adjustment was not needed.

- Samples were prepared in triplicate for all solutions and buffers.

- [redacted] (b) (4) however, solubility was not determined at equilibrium. The firm noted that due to the extremely high solubility of the drug substance saturation was not reached. The firm selected a concentration of 5 mg/mL to conduct solubility testing, which is 2.5 times higher than the concentration needed (2 mg/mL) for the drug substance to be classified as highly soluble. According to the firm's Overall Quality Summary in Module 2.3, Vigabatrin has a solubility of 300 mg/mL over the range of pH 1.2 to 8.0. Because of the high solubility of the API and the fact that the firm used 2.5 times higher than the concentration needed (2 mg/mL) for the drug substance to be classified as highly soluble, the use of 5 mg/mL for solubility testing is acceptable.

- The certificate of analysis for the API lot used (Lot# VB0020315) is located in the analytical method validation report for the permeability study (Study# 15ACTAP6R1GLPS306) under Module 4.2.2.1.

- The firm referenced but did not provide experimental protocol E15-47 "Evaluation of pH Solubility Profile and Stability Studies in Simulated Gastric Fluid (SGF) and Simulated Intestinal fluid (SIF) of Vigabatrin According to FDA's Biopharmaceutics Classification System (BCS) Guidance." The firm will be asked to provide this document.

- The firm referenced the assay method (b) (4); however, the firm provided analytical method (b) (4) "Vigabatrin Tablets: Assay, Content Uniformity, and Blend Uniformity for Release and Stability." The firm will be asked to identify the changes between the document version referenced and the version submitted.

- The analytical method used by the firm is stability-indicating; however, the firm's provided method validation is inadequate.

(b) (4)

(b) (4)

Is the Solubility Testing Acceptable (Y/N): No

3.5.2 Permeability Study Validation

3.5.2.1 Model Compound Validation Study

Table 5. Study Information

Study No.	15ACTAP6R1GLPS305
Method (i.e. in vivo mass balance/absolute BA/intestinal permeability)	In situ rat intestinal perfusion
Rationale for method selection	(b) (4) . Therefore, per the BCS Guidance (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070246.pdf), a non-clinical in situ permeability method is an adequate system to support the high permeability classification of this drug substance.
Study Title	In Situ Rat Intestinal Perfusion Study of Vigabatrin According to the Biopharmaceutics Classification System (BCS) Guidelines Issued by the United States Food and Drug Administration
Study Objective	To assess the in situ permeability of vigabatrin using single-pass rat intestinal perfusion. The study was conducted according to the BCS guidelines issued by the United States Food and Drug Administration.
Permeability Site & Address	(b) (4)
Analytical Site & Address	
Study Dates	December 11, 2015 to December 21, 2015

Table 6. Materials and Methods for Validation of Permeability Study

Reagents & Materials	(b) (4)

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(b) (4)

Table 8. Standard Operating Procedures

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Evaluation of pH solubility profile and stability in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) of vigabatrin according to FDA's Biopharmaceutics Classification System guidance (BCS)
		Validation of analytical methods for transport media
		Sample analysis and acceptance of analytical data obtained by HPLC or LC-MS/MS for GLP studies
		Validation of stock preparation, stock solution stability, and internal standard stability

(b) (4)

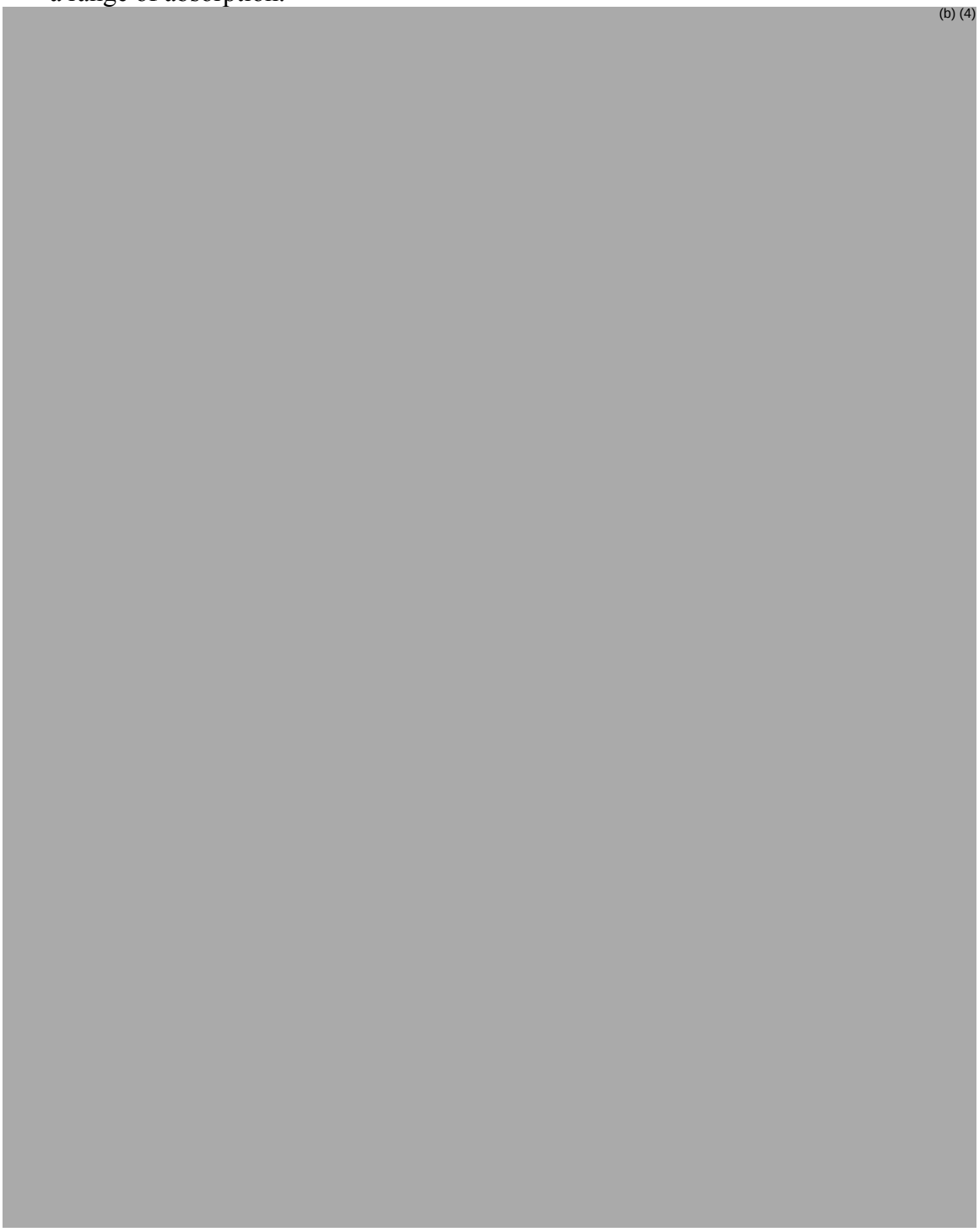
Did the firm conduct its validation using 20 or more model compounds? Y/N	**Yes**
Did the model compounds demonstrate permeability over a range of low (< 50%), moderate (50-89%) and high (≥ 90%)? Y/N	**Yes**
Was the sampling time schedule the same for all model compounds? Y/N	**Yes**
Is the method reliable to differentiate between drug substances of low and high permeability? Y/N	**Yes**

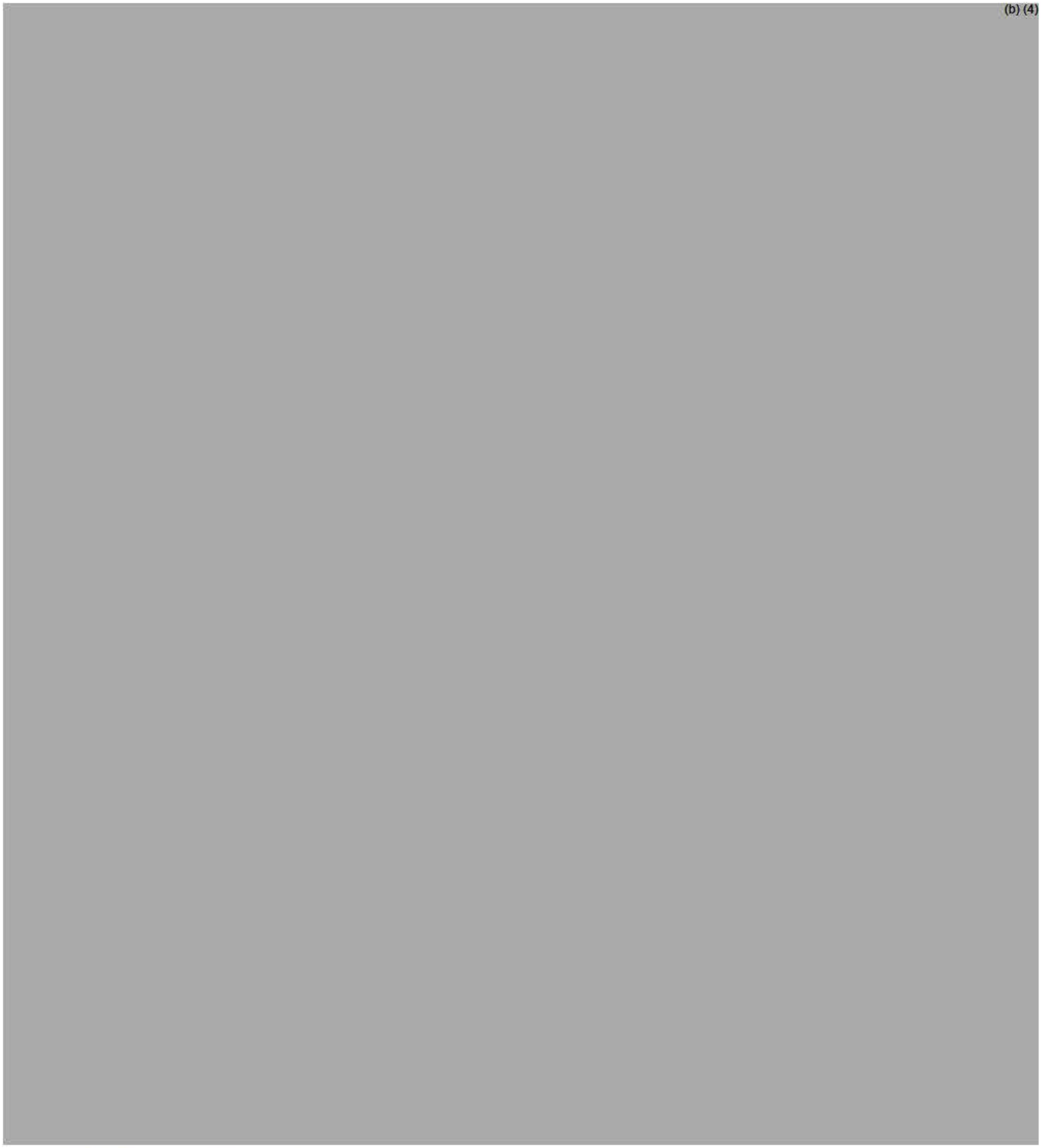
Reviewer's Comments:

- The BCS Guidance recommends that 20 model drugs representing a range of low (e.g. <50%), moderate (e.g. 50-84%) and high (≥85%) absorption be tested to demonstrate method suitability.[1]

- The firm provided summary tables for the testing of 20 model drugs representing a range of absorption.

(b) (4)





3.5.2.2 Study Ruggedness

- The firm did not provide ruggedness data.

3.5.3 In vitro Permeability Study (Pivotal)

Table 10. Analytical Method Validation

Study No.	15ACTAP6R1GLPS305		
Study Title	In Situ Rat Intestinal Perfusion Study of Vigabatrin According to the Biopharmaceutics Classification System (BCS) Guidelines Issued by the United States Food and Drug Administration		
Study Objective	To assess the in situ permeability of vigabatrin using single-pass rat intestinal perfusion. The study was conducted according to the BCS guidelines issued by the United States Food and Drug Administration.		
Analytical Site	(b) (4)		
Analytical Site Address (permeability lab)			
Analytical Site Address (bioanalytical lab)			
Study Dates	December 11, 2015 to December 21, 2015		
Information Location	(b) (4), validated document management system		
Analyte Name	**Vigabatrin**		
Internal Standard		(b) (4)	
Analytical Method	LC-MS/MS	LC-MS/MS	LC-MS/MS
Standard Curve Range	0.25-20 µM	0.25-20 µM	0.25-20 µM
Limit of Quantitation	0.25 µM	0.25 µM	0.25 µM
Average Recovery of Drug (%)[a]	93.0-100%	N/A	N/A
Average Recovery of IS (%)[a]	N/A	86.6-100%	86.2-97.9%
QC Concentrations (units/mL)	0.25 / 0.50 / 2.00 / 15.0 µM	0.25 / 0.50 / 2.00 / 15.0 µM	0.25 / 0.50 / 2.00 / 15.0 µM
QC Intraday Precision Range (%)	1.64 - 4.66; 1.89 - 9.35; 1.28 - 5.55	1.95 - 2.63; 1.38 - 3.46; 0.873 - 2.53	1.00 - 2.46; 0.921 - 2.21; 1.15 - 2.73
QC Intraday Accuracy Range (%)	97.0 - 102; 101 - 105; 91.5 - 100	100 - 102; 96.7 - 99.9; 100 - 105	96.3 - 101; 94.7 - 96.7; 98.9 - 102
QC Interday Precision Range (%)	3.33 - 8.24	2.02 - 4.05	2.04 - 3.57
QC Interday Accuracy Range (%)	98.6 - 102	100 - 101	97.4 - 99.0
Bench-top Stability (hrs)	4 hr at room temp	4 hr at room temp	4 hr at room temp
Stock (refrigerator) Stability (hrs)	16 days (~384 hr) at 4°C	265 days (~6360 hr) at 4°C	16 days (~384 hr) at 4°C
Processed (autosampler) Stability (hrs)	3 days (~72 hr) at 4°C	3 days (~72 hr) at 4°C	3 days (~72 hr) at 4°C
***Freeze-thaw Stability (cycles)**	N/A	N/A	N/A
***Long-term Storage Stability (days)**	46 hr (~2 days) at 4°C	46 hr (~2 days) at 4°C	46 hr (~2 days) at 4°C
Dilution Integrity	12000-fold w/ 101% accuracy and 3.90% precision	12000-fold w/ 106% accuracy and 3.44% precision	12000-fold w/ 109% accuracy and 2.52% precision
Specificity	No evidence of cross-analyte interference with co-dosed compounds	No evidence of cross-analyte interference with co-dosed compounds	No evidence of cross-analyte interference with co-dosed compounds

[a] Documented in (b) (4) Report No. (b) (4)
N/A: not applicable
*Only if this is applicable.

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- In the pivotal in situ rat intestinal perfusion study report, the firm referenced permeability chromatograms in file [redacted] chromatograms, but they provided file [redacted] chromatograms which are representative chromatograms from the analytical method validation run name 20151114_val_a. The firm should provide the chromatograms from the pivotal permeability study and 100% of the numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. run log) in the instrument printout format.

3.5.3.1 Study Design

Table 11. Permeability Study Design

Study Number	15ACTAP6R1GLPS305
Study Title	In Situ Rat Intestinal Perfusion Study of Vigabatrin According to the Biopharmaceutics Classification System (BCS) Guidelines Issued by the United States Food and Drug Administration
Testing Site	[redacted]
Study Monitor	
Analytical Site	
Study Director	
Study/Analysis Dates	December 11, 2015 to December 21, 2015
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	Samples were analyzed on the day of collection or within the appropriate validated stability interval at 4°C
Testing Conditions	
SOP	All procedures are described in the study-specific Master Study Protocol, and the statistical rationale for acceptance criteria for test compound data is documented in [redacted] Report No. [redacted] Acceptance Criteria.
Sample Analysis	LC-MS/MS
Internal Control Compounds	[redacted]

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(b) (4)

Is this a passively transported drug, and is there information to support this?
Per the BCS guidance, an apparent passive transport mechanism can be assumed when one of the following conditions is satisfied:[1]

1. A linear (pharmacokinetic) relationship between the dose (e.g., relevant clinical dose range) and measures of bioavailability (area under the concentration-time curve) or a drug is demonstrated in humans.
2. Lack of dependence of the measured in vivo or in situ permeability is demonstrated in an animal model on initial drug concentration (e.g., 0.01, 0.1, and 1 times the highest strength dissolved in 250 mL) in the perfusion fluid.
3. Lack of dependence of the measured in vitro permeability on initial drug concentration (e.g., 0.01, 0.1, and 1 times the highest strength dissolved in 250 mL) is demonstrated, or on transport direction (e.g., no statistically significant difference in the rate of transport between the apical-to-basolateral and basolateral-to-apical direction for the drug concentrations selected) using a suitable in vitro cell culture method that has been shown to express known efflux transporters (e.g., P-gp).

(b) (4)

. Therefore, the first two conditions are satisfied, indicating that a passive transport mechanism can be assumed.

3.5.4 Non-Specific Binding Permeability Study

Study Report	15ACTAP6R1_NSB
Chemical Stability	The chemical stability of Vigabatrin (API) was evaluated in simulated gastric fluid (without enzyme) and simulated intestinal fluid (without enzyme).
Non-Specific Binding Method	(b) (4)
Non-Specific Binding Assessment	The firm compared the inlet concentration to the outlet concentration.
Permeability	N/A
Tolerability	N/A
Is Non-Specific Binding to the Device Minimal? Y/N	Yes
Is the Rate of Diffusion of the test compound in the Cell Free System high? Y/N	N/A

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Reviewer's Comment:

- The firm determined non-specific binding of Vigabatrin, (b) (4) (b) (4) using ex vivo rat jejunal sections (5 cm each from two rats).

- The firm measured non-specific binding at 0-10, 10-20, and 20-30 minutes. These time intervals are different from the time intervals used for the perfusion studies of 0-15, 15-30, 30-45, 45-60, 60-75, and 75-90 minutes. The firm should explain why the time intervals are different between the non-specific binding study and the pivotal in situ rat intestinal perfusion study.

3.5.5 Instability in the Gastrointestinal Tract

(b) (4)

Reviewer's Comments:

- The firm referenced but did not submit protocol E15-47. The firm will be asked to provide this document.

- The firm used the same analytical method to measure Vigabatrin in the GI stability and solubility studies; therefore, the same deficiencies apply to both the GI stability and the solubility studies.

- Per the BCS Guidance, simulated fluids such as Gastric and Intestinal Fluids, USP are acceptable to use for GI stability studies. The firm used Simulated Gastric Fluid (SGF) and Simulated Intestinal Fluid (SIF), but they did not include enzymes in these fluids. Per USP, SGF should contain pepsin, and SIF should contain pancreatin. The firm's SGF and SIF do not meet USP requirements; therefore, the GI stability results are not adequate. The firm will be asked to repeat their GI stability experiments using SGF and SIF that conform to USP requirements (including enzymes).

3.6 Formulation

Location in appendix	Section 4.1, Page 37
If a tablet, is the RLD scored?	Yes
If a tablet, is the test product biobatch scored	Yes
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	--

3.7 In Vitro Dissolution

3.7.1 Recommended Dissolution Method

Location of Dissolution Review	http://panorama fda.gov/task/view?ID=5858bc9f004b607b8cdb81bbb14c78a8
Source of Method (USP, FDA or Firm)	USP
Medium	Water
Volume (mL)	900
USP Apparatus type	2 (Paddle)
Rotation (rpm)	50
USP specifications	NLT 75% (Q) in 30 min
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	Yes
If no, reason why F2 not calculated	N/A
Is method acceptable?	**Inadequate**
If not then why?	Specification needs to be revised

3.7.2 Multimedia Dissolution Testing

Lot No. of Test Product & Manufacture Date	1115900057-Jun 2015
Lot No. of Reference Product & Expiration Date	3132857-May 2018
Medium 1	0.1 N HCl
Medium 2	pH 4.5 Acetate Buffer
Medium3	pH 6.8 Phosphate Buffer
Volume (mL)	500
USP Apparatus type	II (Paddle)
Rotation (rpm)	75
Are both T & R rapidly dissolving?	No, (b) (4) Profiles are not similar.

Dissolution Method #	(b) (4)
Deaeration/degassing of the medium (Yes/No)	Yes

Filter Description (if used in dissolution testing)	(b) (4)
Sinker Description (if used in dissolution testing)	N/A
Mesh Size Description (if basket used in dissolution testing)	N/A
Sampling (manual/Auto/fiber optics)	(b) (4)
CoA of Test Product (location in the submission)	Module 3.2.P.5.4
CoA of Reference Product (location in the submission)	Module 2.7

3.8 Waiver Request(s)

Strengths for which waivers are requested	500 mg
Is dissolution acceptable?	Yes
Waivers granted?	**No**
If not then why?	See deficiency comments in Section 3.9

3.9 Deficiency Comments

Please see Bioequivalence Deficiencies to be Provided to the Applicant for list of deficiencies.

APPEARS THIS WAY ON ORIGINAL

4 APPENDIX

4.1 Formulation Data

4.1.1 Test Formulation

Ingredient	Amount (mg) / Tablet	Amount (%) / Tablet
Cores		
Vigabatrin, USP	500	(b) (4)
Povidone, USP (b) (4)	(b) (4)	(b) (4)
(b) (4)		
Microcrystalline cellulose (b) (4) NF		
Sodium starch glycolate		
Magnesium Stearate, NF (b) (4)		
(b) (4)		(b) (4)
Total	**708**	**NA**
(b) (4)		

(b) (4)

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Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	The formulation is acceptable.

Reviewer's Comments

The maximum daily intake of inactive ingredients was calculated based on a maximum daily dose of 3000 mg (6 x 500 mg tablets) for Vigabatrin Tablets. All inactive ingredients are within the IIG limits. The test and reference products are qualitatively and quantitatively the same except for the tablet coating.

The formulation is acceptable.

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(b) (4)

Reviewer's Comments

- The quality control dissolution method and specification were reviewed by OPQ and determined to be inadequate pending acceptance of a tighter specification.

- The firm used the USP method for quality control and product release dissolution testing.

USP Apparatus	II (Paddle)
Rotational Speed (rpm)	50
Temperature (°C)	37 ± 0.5
Medium	Water
Volume (mL)	900
Specification	NLT 75% (Q) in 30 min

- To support the BCS waiver request, the firm submitted multimedia dissolution data. The firm used 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer. The test product meets the BCS criteria for rapidly dissolving (≥ 85% in 30 minutes) in all three media; (b) (4)

- Per the BCS guidance, USP Apparatus II at 50 rpm is recommended, but 75 rpm can be used when appropriately justified. (b) (4) The firm used 50 rpm for the QC method.

- Both the test and the reference products are scored tablets. The firm submitted dissolution data using the USP method for the split tablets using both manual and mechanical splitting. The dissolution results for the split tablets of the test product are similar to the dissolution of the whole tablets.

- Per the BCS guidance, f2 should be used to compare the dissolution profiles of the test and reference products. The f2 values comparing the test and reference products are provided below:

Medium	**F2 Metric for Test vs RLD**
Water (Batch#1115900057)	13.88
Water (Batch#1115900058)	11.78
Water (Batch#1115900060)	12.74
0.1N HCl	13.44
pH 4.5 Acetate Buffer	14.04
pH 6.8 Phosphate Buffer	14.98

- Per the BCS guidance the RLD must meet the criteria for BCS class 1, and the test product should exhibit a similar dissolution profile to the reference product. The RLD dissolution does not demonstrate that the product is rapidly dissolving because not all units dissolve >85% in 30 minutes. The f2 values comparing the test and reference product dissolution are <15; therefore, the test and reference product dissolution profiles are not similar and do not meet the BCS guidance recommendations for classification as BCS class 1.

- The dissolution testing is inadequate with respect to supporting the BCS waiver request.

4.3 NDA 020427 Mass Balance Study

In NDA 020427 the firm conducted a mass balance study using 1.5 g of ^{14}C-Vigabatrin administered as a single oral dose in six healthy male subjects. The firm noted that two of the six subjects were outliers. Both the study summary and report from the NDA and the resultant publication are attached.

NDA 020427 Mass Balance Study.pdf

PK and metabolism of Vigabatrin following a

Pharmacokinetic Parameters of ^{14}C and Parent Drug Following A 1.5 Gram Single Oral Dose of ^{14}C-Vigabatrin in 6 Male Volunteers

(b) (6)

NOTE TO THE RPM: The applicant's response to the Complete Response (CR) letter below may result in a reformulated product.

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 209822

APPLICANT: Teva Pharmaceuticals USA

DRUG PRODUCT: Vigabatrin Tablets, USP, 500 mg

The Division of Bioequivalence II has completed its review and has identified the following deficiencies:

Dissolution Testing

1. Per the CDER Guidance for Industry, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (BCS), May 2015, the reference listed drug (RLD) must meet the criteria for BCS class 1, and the test product should exhibit a similar dissolution profile to the reference product. The RLD dissolution does not demonstrate that the product is rapidly dissolving because not all units dissolve >85% in 30 minutes in water and the three other media tested. The f2 values comparing the test and reference product dissolution are <15; therefore, the test and reference product dissolution profiles are not similar and do not meet the BCS guidance recommendations for classification as BCS class 1.

Medium	F2 Metric for Test vs RLD
Water (Batch#1115900057)	13.88
Water (Batch#1115900058)	11.78
Water (Batch#1115900060)	12.74
0.1N HCl	13.44
pH 4.5 Acetate Buffer	14.04
pH 6.8 Phosphate Buffer	14.98

Solubility and Gastrointestinal Tract Stability Testing

2. You referenced but did not provide experimental protocol E15-47 "Evaluation of pH Solubility Profile and Stability Studies in Simulated Gastric Fluid (SGF) and Simulated Intestinal fluid (SIF) of Vigabatrin According to BCS Guidance." Please provide this document.
3. You referenced the assay method (b) (4); however, you provided analytical method (b) (4) "Vigabatrin Tablets: Assay, Content Uniformity, and Blend Uniformity for Release and Stability." Please identify the changes between the document version referenced and the version submitted.
4. Per the BCS Guidance, simulated fluids such as Gastric and Intestinal Fluids, USP are acceptable to use for GI stability studies. You used Simulated Gastric Fluid (SGF) and Simulated Intestinal Fluid (SIF) but did not include enzymes in these fluids. Per USP, SGF should contain pepsin, and SIF should contain pancreatin. Your SGF and SIF do not

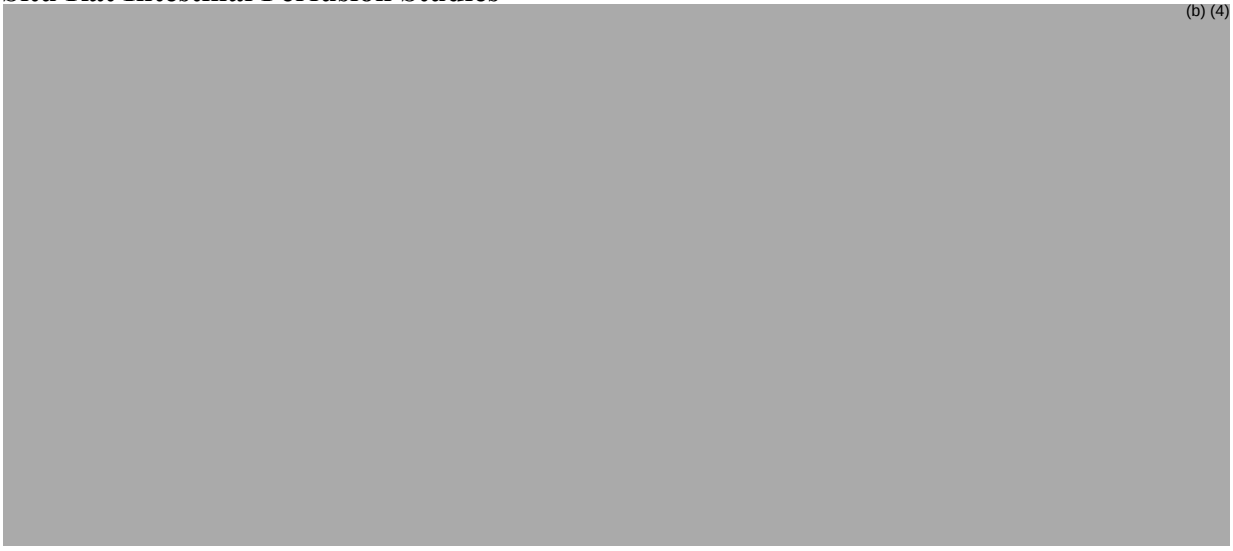
meet USP requirements; therefore, the GI stability results are not adequate. Please repeat your GI stability experiments using SGF and SIF that conform to USP requirements (including enzymes).

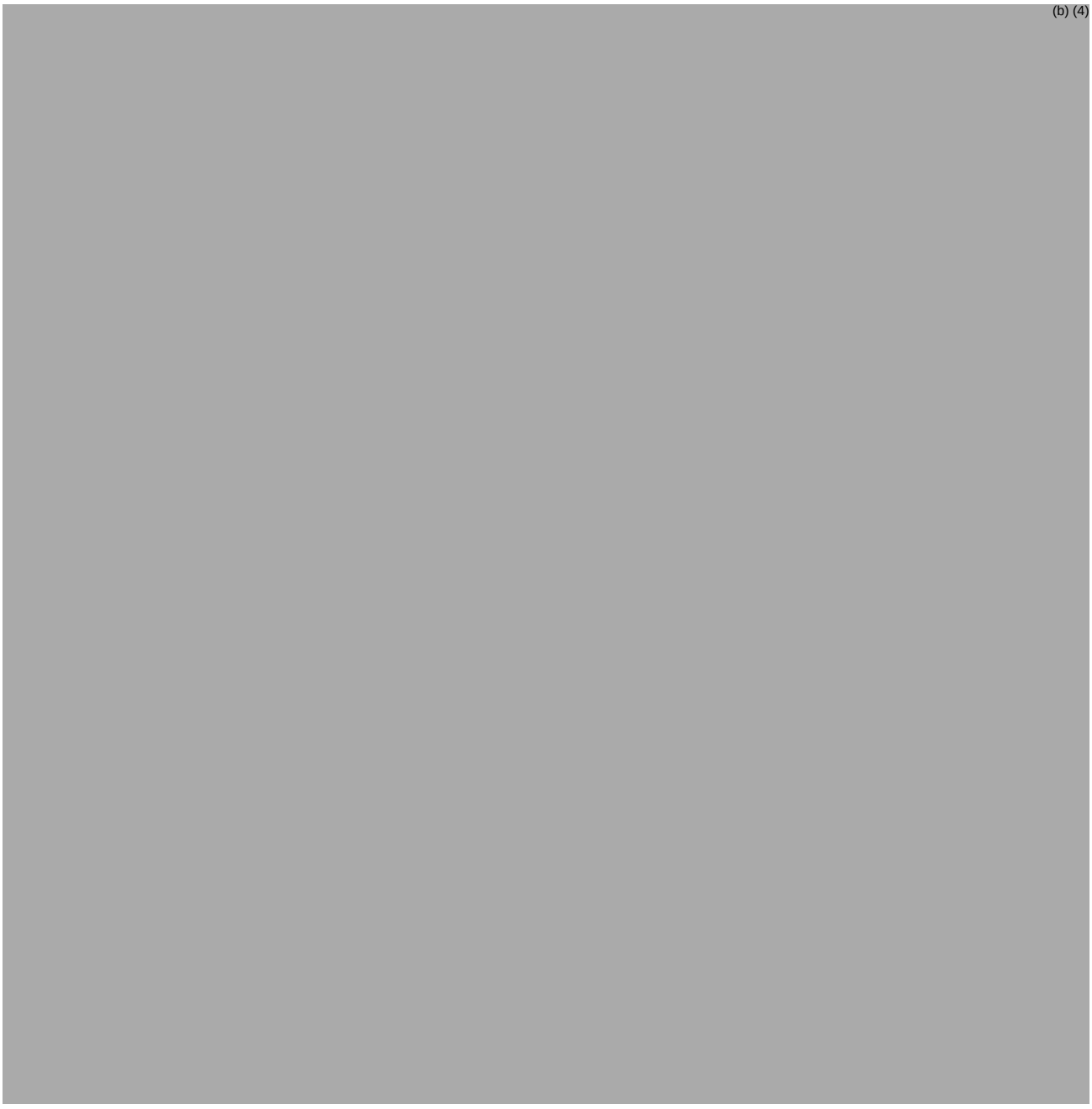
Analytical Method for Solubility and Gastrointestinal Tract Stability Testing

(b) (4)

In Situ Rat Intestinal Perfusion Studies

(b) (4)





Analytical Method for In Situ Rat Intestinal Permeability Studies

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R. Ph.
Director, Division of Bioequivalence II
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.4 Outcome Page

ANDA: 209822

Reviewer: Avaritt, Brittany **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Vigabatrin Tablets, USP, 500 mg

Items:

ID	***Letter Date***	***Productivity Category***	***Sub Category***	***Score***	***Subtotal***		
31502	12/16/2016	BIO	ANDA Original [1]	1	1	Edit	Delete
31502	12/16/2016	Parallel	BCS Dissolution (Irrespective of the number of strenghs) [0.25]	0.25	0.25	Edit	Delete
31502	12/16/2016	Parallel	BCS Permeability Study (Stability Data - Solubility Study Not Classified by BCS Committee) (For each study) [1]	2	2	Edit	Delete
				Total:	3.25		

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209822

OTHER REVIEWS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 20, 2017

TO: Dale Conner, Pharm.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

FROM: Kara A. Scheibner, Ph.D.
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

Makini Cobourne-Duval, Ph.D.
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Deputy Director
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance inspection of [redacted] (b) (4)

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of [redacted] (b) (4), conducted at [redacted] (b) (4) (D) (4).

Form FDA 483 was issued at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI).

Objectionable conditions were observed that likely do not impact the outcome of the audited studies. However, we expect to receive additional data in response to the observations that may or may not alter the assessment of study outcome. Thus, we recommend that data be accepted for Agency review, pending evaluation of the additional data. Data from other studies using

similar methods should be reviewed carefully (**see Attachment 1**) and the observations described herein should be considered in evaluating other studies.

(b) (4)

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[redacted]

ADDITIONAL DISCUSSION ITEMS:

Documentation practices: In addition to the items cited in **Observation 2**, other documentation practices could be strengthened by the firm. Examples include: documentation of details of run failures during method validation; documentation of instrument errors (e.g. retention time drift, system leak, etc.); documentation of why runs were not used despite meeting acceptance criteria; documentation of why a chromatogram was manually integrated.

Investigations: We noted multiple instances when laboratory investigations were apparently conducted; however, these were not documented.

Reporting Errors: We found numerous instances of incorrect values reported, incorrect table numbers referenced in the text, and missing runs in method validation and study reports. We identified these errors to the firm throughout the inspection.

Conclusion:

Objectionable findings were observed during this inspection and Form FDA 483 was issued. The final inspection classification is Voluntary Action Indicated (VAI).

After reviewing the inspectional findings and the firm's response to Form FDA 483, the objectionable findings do not likely impact the reliability of data from the audited studies. We recommend accepting the analytical data for further Agency review. However, this conclusion will be re-assessed upon receipt and evaluation of expected additional data from the firm. If the assessment of these studies changes, we will update this review accordingly.

Due to significant documentation issues, and concerns regarding the handling of precision and accuracy data in the audited method validations, the overall performance of the site was not adequate. The impact on other studies that were not reviewed during this inspection is unknown. We were able to assess likelihood of study impact from these observations on the current studies due to access to source study data and the firm's responses.

Thus, studies using similar methods conducted prior to 2016 should be carefully evaluated during Agency review (**see Attachment 1 below**), and future inspections will be required to verify that proposed changes were implemented and that current observations do not affect other studies.

Kara A. Scheibner, Ph.D.
Pharmacologist

Makini Cobourne-Duval, Ph.D.
Pharmacologist

Final Classification:

VAI - [redacted] (b) (4)

cc:
OTS/OSIS/Kassim/Choe/Kadavil/Turner-Rinehardt/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDBE/Cho/Haidar/Choi/Skelly/Au/Scheibner/Cobourne-Duval

Draft: KAS 07/18/2017
Edit: MFS 07/19/2017;SHH 07/20/2017

[redacted] (b) (4)

(b) (4)

Kara A. Scheibner -S

Digitally signed by Kara A. Scheibner -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001534820, cn=Kara A. Scheibner -S
Date: 2017.07.20 15:10:25 -04'00'

Name

Makini Cobourne-duval -S

Digitally signed by Makini Cobourne-duval -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001996263, cn=Makini Cobourne-duval -S
Date: 2017.07.21 00:18:27 -04'00'

Name

Sam H. Haidar -S

Digitally signed by Sam H. Haidar -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sam H. Haidar -S, 0.9.2342.19200300.100.1.1=1300123664
Date: 2017.07.20 21:13:08 -04'00'

Name

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209822

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Approval Type: ☒ **FULL APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)**

RPM: Kimberly McCullough Team Leader: Bic Nguyen

☒ **PI** ☐ **PII** ☐ **PIII** ☐ **PIV** (*eligible for 180 day exclusivity* ☐ **Yes** ☐ **No**) ☐ **MOU** ☒ **RX or** ☐ **OTC**

ANDA #: 209822 Applicant: Teva Pharmaceuticals USA, Inc.
Established Product Name: Vigabatrin Tablets USP, 500 mg

Basis of Submission (RLD): NDA–020427 Sabril tablets, 500 mg by Lundbeck

Basis Of Submission Discontinued? Yes ☐ No ☒

If yes, has FR published indicating the Agency determined the product was not withdrawn for reasons of safety or effectiveness?

Yes ☐ FR Notice dated _____; Document Citation _____; FR. _____(Example: 78 FR 67365)

No ☐ Consult completed but not yet published in FR

(Is ANDA based on an approved Suitability Petition? ☐ Yes ☒ No, if yes, use SP language in template)

Does the ANDA contain REMS? ☒ Yes ☐ No *REMS Draft Letter Sent to Chuck 12/12/2018*

Regulatory Project Manager Evaluation: **Date:** _____

☒ Date (Received) Acceptable for Filing -- Date **12/16/2016**

☒ Date last Complete Response (CR) letter was issued -- Date **9/10/2018**

☐ Previously reviewed and tentatively approved (if applicable) --- Date **N/A**

YES	NO	
☒	☐	All submissions have been reviewed and relevant disciplines are adequate and finalized in the platform (Date or N/A)

Date of Acceptable Bioequivalence **6/27/2018**
- Date of BE Guidance (if any) **3/2015**

Date of Acceptable Labeling **12/12/2018**
- Date of last RLD labeling update **8/21/2018**

Date of Acceptable Quality **12/27/2018**
- DMF No(s). (b) (4) Date(s) Acceptable **9/24/2018**
- No outstanding DMF review amendments ☒
- Date of Acceptable Overall Manufacturing Inspection **12/12/2018**

If applicable:
Date of Acceptable Microbiology **N/A**
Date of Acceptable Clinical Review **N/A**
Date of Acceptable Dissolution **8/7/2018**
Date of Acceptable REMS **8/2/2018**

☒	☐	**MMA:** All amendments submitted to the Agency on or after December 5, 2016 contain (1) a patent certification or section viii statement, (2) a recertification, or (3) a verification statement per 21 CFR 314.96(d).

MMA Summary 209822

Date	Amend #	MMA?	Type?	If No??
3/29/2017	3	YES	REMS amendment	
4/04/2017	4	YES	Labeling ECD Response	
4/26/2017	5	YES	REMS amendment	
4/27/2017	6	YES	Patent Amendment	
5/24/2017	7	YES	REMS amendment	
6/22/2017	8	YES	REMS amendment	
8/23/2017	9	YES	REMS amendment	
9/26/2017	10	YES	Withdraw REMS	
9/12/2018	11	YES	Response to CR Letter	
4/06/2018	12	YES	REMS amendment	
10/19/2018	13	YES	Response to CR Letter	

☐	☒	Are consults pending for any discipline?

☒	☐	OSIS Clinical Endpoint and Bioequivalence Site Inspections are acceptable Adequate per review done 9/12/2017
☒	☐	Is there a pending legal or regulatory issue (refer to Policy Alert Tracker)? Andrea Bautista added memo and confirmed AP If YES → OGD Policy Lead confirmed ANDA may proceed ☒; Memo uploaded (if applicable) ☒ 1/03/2019
☐	☒	Has there been an amendment providing for a major change in formulation or new strength since filing? If YES→Verify a second filing review was completed (if applicable) and that all disciplines completed new reviews ☐
☒	☐	Is ANDA a Priority Approval (First generic, drug shortage, PEPFAR, other OGD Communications priorities)? If YES → Email OGD Communications Staff or Division liaison 30 to 60 days prior to approval, Date emailed **12/17/2018**
Review Discipline/Division and RPM TL Endorsements		
☒	☐	Applicable review discipline/division endorsements completed
☒	☐	RPM Team Leader endorsement completed

Additional Notes (if applicable)

Teva Pharmaceuticals USA, Inc.
400 Interpace Parkway, Building A
Parsippany, NJ 07054

Attention: Bernard Domnic
Associate Director, Regulatory Affairs

RegulatoryAffairsUS@actavis.com
(b) (6)

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 1/3/2019
Name: IM for MHS

Patent/Exclusivity Certification:
☒ **PI** ☐ **PII** ☐ **PIII** ☐ **PIV** ☐ **section viii**
If Paragraph IV Certification- did applicant:
Notify patent holder/NDA holder: Yes ☐ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Has case been settled: Yes ☐ No ☐
Applicant addressed all listed exclusivities Yes ☐ No ☐

Do the patent and exclusivity certifications align? Yes ☐ No ☐
Have there been any revisions to the use code since the original submission? Yes ☐ No ☐

RLD = **Sabril** NDA# **20427** ☒ **RX or** ☐ **OTC**
Date Checked in Orange Book#: **1/3/2019**

Type of Letter:
☒ APPROVAL
☐ TENTATIVE APPROVAL
☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH)

LETTER RECOMMENDED FOR DRUGS@FDA Yes ☒ No ☐

Forfeiture Information
Is a forfeiture memo needed for the first applicant: Yes ☐ No ☐
If yes, the date forfeiture memo was completed
Date _____ ANDA # _____

180 Day Exclusivity Information
Is applicant eligible for 180 day exclusivity Yes ☐ No ☒
☐ Sole
☐ Shared
ANDA Exclusivity for each strength: Yes ☐ No ☐
Which strength(s) eligible _____

Comments:

BOS = Sabril Tablets (NDA 20427) Application submission 12/16/2016 with a PI certification. Acknowledgment letter signed 1/9/2017.

There remains no unexpired patents or exclusivities listed in the OB to the NDA. There are two pending CPs involving AED products, 2006-P-0461 and 2006-P-0405, that the Agency has determined does not prevent an action on this ANDA 9see memo in ANDA program.

Teva's ANDA is eligible for Full Approval, and will be the first ANDA approved for the drug product.

180 Day Exclusivity Status/Landscape: N/A (not a CGT ANDA)
Citizen Petitions Impact: does not prevent an action on this ANDA
First Legally Approvable Date: upon the completion of the full technical review
If Tentative Approval, anticipated full approval date: N/A

2. Final Decision

Date: 1/14/2019
Name: sgk

ANDA received on **12/16/2016** for the **500 mg** strength
RTR'd? Yes ☐ No ☒ If yes, RTR'd on Enter date
Priority Status? Yes ☒ No ☐ If yes, prioritization factor is **First Generic**
Basis of Submission (RLD)

Drug Name	**Sabril Tablets**
NDA #	**020427**
Applicant Name	**Lundbeck Pharmaceuticals, LLC**

☒ Verified the following:

1. Completion of the following endorsement tasks, if applicable:
   a. Division of Legal and Regulatory Support Endorsement
   b. Paragraph IV Evaluation
   c. REMS Endorsement
   d. Quality Endorsement
   e. Bioequivalence Endorsement
   f. Clinical-Bioequivalence Endorsement
   g. Labeling Endorsement
   h. RPM Team Leader Endorsement
2. All applicable endorsement tasks are completed in the platform within 30 days of potential approval.
3. No updates to patents and/or exclusivities in Orange Book since the Division of Legal and Regulatory Support Endorsement
4. No Reference Listed Drug updates at Drugs@FDA since the Labeling Endorsement
5. No issues listed on the current version of the Policy alert list since the RPM Team Leader Endorsement
6. No new alerts in the Submission Facility Status View since the Quality Endorsement
7. Overall Inspection Recommendation of Approve of the current project (see screenshot below)
8. No new DMF amendments since Quality Endorsement
9. No amendments received since the RPM Team Leader Endorsement

This ANDA is ready for **FULL** APPROVAL.

****INCLUDE SNIP OF SUBMISSION FACILITY STATUS VIEW AT THE TIME OF APPROVAL****

Following this page, 2 Pages Withheld in Full as (b)(4)

Product 001
VIGABATRIN (SABRIL) TABLET 500MG

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent

There are no unexpired patents for this product in the Orange Book database.

Exclusivity Data

Product No	Exclusivity Code	Exclusiv

There is no unexpired exclusivity for this product in the Orange

REFERENCES / ASSOCIATED DOCUMENTS

4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

REVISION HISTORY

Version	Effective date	Name	Role	Summary of changes
01	10/1/2014	Heather Strandberg	Author	New Form
02	10/03/2017	Kevin Denny	Reviser	• Update form to reflect revisions to SOP 4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA, Version 04 • Remove content adequately captured in the platform • Update information captured in the Division of Legal and Regulatory Support Endorsement section • Other minor administrative corrections to format and content
03	1/24/18	Kevin Denny	Reviser	• Update Final Decision section

REMS REVIEW TEMPLATE

ANDA Number 209822 **Date Today** 12/13/2018

Drug Name, Dosage Form and Strength (Optional if Stated Below)

Vigabatrin 500 mg Tablets

Optional Notes

REMS Status

☑ Approved Date Approved CLICK TO ENTER A DATE

☐ Deficient – CR MAJOR

Are any REMS Amendments deferred to the next Review Cycle?

☑ No ☐ Yes Which One (date)? CLICK TO ENTER A DATE

Language Below is to be inserted in the Full approval Action Letter

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FD&C Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].
In accordance with section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA under section 505(j) is subject to certain elements of the REMS required for the applicable listed drug.

The details of the REMS requirements were outlined in our REMS notification letter dated January 11, 2017. In that letter, you were also notified that pursuant to section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA and the listed drug it references must use a single, shared system for elements to assure safe use (ETASU), unless FDA waives that requirement.

Your final proposed REMS, submitted on April 6, 2018; is approved, and will be posted on the FDA REMS website: http://www.fda.gov/rems

The REMS consists of a ETASU and an implementation system.

Your REMS must be fully operational before you introduce Vigabatrin into interstate commerce.

The Vigabatrin REMS uses a shared system for the ETASU. This shared system REMS Program currently includes the products listed on the FDA REMS website, available at http://www.fda.gov/rems. Other products may be added in the future if additional NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

We remind you that you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FD&C Act.

We also remind you that section 505-1(f)(8) of the FD&C Act prohibits holders of an approved covered application from using any element to assure safe use to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing a REMS assessment or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

ANDA 209822 REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA 209822/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 209822/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 209822/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES
SUBMITTED IN SUPPLEMENT XXX

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR ANDA 209822

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment

forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

In addition to submitting the proposed REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS submission.

For more information on submitting REMS in SPL format, please email REMSWebsite@fda.hhs.gov

ANDA 209822

AMENDMENT ACKNOWLEDGEMENT
Priority
Minor

Teva Pharmaceuticals USA, Inc.
200 Elmora Avenue, Suite B
Elizabeth, NJ 07207
Attention: Madhulika Joshi
Associate Director, Regulatory Affairs

Dear Madam:

This is in reference to your amendment received on October 19, 2018, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Vigabatrin Tablet USP, 500 mg.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments Reauthorization of 2017 (GDUFA II). FDA has made an initial determination that this is a minor amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. The GDUFA goal date for review of this priority minor amendment is January 18, 2019.

If you have any questions, contact Kimberly McCullough, Regulatory Project Manager, at (240) 402 - 9021.

Sincerely,

{See appended electronic signature page}

Kimberly McCullough
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Kimberly McCullough

Digitally signed by Kimberly McCullough
Date: 10/31/2018 11:56:56PM
GUID: 525d9c4900038bd46a3ecdae8355361b

Recommendation: Complete Response - Minor

ANDA 209822
Review # 2

Drug Name/Dosage Form	Vigabatrin Tablets, USP
Strength	500 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Teva Pharmaceuticals USA
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original submission	*12/16/2016*	*All*
Response to CR Major	*3/12/2018*	*All*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance		
Drug Product	Ravi Erukulla	Yuping Niu
Process	Tianhong Tim Zhou	Nallaperumal Chidambaram
Microbiology		
Facility	Steven Fong	Zhihao Peter Qiu
Biopharmaceutics	Yang Zhao	Ta-Chen Wu
Regulatory Business Process Manager	Brandie Adams	
Application Technical Lead	Yuping Niu	
Laboratory (OTR)		
ORA Lead		
Environmental		

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	Reviewer
Type II					
[redacted] (b) (4)			*Adequate*	10/03/2017 per GDRP	Dai W. (Amendment 11)
Type III					
[redacted] (b) (4)			N/A		
			N/A		
			N/A		
			N/A		
			N/A		
			N/A		
			N/A		
			N/A		
Type IV					

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed).

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	020427	RLD

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

Abbreviated Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

The application is not recommended for approval due to quality related deficiencies summarized in Section II. OPQ recommends issuing a Complete Response Letter – **Minor**.

II. Quality Assessment Overview

A. Drug Substance, Drug Product, and Labeling: Inadequate-Minor

DMF (b) (4), for drug substance Vigabatrin manufactured by (b) (4) (b) (4) is adequate. The drug substance is compendial.

The drug product is an immediate release tablet, and compendial.

No labeling issue was found.

B. Process: Adequate

C. Facility: Adequate

D. Biopharmaceutics: Adequate

E. Microbiology *(covered under* **Process**):

List of Deficiencies for Complete Response

I. Drug Substance Deficiencies

1. (b) (4)

2.

3.

4. (b) (4)

II. Drug Product Deficiencies

1. (b) (4)

Application Technical Lead Name and Date: Yuping Niu, 8-20-2018

Yuping Niu

Digitally signed by Yuping Niu
Date: 8/20/2018 04:50:55PM
GUID: 508da704000288fa0afbf45b29fc643c

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 3/28/2018

TO: Office of Bioequivalence
Office of Generic Drugs

FROM: Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: ANDA 209822

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. Although the last inspection was classified as a VAI, based on the inspectional outcome and our recommendation to the review division, an inspection is not needed at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	Actavis Elizabeth, LLC.	200 Elmora Avenue, Elizabeth, NJ

Nicola Fenty-stewart -S

Digitally signed by Nicola Fenty-stewart -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001347020, cn=Nicola Fenty-stewart -S
Date: 2018.03.30 07:58:10 -04'00'

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 3/28/2018

TO: Office of Bioequivalence
Office of Generic Drugs

FROM: Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: (b) (4)
ANDA 209822

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical		(b) (4)

Nicola Fenty-stewart -S

Digitally signed by Nicola Fenty-stewart -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001347020, cn=Nicola Fenty-stewart -S
Date: 2018.03.30 09:25:12 -04'00'

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 3/28/2018

TO: Office of Bioequivalence
Office of Generic Drugs

FROM: Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without on-site inspection**

RE: ANDA 209822

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Watson Therapeutics, Inc.	3400 Enterprise Way, Miramar, FL

Nicola Fenty-stewart -S

Digitally signed by Nicola Fenty-stewart -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001347020, cn=Nicola Fenty-stewart -S
Date: 2018.03.30 09:21:47 -04'00'

ANDA 209822

AMENDMENT ACKNOWLEDGEMENT
Priority
Major

Teva Pharmaceuticals USA, Inc.
200 Elmora Ave, Suite B
Elizabeth, NJ 07207
Attention: Janak Jadeja
Director, Regulatory Affairs

Dear Madam:

This is in reference to your amendment received on March 12, 2018, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Vigabatrin Tablet USP, 500 mg.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments Reauthorization of 2017 (GDUFA II). FDA has made an initial determination that this is a major amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of ANDAs, Amendments, and Supplements*. If FDA determines that an inspection is not required to validate the information contained in this priority major amendment, the GDUFA goal date for review of this priority major amendment is September 11, 2018. If FDA determines that an inspection is required to validate the information contained in this priority major amendment and a Pre-Submission Facility Correspondence (PFC) was not submitted or not accepted, the GDUFA goal date for review of this priority major amendment is January 11, 2019

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, contact Kimberly Moore-Mccullough, Regulatory Project Manager, at (240) 402-9021.

Sincerely,

{See appended electronic signature page}

Kimberly Moore-Mccullough
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Kimberly McCullough

Digitally signed by Kimberly McCullough
Date: 3/24/2018 10:14:19PM
GUID: 525d9c4900038bd46a3ecdae8355361b

Recommendation: Minor CR (CR due to BE)

ANDA 209822
Review #1

Drug Name/Dosage Form	Vigabatrin Tablets, USP
Strength	500 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Teva Pharmaceuticals USA 200 Elmora Ave. Elizabeth NJ 07207, regulatoryaffairsUS@actavis.com
US agent, if applicable	Janak Jadeja, R.Ph., Director, Regulatory Affairs

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original submission	12/16/2016	All Quality disciplines
Administrative change	02/08/2017	DP, Process
Response to Information Request – REMS correspondence	1/13/2017	Process
Multiple Categories/Subcategories – REMS amendment	03/29/2017	Process
Response to ECD/Labeling	04/04/2017	Process
REMS Amendment	04/26/2017	Process
Expedited Review Request	04/27/2017	Process
REMS Amendment	05/27/2017	Process
Response to ECD/Bioequivalence, Withdrawal Request	9/26/17	DP, Facilities

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Xianru Sun	Bapu Gaddam
Drug Product	Ravi Erukulla	Yuping Niu
Process	Tianhong Tim Zhou	Nallaperumal Chidambaram
Microbiology	N/A	N/A
Facility	Steven Fong	
Biopharmaceutics	Yang Zhao	Ta-Chen Wu
Regulatory Business Process Manager	Brijet Burton	
Application Technical Lead	Yuping Niu	
Laboratory (OTR)	N/A	

ORA Lead	Michael Tollon Caryn Mcnab	
Environmental	N/A	

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
			(b) (4)	Adequate	10/03/2017 per GDRP	Dai W
	Type III *(if applicable)*					
	Type IV *(if applicable)*					
	Other					

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	020427	RLD

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Abbreviated Executive Summary

I. Recommendations and Conclusion on Approvability

The application is not recommended for approval due to quality related deficiencies summarized in Section II. OPQ recommends issuing a Complete Response Letter – Minor

II. Quality Assessment Overview

A. Drug Substance, Drug Product, and Labeling: Inadequate/Minor

DMF (b) (4) for drug substance Vigabatrin manufactured by (b) (4) (b) (4) is adequate. The drug substance is compendial. Deficiencies were identified in analytical methods.

The drug product is an immediate release tablet, and compendial. Deficiencies were identified in split tablets study, stability data, and analytical method validation.

No labeling issue was found.

B. Process: Inadequate /Minor

The manufacturing process (b) (4)

C. Facility: Adequate

D. Biopharmaceutics: Inadequate/Minor

The proposed dissolution method is the FDA database dissolution method and acceptable. Deficiencies were identified related to the proposed dissolution specification.

E. Microbiology (if applicable): under **Process**

List of Deficiencies for Complete Response

The following deficiencies are MINOR deficiencies:

A. Drug substance

1. (b) (4)
2.
3.
4.

Section B:

1. (b) (4)

B. Drug product

1. (b) (4)
2.
3.
4.

5. (b) (4)

6.

7.

8.

9.

10.

Section B:

1. (b) (4)

2. Please provide all available long term stability data in your next amendment.

C. Process

1. (b) (4)

2.

D. Biopharmaceutics

1. Your proposed acceptance criterion of "Q=75% dissolved in 30 minutes" is permissive and NOT acceptable. Based on the provided dissolution data, we recommend a dissolution acceptance criterion of "Q= (b) (4)% in 15 minutes" for your proposed drug products. Note that sometimes dissolution Stage 2 testing, and occasional Stage 3 testing may be needed.

2. Submit a copy of the updated drug product specification table with the revised acceptance criterion for the dissolution test and update other section of your submission as appropriate.

Application Technical Lead Name and Date: Yuping Niu 10-05-2017

Yuping Niu

Digitally signed by Yuping Niu
Date: 10/05/2017 02:25:12PM
GUID: 508da704000288fa0afbf45b29fc643c

REMS TEMPLATE

Information to be added to the Action Letter for all SS REMS

ANDA Number 209822

ANDA Applicant Name Teva

Drug Name, Dosage Form and Strength

Vigabatrin Tablets 500mg

If needed For Reference Only - RLD Number, Holder, and Established Name

NDA 20427 Sabril

REMS Status at this time is

☑ Acceptable ☐ Deficient - CR Minor ☐ Deficient - CR MAJOR

We acknowledge receipt of your REMS amendment(s)

Dates of Amendments to acknowledge in the Action Letter are Listed Below

1.	6/22/17	**6.**	
2.		**7.**	
3.		**8.**	
4.		**9.**	
5.		**10.**	

Are any REMS Amendments deferred to the next review cycle?

☑ No ☐ Yes-Which One (Date)?

Is there an Attachment or Medguide to be sent with this Action Letter?

☑ No ☐ Yes - Please attach or send to the RPM

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

As described in our letter dated January 11, 2017, section 505-1 of the FD&C Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA under section 505(j) is subject to certain elements of the REMS required for the applicable reference listed drug (RLD).

There is an approved REMS for the applicable RLD, Sabril (vigabatrin), to ensure the benefits of the drug outweigh the risk of vision loss associated with vigabatrin.

We acknowledge receipt of your proposed REMS included in your June 22, 2017 submission, which contains elements to assure safe use, an implementation system and timetable for submission of assessments.

(b) (4)

The REMS, should your application be approved, will create enforceable obligations.
For administrative purposes, designate the proposed REMS submission "**PROPOSED REMS for ANDA 209822**" and all subsequent submissions related to the proposed REMS "**PROPOSED REMS for ANDA 209822 -AMENDMENT**."

To facilitate review of your submission, we request that you submit your proposed REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 9/6/2017

TO: Office of Bioequivalence
Office of Generic Drugs

FROM: Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: ANDA 209822

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

Although the last inspection was classified as a VAI, based on the inspectional outcome and our recommendation to the review division, an inspection is not needed at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	Actavis Elizabeth, LLC.	200 Elmora Avenue, Elizabeth, NJ

Nicola M. Nicol -S

Digitally signed by Nicola M. Nicol -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001347020, cn=Nicola M. Nicol -S
Date: 2017.09.08 14:19:51 -04'00'

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 209822

INFORMATION REQUEST

TEVA PHARMACEUTICALS USA
Attention: Janak Jadeja, R.Ph.
Director, Regulatory Affairs
200 ELMORA AVE
ELIZABETH, NJ 07207

Dear Janak Jadeja, R.Ph:
Please refer to your Abbreviated New Drug Application (ANDA) dated December 16, 2016, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for VIGABATRIN TABLET USP, 500MG.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than **August 11, 2017**, in order to continue our evaluation of your ANDA.

A. Drug Substance

1. (b) (4)
2.
3.

4. (b) (4)

(b) (4)

B. Drug Product

1. (b) (4)

2.

3.

4.

5.

6.

7.

8. (b) (4)

9. [redacted]

C. Process

1. (b) (4)

2. [redacted]

D. Facility

E. Biopharmaceutics

1. The proposed acceptance criterion of "Q=75% dissolved in 30 minutes" is permissive and NOT acceptable. Based on the provided dissolution data, we recommend a dissolution acceptance criterion of "Q= (b) (4) % in 15 minutes" for your proposed drug products. Note that sometimes dissolution Stage 2 testing, and occasionally Stage 3 testing may be needed, which is acceptable.

2. Submit a copy of the updated drug product specification table with the revised acceptance criterion for the dissolution test and update other section of your submission as appropriate.

If you do not submit a complete response by **August 11, 2017**, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

Please note, if information or data submitted exceeds the data requested in the IR/ECD this may result in conversion to a Tier 2 Unsolicited Amendment (i.e., an amendment with information not requested by FDA).

If the submitted data is determined to be a tier 2 unsolicited amendment, this may affect the goal date.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY

If you have any questions, please contact me, Regulatory Business Process Manager, at 240-402-4878.

Sincerely,

{See appended electronic signature page}

Brijet Burton, MS, MPP, PA-C
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

EASILY CORRECTABLE DEFICIENCY

ANDA 209822

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Teva Pharmaceuticals USA

TEL: 908-659-2595

ATTN: Janak Jadeja

EMAIL: RegulatoryAffairsUS@actavis.com

FROM: Sunny Pyon

FDA CONTACT EMAIL:
Sunny.Pyon@fda.hhs.gov

Dear Mr. Jadeja:

This communication is in reference to your abbreviated new drug application (ANDA) dated December 16, 2016, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Vigabatrin Tablets USP, 500 mg.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
LABELING
REFERENCE # 13884630

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Labeling Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

We have completed our review and have the following comments:

LABELING:

1. PRESCRIBING INFORMATION
   a. HIGHLIGHTS, WARNINGS AND PRECAUTIONS: Please include as the first bullet "Abnormal MRI signal changes have been reported in some infants with Infantile Spasms receiving vigabatrin (5.3)".
   b. FULL PRESCRIBING INFORMATION: CONTENTS, WARNINGS AND PRECAUTIONS: Please include "5.3 Magnetic Resonance Imaging (MRI) Abnormalities".
   c. FULL PRESCRIBING INFORMATION
      i. WARNING BOX, last sentence: Please complete the REMS Program website and phone number when available.
      ii. DOSAGE AND ADMINISTRATION, 2.1 Important Dosing and Administration Instructions: Please add as the third paragraph the following: "Vigabatrin tablets and powder for oral solution are bioequivalent. Either tablet or powder can be used for CPS."
      iii. DOSAGE FORMS AND STRENGTHS: If your drug product complies with the Guidance for Industry Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation, we recommend updating the tablet description to state functionally-scored.
      iv. WARNINGS AND PRECAUTIONS, 5.2 Vigabatrin REMS Program: Please complete the REMS Program website and phone number when available.
      v. WARNINGS AND PRECAUTIONS: Please include the "5.3 Magnetic Resonance Imaging (MRI) Abnormalities in Infants" section.
      vi. WARNINGS AND PRECAUTIONS, 5.4 Neurotoxicity, second paragraph, last sentence: Please revise "...clinically in children" to read "…clinically in infants and children".
      vii. WARNINGS AND PRECAUTIONS, 5.4 Neurotoxicity: Please include as the last paragraph "Abnormal MRI signal changes characterized by increased T2 signal and restricted diffusion in a symmetric pattern involving the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants treated for Infantile Spasms with vigabatrin. Studies of the effects of vigabatrin on MRI and EP in adult epilepsy patients have demonstrated no clear-cut abnormalities [see Warnings and Precautions (5.3)]."
      viii. ADVERSE REACTIONS, 6.1 Clinical Trial Experience, Table 6: Please indent "Psychomotor hyperactivity" in the first column to preserve formatting.
      ix. USE IN SPECIFIC POPULATIONS, 8.3 Nursing Mothers: Please revise "[see Warnings and Precautions (5.4)]" to read "[see Warnings and Precautions (5.3, 5.4)]"
      x. USE IN SPECIFIC POPULATIONS, 8.4 Pediatric Use: Please include as the third paragraph "Abnormal MRI signal changes were observed in infants [see Warnings and Precautions (5.3, 5.4)]."

2. MEDICATION GUIDE
   We encourage you to include the U.S. contact information (i.e.; telephone number) of your firm in case the patient has questions about this drug product. Please include this information at the end of the "General information" section of the Medication Guide.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

If you have questions regarding these deficiencies or would like acknowledgement of receipt of your amendment upon submission, please contact the Labeling Project Manager, Sunny Pyon, at Sunny.Pyon@fda.hhs.gov.

Sincerely,

Sunny Pyon -S

Digitally signed by Sunny Pyon -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sunny Pyon -S, 0.9.2342.19200300.100.1.1=2001673604
Date: 2017.03.23 12:26:10 -04'00'

Sunny Pyon, Pharm.D.
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 209822

ACKNOWLEDGEMENT
ANDA RECEIPT

Teva Pharmaceutical USA
200 Elmora Avenue
Elizabeth, NJ 07207
Attention: Janak Jadeja

Dear Janak Jadeja:

We acknowledge receipt of your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act.

NAME OF DRUG: Vigabatrin Tablets USP, 500 mg

DATE OF APPLICATION: December 16, 2016

DATE (RECEIVED) ACCEPTABLE FOR REVIEW: December 16, 2016

This application is subject to the provisions of the Generic Drug User Fee Amendments of 2012 (GDUFA). The GDUFA goal date for review of this application is October 15, 2017. Please identify any related communications with the ANDA number referenced above. If you have any questions, contact Vincent Sansone, Project Manager Team Leader, at Vincent.Sansone@FDA.HHS.GOV[1] or 240-402-9075. Sign up for Generic Drug e-mail updates.[2]

Sincerely,

Ilinca Duveau -S

Digitally signed by Ilinca Duveau -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ilinca Duveau -S, 0.9.2342.19200300.100.1.1=2000664376
Date: 2017.01.09 10:17:24 -05'00'

Ilinca Duveau, Pharm.D.
Team Leader (Acting)
Division of Filing Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

[1] Secure email between CDER and applicants may be useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.
[2] https://service.govdelivery.com/accounts/USFDA/subscriber/new?topic_id=USFDA_476