CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA216235Orig1s000

Name: **Carbamazepine Extended-Release Tablets** USP, 100mg, 200mg and 400mg

Sponsor: Sciecure Pharma Inc

Approval Date: March 02, 2023

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA216235Orig1s000

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Other Action Letters	**X**
Labeling	**X**
Labeling Review(s)	**X**
Bioequivalence Review(s)	**X**
Chemistry Review(s)	**X**
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA216235Orig1s000

APPROVAL LETTER

ANDA 216235

ANDA APPROVAL

Sciecure Pharma Inc.
11 Deer Park Drive, Unit 120
Monmouth Junction, NJ 08852
Attention: Nuo Wang
CTO

Dear Nuo Wang:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on May 21, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Carbamazepine Extended-Release Tablets USP, 100 mg, 200 mg, and 400 mg.

Reference is also made to the complete response letter issued by this office on March 16, 2022, 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 meets the requirements for approval under the FD&C Act. Accordingly the ANDA is **approved**, effective on the date of this letter. We have determined your Carbamazepine Extended-Release Tablets USP, 100 mg, 200 mg, and 400 mg, to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Tegretol XR Extended-Release Tablets, 100 mg, 200 mg, and 400 mg, of Novartis Pharmaceuticals Corporation.

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.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

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: https://www.fda.gov/media/128163/download).

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: https://www.fda.gov/media/73013/download. Information and Instructions for completing the form can be found at: https://www.fda.gov/media/132152/download. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/opdp-ectd.

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. ANDAs that identify at least one facility that is referenced in an approved ANDA are 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 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 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.

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: https://www.fda.gov/media/71211/download. The SPL will be accessible via publicly available labeling repositories.

We remind you that you must continually monitor available labeling resources such as DRUGS@FDA for changes to your RLD's labels and labeling and make any necessary revisions to your labels and labeling. More information on post-approval labeling changes may be found in the guidance for industry titled "Changes to an Approved NDA or ANDA" at: https://www.fda.gov/media/71846/download.

Sincerely yours,

{See appended electronic signature page}

For Edward M. Sherwood
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).

Catherine Poole

Digitally signed by Catherine Poole
Date: 3/02/2023 10:39:09AM
GUID: 5407887a000a1c0c26055eafb8e3258a

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209397Orig1s000

OTHER ACTION LETTERS

ANDA 216235

COMPLETE RESPONSE

Sciecure Pharma Inc.
11 Deer Park Drive, Unit 120
Monmouth Junction, NJ 08852
Attention: Nuo Wang
CTO

Dear Nuo Wang:

This is in reference to your abbreviated new drug application (ANDA) received for review on May 21, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Carbamazepine Extended-Release Tablets USP, 100 mg, 200 mg, and 400 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

(b) (4)

Biopharmaceutics

3. In your response letter dated September 10, 2021, we noted that you have explored all the dissolution method conditions and discriminating ability with RLD as the target drug product. You should explore the dissolution method conditions with your proposed drug product. Accordingly, we request that you submit data obtained with the proposed product. In addition, for discriminating ability testing, your reference batch should be reference target product (e.g., bio-batch).

4. You submitted an in-vitro in-vivo correlation (IVIVC) study to support that revised USP acceptance criteria for the selected dissolution method will be able to reject product that is not bioequivalent to the reference-target drug product. However, your IVIVC study is deemed not acceptable at this time because of the insufficient data/justification provided. As outlined in the FDA Guidance for Industry *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations* (September 1997) three or more formulations with different release rates are recommended to define an IVIVC. Exceptions to this may be considered for formulations for which in vitro dissolution is independent of the dissolution test conditions (e.g., medium, agitation, pH, volume).

   Please submit the following information/data to aid in the regulatory decision making in terms of the acceptability of the proposed IVIVC model, if you still want to pursue the model:

   a. A modeling summary report, which provides an overview of the modeling strategy and details of the modeling procedures, including model development, model verification/modification, and model application in a step-by-step process. Inclusion of a flow chart, decision tree, or other similar representation is preferred for clarity.

   b. Demonstrate that the dissolution of the proposed drug product is dependent or independent of dissolution conditions.

   c. As part of the validation steps, follow the “leave-one out” cross validation approach in the construction and validation of your model to challenge its robustness.

   d. Provide side by side comparative formulation composition for all batches used in the model development and external predictions.

   e. Submit the executable project files (e.g., .phxproj, .xlsx or .xls, .sas) for the IVIVC model development and internal/external validation. Provide all relevant input including complete in vitro and in vivo data (i.e., individual, mean, % CV, profiles, in .csv, .xlsx or .xls, or .xpt format) and output files used in the construction and validation of the IVIVC model.

f. Provide definition file(s) listing all input and output files, and the use or purpose of each of this files in an appropriate format (e.g., .pdf, .xpt, .xls). In addition, provide the hyperlinks for each data file and instructions for extracting these files.

g. Provide the IVIVC predictions including the output files and summary table supporting your revised dissolution acceptance criteria, if any.

Note that the FDA's final decision regarding the acceptability of the IVIVC model will be made based on the totality of the supportive data and relevant information provided in the submission, which should include demonstration of a robust model predictability.

5. Based on the submitted in vitro dissolution profile data, your proposed in vitro dissolution acceptance criteria are wide for your drug product and not acceptable. Note that per the current Agency's guideline for proper setting of the dissolution specification, drug product acceptance criteria are set primarily based on the performance of the bio-batch/exhibit batches at release. In addition, selection of the in vitro drug dissolution acceptance criteria ranges is based on mean target value ±10% and >80% for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved IVIVC model, physiologically based absorption and pharmacokinetic model, safe space etc. Since your submitted IVIVC model is not acceptable at this time, we recommend the following acceptance criteria for the proposed generic drug product based on the biobatch data:

3 hr 18-38%
6 hr 46-66%
12 hr 70-90%
24 hr NLT 80%

We request that you acknowledge your acceptance of the recommended acceptance criteria for all the strengths of your drug product at release and on stability and update your drug product release and stability specifications accordingly. In addition, please be advised that all proposed exhibit batches are expected to meet the revised dissolution specification in your stability program through your proposed expiry period. If stability failure occurs at Level 1 (L1), then Level 2 (L2) testing, and if necessary Level 3 (L3) testing should be conducted. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

(b) (4)

(b) (4)

LABELING

1. CONTAINER LABEL

   Relocate the precautionary statement, "Carbamazepine Extended-Release Tablets must be swallowed whole and never crushed or chewed.", to the principal display panel to be consistent with the Reference Listed Drug (RLD) labeling. Ensure to use a method to increase the prominence of the precautionary statement (e.g., boxing, contrasting colors, and/or some other means).

2. PRESCRIBING INFORMATION

   a. Product Title: Remove the "USP" descriptor, such as "Carbamazepine Extended-Release Tablets".

   b. DESCRIPTION, 3rd paragraph, 1st sentence: Revise (b) (4) to "Each Carbamazepine Extended-Release Tablet intended for oral administration contains 100 mg, 200 mg, or 400 mg of carbamazepine." (note "and 400 mg" is revised to "or 400 mg" for clarity).

   c. PRECAUTIONS (note the cross-references are removed, as your revised proposed labeling removed the referenced information in the corresponding section)

1. **General**, 6th paragraph: Revise [redacted] (b) (4) [redacted]." to "Since a given dose...unwanted side effects."

2. **Drug Interactions**, 1st paragraph, last sentence: Revise [redacted] (b) (4) [redacted])." to "Because the extent...or diluents."

d. DOSAGE AND ADMINISTRATION, **Epilepsy**

1. ***Children 6 to 12 years of age-Initial***, 1st sentence: Revise [redacted] (b) (4) [redacted] to "100 mg twice a day for Carbamazepine Extended-Release Tablets (200 mg/day)." to be consistent with the RLD labeling.

2. ***Children under 6 years of age-Initial***, 1st sentence: [redacted] (b) (4) [redacted] to "10 to 20 mg/kg/day twice a day or three times a day as tablets (chewable or conventional), or four times a day as suspension." for clarity and to minimize misuse of your proposed drug product.

e. DOSAGE AND ADMINISTRATION, **Dosage Information** table: Widen the cell(s), where applicable, to ensure words (e.g., intervals, increments, etc.) are not wrapped to the next line for better readability.

f. HOW SUPPLIED, each strength: Revise your product descriptions for clarity. For example, revise [redacted] (b) (4) [redacted] to "...one drill hole on one side and imprinted with XXXX in black ink on the other side in a top semi-circle shape around the center."

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.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), 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.

DRUG SUBSTANCE / BIOEQUIVALENCE

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 aware of FDA's recommendations for the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence (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.

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. If your submission includes gratuitous information in addition to the category or categories below, clearly identify the type of information submitted immediately following the wording below:

RESUBMISSION
MAJOR
COMPLETE RESPONSE AMENDMENT
DRUG PRODUCT / BIOPHARMACEUTICS / MANUFACTURING / 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 as 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. A partial response to this letter does not fulfill the requirements in 21 CFR 314.110(b)(1) and therefore 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 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.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including by fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure you stay up to date with the Agency's current thinking on topics through guidances for industry, including product-specific guidances.

If you have any questions, call LCDR Daniil Marchuk, Regulatory Project Manager, Division of Project Management, at (240) 402 - 4322.

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).

Aaron Sigler

Digitally signed by Aaron Sigler
Date: 3/16/2022 03:43:53PM
GUID: 508da6fa0002827f1a9f2526d1b2cc69

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

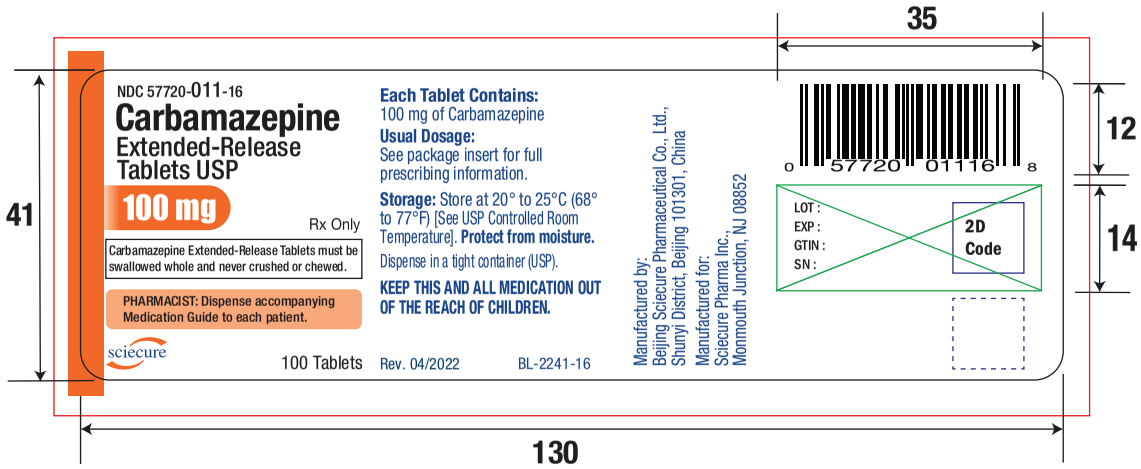
ANDA216235Orig1s000

LABELING

Proposed Bottle Labeling (100 mg)

Description:
Carbamazepine Extended-Release Capsule
100 mg - Label

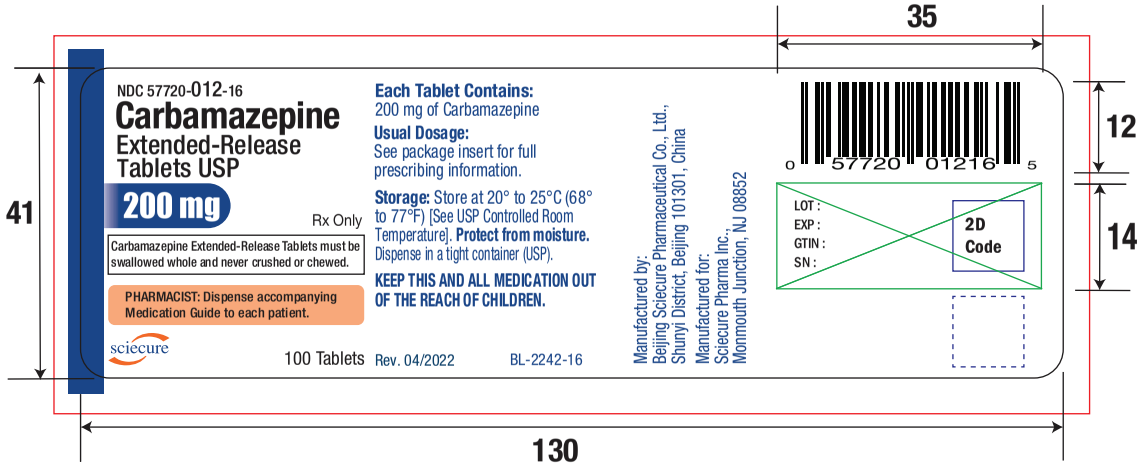
(b) (4)



Proposed Bottle Labeling (200 mg)

Description:
Carbamazepine Extended-Release Capsule
200 mg - Label

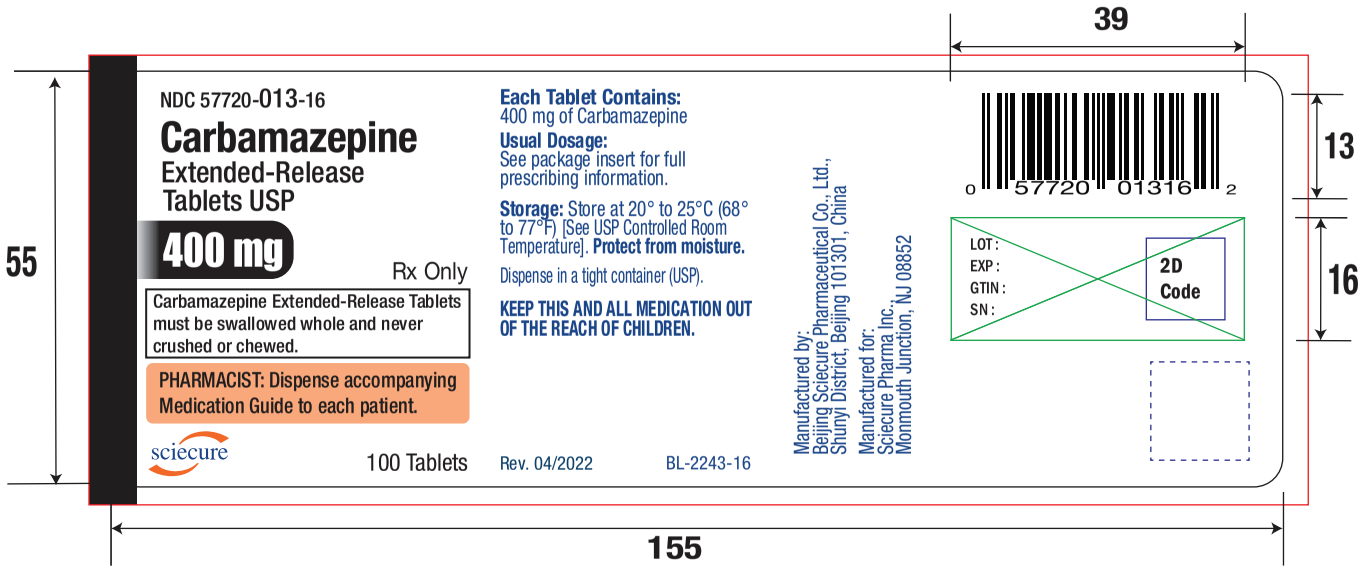
(b) (4)



Proposed Bottle Labeling (400 mg)

Description:
Carbamazepine Extended-Release Capsule
400 mg - Label

(b) (4)



Carbamazepine Extended-Release Tablets

Sciecure Pharma Inc.

Carbamazepine Extended-Release Tablets, USP

100 mg, 200 mg, 400 mg

Rx only

Prescribing Information

WARNINGS

SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE

SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH CARBAMAZEPINE. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS OF ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH CARBAMAZEPINE. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH CARBAMAZEPINE UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE WARNINGS AND PRECAUTIONS, LABORATORY TESTS).

APLASTIC ANEMIA AND AGRANULOCYTOSIS

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE. DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5 TO 8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

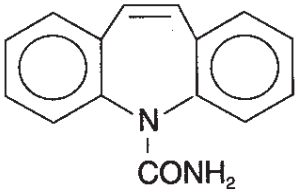
BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON CARBAMAZEPINE ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT

EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing Carbamazepine Extended-Release Tablets, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available for oral administration as extended-release tablets of 100, 200, and 400 mg. Its chemical name is 5*H*-dibenz[*b,f*]azepine-5-carboxamide, and its structural formula is:



Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27.

Each Carbamazepine Extended-Release Tablet intended for oral administration contains 100 mg, 200 mg or 400 mg of carbamazepine. In addition, each extended-release tablet contains the following inactive ingredients:

Inactive Ingredients: Hypromellose, hydroxyethyl cellulose, cellulose acetate, polyethylene glycol, mannitol, dextrates, sodium lauryl sulfate, and magnesium stearate. Each tablet is printed with Opacode Black S-1-17823 ink which contains ammonium hydroxide, iron oxide black, isopropyl alcohol, n-butyl alcohol, propylene glycol and shellac.

FDA approved dissolution test specifications differ from USP.

CLINICAL PHARMACOLOGY

In controlled clinical trials, carbamazepine has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

Mechanism of Action

Carbamazepine has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation.

Carbamazepine greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Carbamazepine is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

The principal metabolite of carbamazepine, carbamazepine-10,11-epoxide, has anticonvulsant activity as demonstrated in several in vivo animal models of seizures. Though clinical activity for the epoxide has been postulated, the significance of its activity with respect to the safety and efficacy of carbamazepine has not been established.

Pharmacokinetics

In clinical studies, carbamazepine suspension, conventional tablets, and extended-release tablets delivered

equivalent amounts of drug to the systemic circulation. However, the suspension was absorbed somewhat faster, and the extended-release tablet slightly slower, than the conventional tablet. The bioavailability of the extended-release tablet was 89% compared to suspension. Following a twice a day dosage regimen, the suspension provides higher peak levels and lower trough levels than those obtained from the conventional tablet for the same dosage regimen. On the other hand, following a three times a day dosage regimen, carbamazepine suspension affords steady-state plasma levels comparable to carbamazepine tablets given twice a day when administered at the same total mg daily dose. Following a twice a day dosage regimen, carbamazepine extended-release tablets afford steady-state plasma levels comparable to conventional carbamazepine tablets given four times a day, when administered at the same total mg daily dose. Carbamazepine in blood is 76% bound to plasma proteins. Plasma levels of carbamazepine are variable and may range from 0.5 to 25 mcg/mL, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 mcg/mL. In polytherapy, the concentration of carbamazepine and concomitant drugs may be increased or decreased during therapy, and drug effects may be altered (see PRECAUTIONS, Drug Interactions). Following chronic oral administration of suspension, plasma levels peak at approximately 1.5 hours compared to 4 to 5 hours after administration of conventional carbamazepine tablets, and 3 to 12 hours after administration of carbamazepine extended-release tablets. The CSF/serum ratio is 0.22, similar to the 24% unbound carbamazepine in serum. Because carbamazepine induces its own metabolism, the half-life is also variable. Autoinduction is completed after 3 to 5 weeks of a fixed dosing regimen. Initial half-life values range from 25 to 65 hours, decreasing to 12 to 17 hours on repeated doses. Carbamazepine is metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10,11-epoxide from carbamazepine. Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine- 10,11 epoxide. After oral administration of ^{14}C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged carbamazepine.

The pharmacokinetic parameters of carbamazepine disposition are similar in children and in adults. However, there is a poor correlation between plasma concentrations of carbamazepine and carbamazepine dose in children. Carbamazepine is more rapidly metabolized to carbamazepine-10,11-epoxide (a metabolite shown to be equipotent to carbamazepine as an anticonvulsant in animal screens) in the younger age groups than in adults. In children below the age of 15, there is an inverse relationship between CBZ-E/CBZ ratio and increasing age (in one report from 0.44 in children below the age of 1 year to 0.18 in children between 10 to 15 years of age).

The effects of race and gender on carbamazepine pharmacokinetics have not been systematically evaluated.

INDICATIONS AND USAGE

Epilepsy

Carbamazepine is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of Carbamazepine as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types.
2. Generalized tonic-clonic seizures (grand mal).
3. Mixed seizure patterns which include the above, or other partial or generalized seizures. Absence seizures (petit mal) do not appear to be controlled by Carbamazepine Extended-Release Tablets (see PRECAUTIONS, General).

Trigeminal Neuralgia

Carbamazepine is indicated in the treatment of the pain associated with true trigeminal neuralgia.

Beneficial results have also been reported in glossopharyngeal neuralgia.

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

CONTRAINDICATIONS

Carbamazepine should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase (MAO) inhibitors is not recommended. Before administration of carbamazepine, MAO inhibitors should be discontinued for a minimum of 14 days, or longer if the clinical situation permits.

Coadministration of carbamazepine and nefazodone may result in insufficient plasma concentrations of nefazodone and its active metabolite to achieve a therapeutic effect. Coadministration of carbamazepine with nefazodone is contraindicated.

WARNINGS

Serious Dermatologic Reactions

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with carbamazepine treatment. The risk of these events is estimated to be about 1 to 6 per 10,000 new users in countries with mainly Caucasian populations. However, the risk in some Asian countries is estimated to be about 10 times higher. Carbamazepine should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered.

SJS/TEN and HLA-B*1502 Allele

Retrospective case-control studies have found that in patients of Chinese ancestry there is a strong association between the risk of developing SJS/TEN with carbamazepine treatment and the presence of an inherited variant of the HLA-B gene, HLA-B*1502. The occurrence of higher rates of these reactions in countries with higher frequencies of this allele suggests that the risk may be increased in allele-positive individuals of any ethnicity.

Across Asian populations, notable variation exists in the prevalence of HLA-B*1502. Greater than 15% of the population is reported positive in Hong Kong, Thailand, Malaysia, and parts of the Philippines, compared to about 10% in Taiwan and 4% in North China. South Asians, including Indians, appear to have intermediate prevalence of HLA-B*1502, averaging 2% to 4%, but higher in some groups. HLA-B*1502 is present in less than 1% of the population in Japan and Korea.

HLA-B*1502 is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, and Native Americans).

Prior to initiating carbamazepine therapy, testing for HLA-B*1502 should be performed in patients with ancestry in populations in which HLA-B*1502 may be present. In deciding which patients to screen, the rates provided above for the prevalence of HLA-B*1502 may offer a rough guide, keeping in mind the limitations of these figures due to wide variability in rates even within ethnic groups, the difficulty in ascertaining ethnic ancestry, and the likelihood of mixed ancestry. Carbamazepine should not be used in patients positive for HLA-B*1502 unless the benefits clearly outweigh the risks. Tested patients who are found to be negative for the allele are thought to have a low risk of SJS/TEN (see **BOXED WARNING** and **PRECAUTIONS**, **Laboratory Tests**).

Over 90% of carbamazepine treated patients who will experience SJS/TEN have this reaction within the first few months of treatment. This information may be taken into consideration in determining the need for screening of genetically at-risk patients currently on carbamazepine.

The HLA-B*1502 allele has not been found to predict risk of less severe adverse cutaneous reactions from carbamazepine such as maculopapular eruption (MPE) or to predict Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Chinese ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding use of other drugs associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable.

Hypersensitivity Reactions and HLA-A*3101 Allele

Retrospective case-control studies in patients of European, Korean, and Japanese ancestry have found a moderate association between the risk of developing hypersensitivity reactions and the presence of HLA-A*3101, an inherited allelic variant of the HLA-A gene, in patients using carbamazepine. These hypersensitivity reactions include SJS/TEN, maculopapular eruptions, and Drug Reaction with Eosinophilia and Systemic Symptoms (see **DRESS/Multiorgan hypersensitivity** below).

HLA-A*3101 is expected to be carried by more than 15% of patients of Japanese, Native American, Southern Indian (for example, Tamil Nadu) and some Arabic ancestry; up to about 10% in patients of Han Chinese, Korean, European, Latin American, and other Indian ancestry; and up to about 5% in African-Americans and patients of Thai, Taiwanese, and Chinese (Hong Kong) ancestry.

The risks and benefits of carbamazepine therapy should be weighed before considering carbamazepine in patients known to be positive for HLA-A*3101.

Application of HLA genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management. Many HLA-B*1502-positive and HLA-A*3101-positive patients treated with carbamazepine will not develop SJS/TEN or other hypersensitivity reactions, and these reactions can still occur infrequently in HLA-B*1502-negative and HLA-A*3101-negative patients of any ethnicity. The role of other possible factors in the development of, and morbidity from, SJS/TEN and other hypersensitivity reactions, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring, have not been studied.

Aplastic Anemia and Agranulocytosis

Aplastic anemia and agranulocytosis have been reported in association with the use of carbamazepine (see BOXED WARNING). Patients with a history of adverse hematologic reaction to any drug may be particularly at risk of bone marrow depression.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, has occurred with carbamazepine. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. This disorder is variable in its expression, and other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Carbamazepine should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Hypersensitivity

Hypersensitivity reactions to carbamazepine have been reported in patients who previously experienced this reaction to anticonvulsants including phenytoin, primidone, and phenobarbital. If such history is present, benefits and risks should be carefully considered and, if carbamazepine is initiated, the signs and symptoms of hypersensitivity should be carefully monitored.

Patients should be informed that about a third of patients who have had hypersensitivity reactions to carbamazepine also experience hypersensitivity reactions with oxcarbazepine (Trileptal®).

Anaphylaxis and Angioedema

Rare cases of anaphylaxis and angioedema involving the larynx, glottis, lips, and eyelids have been reported in patients after taking the first or subsequent doses of carbamazepine. Angioedema associated with laryngeal edema can be fatal. If a patient develops any of these reactions after treatment with carbamazepine, the drug should be discontinued and an alternative treatment started. These patients should not be rechallenged with the drug.

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including carbamazepine, 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 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1 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 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 carbamazepine 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.

General

Carbamazepine has shown mild anticholinergic activity that may be associated with increased intraocular pressure; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

The use of carbamazepine should be avoided in patients with a history of hepatic porphyria (e.g., acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda). Acute attacks have been reported in such patients receiving carbamazepine therapy. Carbamazepine administration has also been demonstrated to increase porphyrin precursors in rodents, a presumed mechanism for the induction of acute attacks of porphyria.

As with all antiepileptic drugs, carbamazepine should be withdrawn gradually to minimize the potential of increased seizure frequency.

Hyponatremia can occur as a result of treatment with carbamazepine. In many cases, the hyponatremia appears to be caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The risk of developing SIADH with carbamazepine treatment appears to be dose-related. Elderly patients and patients treated with diuretics are at greater risk of developing hyponatremia. Signs and symptoms of hyponatremia include headache, new or increased seizure frequency, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. Consider discontinuing carbamazepine in patients with symptomatic hyponatremia.

Usage in Pregnancy

Carbamazepine can cause fetal harm when administered to a pregnant woman.

Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. There have also been reports that associate carbamazepine with developmental disorders and congenital anomalies (e.g., craniofacial defects, cardiovascular malformations, and anomalies involving various body systems). Developmental delays based on neurobehavioral assessments have been reported. When treating or counseling women of childbearing potential, the prescribing physician will wish to weigh the benefits of therapy against the risks. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy. Therefore, if therapy is to be continued, monotherapy may be preferable for pregnant women.

In humans, transplacental passage of carbamazepine is rapid (30 to 60 minutes), and the drug is accumulated in the fetal tissues, with higher levels found in liver and kidney than in brain and lung.

Carbamazepine has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10 to 25 times the maximum human daily dosage (MHDD) of 1200 mg on a mg/kg basis or 1.5 to 4 times the MHDD on a mg/m^2 basis. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose

some hazard to the developing embryo or fetus.

Tests to detect defects using currently accepted procedures should be considered a part of routine prenatal care in childbearing women receiving carbamazepine.

There have been a few cases of neonatal seizures and/or respiratory depression associated with maternal carbamazepine and other concomitant anticonvulsant drug use. A few cases of neonatal vomiting, diarrhea, and/or decreased feeding have also been reported in association with maternal carbamazepine use. These symptoms may represent a neonatal withdrawal syndrome.

To provide information regarding the effects of in utero exposure to carbamazepine, physicians are advised to recommend that pregnant patients taking carbamazepine 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/.

PRECAUTIONS

General

Before initiating therapy, a detailed history and physical examination should be made.

Carbamazepine should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients' carbamazepine has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac conduction disturbance, including second- and third-degree AV heart block; cardiac, hepatic, or renal damage; adverse hematologic or hypersensitivity reaction to other drugs, including reactions to other anticonvulsants; or interrupted courses of therapy with carbamazepine.

AV heart block, including second- and third-degree block, have been reported following carbamazepine treatment. This occurred generally, but not solely, in patients with underlying EKG abnormalities or risk factors for conduction disturbances.

Hepatic effects, ranging from slight elevations in liver enzymes to rare cases of hepatic failure have been reported (see ADVERSE REACTIONS and PRECAUTIONS, Laboratory Tests). In some cases, hepatic effects may progress despite discontinuation of the drug. In addition, rare instances of vanishing bile duct syndrome have been reported. This syndrome consists of a cholestatic process with a variable clinical course ranging from fulminant to indolent, involving the destruction and disappearance of the intrahepatic bile ducts. Some, but not all, cases are associated with features that overlap with other immunoallergenic syndromes such as multiorgan hypersensitivity (DRESS syndrome) and serious dermatologic reactions. As an example, there has been a report of vanishing bile duct syndrome associated with Stevens-Johnson syndrome and in another case an association with fever and eosinophilia.

Since a given dose of carbamazepine suspension will produce higher peak levels than the same dose given as the tablet, it is recommended that patients given the suspension be started on lower doses and increased slowly to avoid unwanted side effects.

Carbamazepine suspension contains sorbitol and, therefore, should not be administered to patients with rare hereditary problems of fructose intolerance.

Information for Patients

Patients should be informed of the availability of a Medication Guide and they should be instructed to read the Medication Guide before taking carbamazepine.

Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, as well as dermatologic, hypersensitivity or hepatic reactions. These symptoms may include, but are not limited to, fever, sore throat, rash, ulcers in the mouth, easy bruising, lymphadenopathy and petechial or purpuric

hemorrhage, and in the case of liver reactions, anorexia, nausea/vomiting, or jaundice. The patient should be advised that, because these signs and symptoms may signal a serious reaction, that they must report any occurrence immediately to a physician. In addition, the patient should be advised that these signs and symptoms should be reported even if mild or when occurring after extended use.

Patients should be advised that serious skin reactions have been reported in association with carbamazepine. In the event a skin reaction should occur while taking carbamazepine, patients should consult with their physician immediately (see WARNINGS).

Patients should be advised that anaphylactic reactions and angioedema may occur during treatment with carbamazepine (see WARNINGS). Advise patients to immediately report signs and symptoms suggesting angioedema (swelling of the face, eyes, lips, or tongue, or difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their healthcare provider.

Patients, their caregivers, and families should be counseled that AEDs, including carbamazepine, may increase the risk of suicidal thoughts and behavior and should be advised 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 about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Carbamazepine may interact with some drugs. Therefore, patients should be advised to report to their doctors the use of any other prescription or nonprescription medications or herbal products.

Caution should be exercised if alcohol is taken in combination with carbamazepine therapy, due to a possible additive sedative effect.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

Patients should be encouraged 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 (see WARNINGS, Usage in Pregnancy subsection).

Laboratory Tests

For genetically at-risk patients (see WARNINGS), high-resolution '*HLA-B*1502 typing*' is recommended. The test is positive if either one or two HLA-B*1502 alleles are detected and negative if no HLA-B*1502 alleles are detected.

Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur (see PRECAUTIONS, General and ADVERSE REACTIONS). Carbamazepine should be discontinued, based on clinical judgment, if indicated by newly occurring or worsening clinical or laboratory evidence of liver dysfunction or hepatic damage, or in the case of active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy, and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with carbamazepine administered alone. Interference with some pregnancy tests has been reported.

Drug Interactions

There has been a report of a patient who passed an orange rubbery precipitate in his stool the day after ingesting carbamazepine suspension immediately followed by Thorazine®* solution. Subsequent testing has shown that mixing carbamazepine suspension and chlorpromazine solution (both generic and brand name) as well as carbamazepine suspension and liquid Mellaril®*, resulted in the occurrence of this precipitate. Because the extent to which this occurs with other liquid medications is not known, carbamazepine suspension should not be administered simultaneously with other liquid medicinal agents or diluents.

Clinically meaningful drug interactions have occurred with concomitant medications and include (but are not limited to) the following:

Agents That May Affect Carbamazepine Plasma Levels

When carbamazepine is given with drugs that can increase or decrease carbamazepine levels, close monitoring of carbamazepine levels is indicated and dosage adjustment may be required.

Agents That Increase Carbamazepine Levels

CYP3A4 inhibitors inhibit carbamazepine metabolism and can thus increase plasma carbamazepine levels. Drugs that have been shown, or would be expected, to increase plasma carbamazepine levels include aprepitant, cimetidine, ciprofloxacin, danazol, diltiazem, macrolides, erythromycin, troleandomycin, clarithromycin, fluoxetine, fluvoxamine, trazodone, olanzapine, loratadine, terfenadine, omeprazole, oxybutynin, dantrolene, isoniazid, niacinamide, nicotinamide, ibuprofen, propoxyphene, azoles (e.g., ketaconazole, itraconazole, fluconazole, voriconazole), acetazolamide, verapamil, ticlopidine, grapefruit juice, and protease inhibitors.

Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine-10,11 epoxide. Coadministration of inhibitors of human microsomal epoxide hydrolase may result in increased carbamazepine-10,11 epoxide plasma concentrations. Accordingly, the dosage of carbamazepine should be adjusted and/or the plasma levels monitored when used concomitantly with loxapine, quetiapine, or valproic acid.

Agents That Decrease Carbamazepine Levels

CYP3A4 inducers can increase the rate of carbamazepine metabolism. Drugs that have been shown, or that would be expected, to decrease plasma carbamazepine levels include cisplatin, doxorubicin HCl, felbamate, fosphenytoin, rifampin, phenobarbital, phenytoin, primidone, methsuximide, theophylline, aminophylline.

Effect of Carbamazepine on Plasma Levels of Concomitant Agents

Decreased Levels of Concomitant Medications

Carbamazepine is a potent inducer of hepatic 3A4 and is also known to be an inducer of CYP1A2, 2B6, 2C9/19 and may therefore reduce plasma concentrations of co-medications mainly metabolized by CYP 1A2, 2B6, 2C9/19 and 3A4, through induction of their metabolism. When used concomitantly with carbamazepine, monitoring of concentrations or dosage adjustment of these agents may be necessary:

- When carbamazepine is added to aripiprazole, the aripiprazole dose should be doubled. Additional dose increases should be based on clinical evaluation. If carbamazepine is later withdrawn, the aripiprazole dose should be reduced.
- When carbamazepine is used with tacrolimus, monitoring of tacrolimus blood concentrations and appropriate dosage adjustments are recommended.
- The use of concomitant strong CYP3A4 inducers such as carbamazepine should be avoided with temsirolimus. If patients must be coadministered carbamazepine with temsirolimus, an adjustment of

temsirolimus dosage should be considered.

- The use of carbamazepine with lapatinib should generally be avoided. If carbamazepine is started in a patient already taking lapatinib, the dose of lapatinib should be gradually titrated up. If carbamazepine is discontinued, the lapatinib dose should be reduced.
- Concomitant use of carbamazepine with nefazodone results in plasma concentrations of nefazodone and its active metabolite insufficient to achieve a therapeutic effect. Coadministration of carbamazepine with nefazodone is contraindicated (see CONTRAINDICATIONS).
- Monitor concentrations of valproate when carbamazepine is introduced or withdrawn in patients using valproic acid.

In addition, carbamazepine causes, or would be expected to cause, decreased levels of the following drugs, for which monitoring of concentrations or dosage adjustment may be necessary: acetaminophen, albendazole, alprazolam, aprepitant, buprenorphone, bupropion, citalopram, clonazepam, clozapine, corticosteroids (e.g., prednisolone, dexamethasone), cyclosporine, dicumarol, dihydropyridine calcium channel blockers (e.g., felodipine), doxycycline, eslicarbazepine, ethosuximide, everolimus, haloperidol, imatinib, itraconazole, lamotrigine, levothyroxine, methadone, methsuximide, mianserin, midazolam, olanzapine, oral and other hormonal contraceptives, oxcarbazepine, paliperidone, phensuximide, phenytoin, praziquantel, protease inhibitors, risperidone, sertraline, sirolimus, tadalafil, theophylline, tiagabine, topiramate, tramadol, trazodone, tricyclic antidepressants (e.g., imipramine, amitriptyline, nortriptyline), valproate, warfarin, ziprasidone, zonisamide.

Other Drug Interactions

- Cyclophosphamide is an inactive prodrug and is converted to its active metabolite in part by CYP3A. The rate of metabolism and the leukopenic activity of cyclophosphamide are reportedly increased by chronic coadministration of CYP3A4 inducers. There is a potential for increased cyclophosphamide toxicity when coadministered with carbamazepine.
- Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.
- Concomitant use of carbamazepine and isoniazid has been reported to increase isoniazid-induced hepatotoxicity.
- Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.
- Concomitant use of carbamazepine with hormonal contraceptive products (e.g., oral, and levonorgestrel subdermal implant contraceptives) may render the contraceptives less effective because the plasma concentrations of the hormones may be decreased. Breakthrough bleeding and unintended pregnancies have been reported. Alternative or back-up methods of contraception should be considered.
- Resistance to the neuromuscular blocking action of the nondepolarizing neuromuscular blocking agents pancuronium, vecuronium, rocuronium and cisatracurium has occurred in patients chronically administered carbamazepine. Whether or not carbamazepine has the same effect on other non-depolarizing agents is unknown. Patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected, and infusion rate requirements may be higher.
- Concomitant use of carbamazepine with rivaroxaban, apixaban, dabigatran, and edoxaban (direct acting oral anticoagulants) is expected to result in decreased plasma concentrations of these anticoagulants that may be insufficient to achieve the intended therapeutic effect. In general, coadministration of carbamazepine with rivaroxaban, apixaban, dabigatran, and edoxaban should be avoided.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

Usage in Pregnancy

(see WARNINGS).

Labor and Delivery

The effect of carbamazepine on human labor and delivery is unknown.

Nursing Mothers

Carbamazepine and its epoxide metabolite are transferred to breast milk. The ratio of the concentration in breast milk to that in maternal plasma is about 0.4 for carbamazepine and about 0.5 for the epoxide. The estimated doses given to the newborn during breastfeeding are in the range of 2 to 5 mg daily for carbamazepine and 1 to 2 mg daily for the epoxide.

Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Substantial evidence of carbamazepine's effectiveness for use in the management of children with epilepsy (see INDICATIONS AND USAGE for specific seizure types) is derived from clinical investigations performed in adults and from studies in several in vitro systems which support the conclusion that (1) the pathogenetic mechanisms underlying seizure propagation are essentially identical in adults and children, and (2) the mechanism of action of carbamazepine in treating seizures is essentially identical in adults and children.

Taken as a whole, this information supports a conclusion that the generally accepted therapeutic range of total carbamazepine in plasma (i.e., 4 to 12 mcg/mL) is the same in children and adults.

The evidence assembled was primarily obtained from short-term use of carbamazepine. The safety of carbamazepine in children has been systematically studied up to 6 months. No longer-term data from clinical trials is available.

Geriatric Use

No systematic studies in geriatric patients have been conducted.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions have been observed in the hemopoietic system and skin (see BOXED WARNING), the liver, and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the lowest dosage recommended.

The following additional adverse reactions have been reported:

Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria, variegate porphyria,

porphyria cutanea tarda.

Skin: Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) (see BOXED WARNING), Acute Generalized Exanthematous Pustulosis (AGEP), pruritic and erythematous rashes, urticaria, photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, diaphoresis, onychomadesis and hirsutism. In certain cases, discontinuation of therapy may be necessary.

Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, thrombophlebitis, thromboembolism (e.g., pulmonary embolism), and adenopathy or lymphadenopathy.

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis, very rare cases of hepatic failure.

Pancreatic: Pancreatitis.

Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis, or pneumonia.

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN, and microscopic deposits in the urine have also been reported. There have been rare reports of impaired male fertility and/or abnormal spermatogenesis.

Testicular atrophy occurred in rats receiving carbamazepine orally from 4 to 52 weeks at dosage levels of 50 to 400 mg/kg/day. Additionally, rats receiving carbamazepine in the diet for 2 years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown.

Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, hyperacusis, neuroleptic malignant syndrome.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Isolated cases of neuroleptic malignant syndrome have been reported both with and without concomitant use of psychotropic drugs.

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes: Scattered punctate cortical lens opacities, increased intraocular pressure (see WARNINGS, General) as well as conjunctivitis, have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System: Aching joints and muscles, and leg cramps.

Metabolism: Fever and chills. Hyponatremia (see WARNINGS, General). Decreased levels of plasma calcium have been reported. Osteoporosis has been reported.

Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol, and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with carbamazepine, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose: adults, 3.2 g (a 24-year-old woman died of a cardiac arrest and a 24-year-old man died of pneumonia and hypoxic encephalopathy); children, 4 g (a 14-year-old girl died of a cardiac arrest), 1.6 g (a 3-year-old girl died of aspiration pneumonia).

Oral LD_{50} in animals (mg/kg): mice, 1100 to 3750; rats, 3850 to 4025; rabbits, 1500 to 2680; guinea pigs, 920.

Signs and Symptoms

The first signs and symptoms appear after 1 to 3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (greater than 60 g) have been ingested.

Respiration: Irregular breathing, respiratory depression.

Cardiovascular System: Tachycardia, hypotension or hypertension, shock, conduction disorders.

Nervous System and Muscles: Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.

Gastrointestinal Tract: Nausea, vomiting.

Kidneys and Bladder: Anuria or oliguria, urinary retention.

Laboratory Findings: Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria, and acetonuria. EEG may show dysrhythmias.

Combined Poisoning: When alcohol, tricyclic antidepressants, barbiturates, or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with carbamazepine may be aggravated or modified.

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.

Elimination of the Drug: Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol.

Measures to Reduce Absorption: Activated charcoal, laxatives.

Measures to Accelerate Elimination: Forced diuresis.

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion is indicated in severe poisoning in small children.

Respiratory Depression: Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen.

Hypotension, Shock: Keep the patient’s legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions: Diazepam or barbiturates.

Warning: Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within 1 week).

Surveillance: Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.

Treatment of Blood Count Abnormalities: If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet, and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) ^{59}Fe-ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels.

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION (SEE TABLE BELOW)

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Medication should be taken with meals.

Conversion of patients from oral carbamazepine tablets to carbamazepine suspension: Patients should be converted by administering the same number of mg per day in smaller, more frequent doses (i.e., twice a day tablets to three times a day suspension).

Carbamazepine Extended-Release Tablets are an extended-release formulation for twice a day administration. When converting patients from carbamazepine conventional tablets to Carbamazepine Extended-Release Tablets, the same total daily mg dose of Carbamazepine Extended-Release Tablets should be administered. **Carbamazepine Extended-Release Tablets must be swallowed whole and never crushed or chewed.** Carbamazepine Extended-Release Tablets should be inspected for chips or cracks. Damaged tablets, or tablets without a release portal, should not be consumed. Carbamazepine Extended-Release Tablet coating is not absorbed and is excreted in the feces; these coatings may be noticeable in the stool.

Epilepsy (SEE INDICATIONS AND USAGE)

Adults and children over 12 years of age-Initial: 200 mg twice a day for Carbamazepine Extended-Release Tablets (400 mg/day). Increase at weekly intervals by adding up to 200 mg/day using a twice a day regimen of Carbamazepine Extended-Release Tablets until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily in children 12 to 15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 800 to 1200 mg daily.

Children 6 to 12 years of age-Initial: 100 mg twice a day for Carbamazepine Extended-Release Tablets (200 mg/day). Increase at weekly intervals by adding up to 100 mg/day using a twice a day regimen of Carbamazepine Extended-Release Tablets until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 400 to 800 mg daily.

Children under 6 years of age-Initial: 10 to 20 mg/kg/day twice a day or three times a day as tablets (chewable or conventional), or four times a day as suspension. Increase weekly to achieve optimal clinical

response administered three times a day or four times a day. ***Maintenance:*** Ordinarily, optimal clinical response is achieved at daily doses below
35 mg/kg. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the therapeutic range. No recommendation regarding the safety of carbamazepine for use at doses above 35 mg/kg/24 hours can be made.

Combination Therapy: Carbamazepine Extended-Release Tablets may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see PRECAUTIONS, Drug Interactions, and Pregnancy).

Trigeminal Neuralgia (SEE INDICATIONS AND USAGE)

Initial: On the first day, 100 mg twice a day for Carbamazepine Extended-Release Tablets, for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg/day using increments of 100 mg every 12 hours for Carbamazepine Extended-Release Tablets, only as needed to achieve freedom from pain. Do not exceed 1200 mg daily. ***Maintenance:*** Control of pain can be maintained in most patients with 400 to 800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

Dosage Information

	Initial Dose			Subsequent Dose			Maximum Daily Dose		
Indication	Tablet*	Extended-Release Tablets[A]	Suspension	Tablet*	Extended-Release Tablets[A]	Suspension	Tablet*	Extended-Release Tablets[A]	Suspension
Epilepsy Under 6 yr	10-20 mg/kg/day twice a day or 3 times a day		10-20 mg/kg/day 4 times a day	Increase weekly to achieve optimal clinical response, 3 times a day or 4 times a day		Increase weekly to achieve optimal clinical response, 3 times a day or 4 times a day	35 mg/kg/24 hr (see Dosage and Administration section above)		35 mg/kg/24 hr (see Dosage and Administration section above)
6-12 yr	100 mg twice a day (200 mg/day)	100 mg twice a day (200 mg/day)	½ tsp 4 times a day (200 mg/day)	Add up to 100 mg/day at weekly intervals, 3 times a day or 4 times a day	Add 100 mg/day at weekly intervals, twice a day	Add up to 1 tsp (100 mg)/day at weekly intervals, 3 times a day or 4 times a day	1000 mg/24 hr		
Over 12 yr	200 mg twice a day (400 mg/day)	200 mg twice a day (400 mg/day)	1 tsp 4 times a day (400 mg/day)	Add up to 200 mg/day at weekly intervals, 3 times a day or 4 times a day	Add up to 200 mg/day at weekly intervals, twice a day	Add up to 2 tsp (200 mg)/day at weekly intervals, 3 times a day or 4 times a day	1000 mg/24 hr (12-15 yr) 1200 mg/24 hr (>15 yr) 1600 mg/24 hr (adults, in rare instances)		
Trigeminal Neuralgia	100 mg twice a day (200 mg/day)	100 mg twice a day (200 mg/day)	½ tsp 4 times a day (200 mg/day)	Add up to 200 mg/day in increments of 100 mg every 12 hr	Add up to 200 mg/day in increments of 100 mg every 12 hr	Add up to 2 tsp (200 mg)/day in increments of 50 mg (½ tsp) 4 times a day	1200 mg/24 hr		

*Tablet = Chewable or conventional tablets

[A] Extended-release Tablets = Carbamazepine Extended-Release Tablets

HOW SUPPLIED

Carbamazepine Extended-Release Tablets, 100 mg – round, white to off-white, beveled edge, biconvex coated (imprinted 2241 on one side in black ink and blank on the other), release portal on one side.

Bottles of 100 ..... NDC 57720-011-16

Carbamazepine Extended-Release Tablets, 200 mg - round, white to off-white, beveled edge, biconvex coated (imprinted 2242 on one side in black ink and blank on the other), release portal on one side.

Bottles of 100 ..... NDC 57720-012-16

Carbamazepine Extended-Release Tablets, 400 mg - round, white to off-white, beveled edge, biconvex coated (imprinted 2243 on one side in black ink and blank on the other), release portal on one side.

Bottles of 100 ..... NDC 57720-013-16

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from moisture. Dispense in tight container (USP).

Manufactured by:
Beijing Sciecure Pharmaceutical Co., Ltd.,
Beijing, China

Manufactured for:
Sciecure Pharma Inc.
Monmouth Junction, New Jersey 08852

PI-224
Rev. 02/2023

MEDICATION GUIDE

Carbamazepine (kar" ba maz' e peen)

Extended-Release Tablets

Read this Medication Guide before you start taking Carbamazepine Extended-Release Tablets and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about Carbamazepine Extended-Release Tablets?

Do not stop taking Carbamazepine Extended-Release Tablets without first talking to your healthcare provider.

Stopping carbamazepine extended-release tablets suddenly can cause serious problems.

Carbamazepine Extended-Release Tablets can cause serious side effects, including:

1. **Carbamazepine extended-release tablets may cause rare but serious skin rashes that may lead to death. These serious skin reactions are more likely to happen when you begin taking carbamazepine extended-release tablets within the first four months of treatment but may occur at later times. These reactions can happen in anyone, but are more likely in people of Asian descent. If you are of Asian descent, you may need a genetic blood test before you take carbamazepine extended-release tablets to see if you are at a higher risk for serious skin reactions with this medicine. Symptoms may include:**
   - skin rash
   - hives
   - sores in your mouth
   - blistering or peeling of the skin

2. **Carbamazepine Extended-Release Tablets may cause rare but serious blood problems. Symptoms may include:**
   - fever, sore throat, or other infections that come and go or do not go away
   - easy bruising
   - red or purple spots on your body
   - bleeding gums or nose bleeds
   - severe fatigue or weakness

3. **Carbamazepine Extended-Release Tablets may cause allergic reactions or serious problems, which may affect organs and other parts of your body like the liver or blood cells. You may or may not have a rash with these types of reactions.**
   Call your healthcare provider right away if you have any of the following:
   - swelling of your face, eyes, lips, or tongue
   - a skin rash
   - painful sores in the mouth or around your eyes
   - unusual bruising or bleeding
   - frequent infections or infections that do not go away
   - fever, swollen glands, or sore throat that do not go away or come and go

- trouble swallowing or breathing
- hives
- yellowing of your skin or eyes
- severe fatigue or weakness
- severe muscle pain

4. **Like other antiepileptic drugs, Carbamazepine Extended-Release Tablets may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**
   Call your healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:
   - thoughts about suicide or dying
   - attempts to commit suicide
   - new or worse depression
   - new or worse anxiety
   - feeling agitated or restless
   - panic attacks
   - trouble sleeping (insomnia)
   - new or worse irritability
   - acting aggressive, being angry, or violent
   - acting on dangerous impulses
   - an extreme increase in activity and talking (mania)
   - other unusual changes in behavior or mood

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 Carbamazepine Extended-Release Tablets without first talking to a healthcare provider.

Stopping carbamazepine extended-release tablets suddenly can cause serious problems. You should talk to your healthcare provider before stopping.

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

What are Carbamazepine Extended-Release Tablets?

Carbamazepine Extended-Release Tablets are a prescription medicine used to treat:

- certain types of seizures (partial, tonic-clonic, mixed)
- certain types of nerve pain (trigeminal and glossopharyngeal neuralgia)

Carbamazepine Extended-Release Tablets are not a regular pain medicine and should not be used for aches or pains.

Who should not take Carbamazepine Extended-Release Tablets?

Do not take Carbamazepine Extended-Release Tablets if you:

- have a history of bone marrow depression.

- are allergic to carbamazepine or any of the ingredients in carbamazepine extended-release tablets. See the end of this Medication Guide for a complete list of ingredients in Carbamazepine Extended-Release Tablets.
- take nefazodone.
- are allergic to medicines called tricyclic antidepressants (TCAs). Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.
- have taken a medicine called a Monoamine Oxidase Inhibitor (MAOI) in the last 14 days. Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.

What should I tell my healthcare provider before taking Carbamazepine Extended-Release Tablets?

Before you take Carbamazepine Extended-Release Tablets, tell your healthcare provider if you:

- have or have had suicidal thoughts or actions, depression, or mood problems
- have or ever had heart problems
- have or ever had blood problems
- have or ever had liver problems
- have or ever had kidney problems
- have or ever had allergic reactions to medicines
- have or ever had increased pressure in your eye
- have any other medical conditions
- drink grapefruit juice or eat grapefruit
- use birth control. Carbamazepine Extended-Release Tablets may make your birth control less effective. Tell your healthcare provider if your menstrual bleeding changes while you take birth control and carbamazepine extended-release tablets.
- are pregnant or plan to become pregnant. Carbamazepine may harm your unborn baby. Tell your healthcare provider right away if you become pregnant while taking carbamazepine extended-release tablets. You and your healthcare provider should decide if you should take carbamazepine extended-release tablets while you are pregnant.
- If you become pregnant while taking carbamazepine extended-release tablets, talk to your healthcare provider about registering with the North American Antiepileptic Drug (NAAED) Pregnancy Registry. The purpose of this registry is to collect information about the safety of antiepileptic medicine during pregnancy. You can enroll in this registry by calling 1-888-233-2334.
- are breastfeeding or plan to breastfeed. Carbamazepine passes into breast milk. You and your healthcare provider should discuss whether you should take carbamazepine extended-release tablets or breastfeed; you should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Taking carbamazepine extended-release tablets with certain other medicines may cause side effects or affect how well they work. Do not start or stop other medicines without talking to your healthcare provider.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take Carbamazepine Extended-Release Tablets?

- Do not stop taking carbamazepine extended-release tablets without first talking to your healthcare provider. Stopping carbamazepine extended-release tablets suddenly can cause serious problems. Stopping seizure medicine suddenly in a patient who has epilepsy may cause seizures that will not stop (status epilepticus).
- Take carbamazepine extended-release tablets exactly as prescribed. Your healthcare provider will tell you

how many carbamazepine extended-release tablets to take.

- Your healthcare provider may change your dose. Do not change your dose of carbamazepine extended-release tablets without talking to your healthcare provider.
- Take carbamazepine extended-release tablets with food.
- **Carbamazepine Extended-Release Tablets:**
  - Do not crush, chew, or break carbamazepine extended-release tablets.
  - Tell your healthcare provider if you cannot swallow carbamazepine extended-release tablets whole.
- If you take too many carbamazepine extended-release tablets, call your healthcare provider or local Poison Control Center right away.

What should I avoid while taking Carbamazepine Extended-Release Tablets?

- Do not drink alcohol or take other drugs that make you sleepy or dizzy while taking carbamazepine extended-release tablets until you talk to your healthcare provider. Carbamazepine extended-release tablets taken with alcohol or drugs that cause sleepiness or dizziness may make your sleepiness or dizziness worse.
- Do not drive, operate heavy machinery, or do other dangerous activities until you know how carbamazepine extended-release tablets affects you. Carbamazepine extended-release tablets may slow your thinking and motor skills.

What are the possible side effects of Carbamazepine Extended-Release Tablets?

See **"What is the most important information I should know about Carbamazepine Extended-Release Tablets?"**

Carbamazepine extended-release tablets may cause other serious side effects. These include:

- Irregular heartbeat - symptoms include:
  - Fast, slow, or pounding heartbeat
  - Shortness of breath
  - Feeling lightheaded
  - Fainting
- Liver problems - symptoms include:
  - yellowing of your skin or the whites of your eyes
  - dark urine
  - pain on the right side of your stomach area (abdominal pain)
  - easy bruising
  - loss of appetite
  - nausea or vomiting

Get medical help right away if you have any of the symptoms listed above or listed in "What is the most important information I should know about Carbamazepine Extended-Release Tablets?"

The most common side effects of Carbamazepine Extended-Release Tablets include:

- dizziness
- drowsiness
- problems with walking and coordination (unsteadiness)
- nausea
- vomiting

These are not all the possible side effects of carbamazepine extended-release tablets. For more information,

ask your healthcare provider or pharmacist.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

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 Carbamazepine Extended-Release Tablets?

- Store Carbamazepine Extended-Release Tablets at 20° to 25°C (68° to 77°F).
  - Keep Carbamazepine Extended-Release Tablets dry.

Keep Carbamazepine Extended-Release Tablets and all medicines out of the reach of children.

General Information about Carbamazepine Extended-Release Tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use carbamazepine extended-release tablets for a condition for which it was not prescribed. Do not give carbamazepine extended-release tablets to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about carbamazepine extended-release tablets. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for the full prescribing information about carbamazepine extended-release tablets that is written for health professionals.

For more information about carbamazepine extended-release tablets, call 1-844-315-4325 .

What are the ingredients in Carbamazepine Extended-Release Tablets?

Active ingredient: carbamazepine USP

Inactive ingredients: Hypromellose, hydroxyethyl cellulose, cellulose acetate, polyethylene glycol mannitol, dextrates, sodium lauryl sulfate, magnesium stearate. Each tablet is printed with Opacode Black S-1-17823 ink which contains ammonium hydroxide, iron oxide black, isopropyl alcohol, n-butyl alcohol, propylene glycol and shellac.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:

Beijing Sciecure Pharmaceutical Co., Ltd.,

Beijing, China

Manufactured for:

Sciecure Pharma Inc.

Monmouth Junction, New Jersey 08852

PI-224
Rev. 12/2022

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA216235Orig1s000

LABELING REVIEW(s)

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	02/14/2023
ANDA Number(s)	216235
Review Number	4
Applicant Name	Sciecure Pharma Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Carbamazepine Extended-Release Tablets USP, 100 mg, 200 mg, and 400 mg
Proposed Proprietary Name	None
Submission Received Date	February 03, 2023
Primary Labeling Reviewer	Susan Rimmel
Secondary Labeling Reviewer	Ellen Hwang

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

On Policy Alert List	☐ Yes	☒ No
Acceptable For Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No

TABLE OF CONTENTS

1 LABELING COMMENTS (C4)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C4)

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C4)

The Division of Labeling has no further questions/comments at this time based on your labeling submission received February 3, 2023.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), 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.

1.3 POST-APPROVAL REVISIONS (C4)

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

2 INSTRUCTIONS FOR ASSESSMENT (C4)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

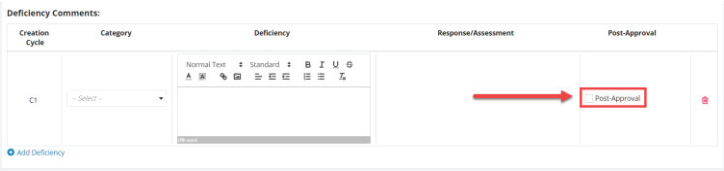
If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.



3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C4)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Draft	100 mg, 200 mg, and 400 mg: 100-count bottles	5/31/2022 (C3)	Satisfactory
Blister	N/A	N/A		
Carton	N/A	N/A		

Table 2: 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	Rev. 02/2023 ; Code: PI-224	2/3/2023	Satisfactory
Medication Guide	Draft	Rev. 12/2022 ; Code: PI-224	2/3/2023	Satisfactory
Patient Information	N/A	N/A		
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C4)

4.1 REGULATORY INFORMATION (C4)

Yes	No	
☒	☐	Are there any applicable issues in **DLR's SharePoint Drug Facts** ? C1/C2 **Antiepileptic drug pregnancy registry (PR)_North American Antiepileptic Drugs (NAAED) PR** (posted 3/30/2016): "There is a pregnancy registry established for the antiepileptic drugs -North American Antiepileptic Drug (NAAED) Pregnancy Registry. It is an independent program and was not established as a result of a PMR. But given that this pregnancy registry handled by a third party and well respected and well used, ANDAs should have the same information in insert labeling (note the website is updated to http://www.aedpregnancyregistry.org from the old one which is http://www.massgeneral.org/aed/): Patients should be encouraged to enroll in the North American Antiepileptic Drug (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 about the North American Drug Pregnancy Registry can be found at http://www.aedpregnancyregistry.org." "**Update 7/2/2019**: A meeting was held with DPMH on 6/17/2019 to discuss the NAAED and whether ANDAs should continue to include the information about the NAAED PR in their

Yes	No	
		insert labeling. DPMH confirmed that this is a disease-based PR that is run by a well respected organization and has been around for a while. The NDAs are required to include this PR information in their insert labeling by DPMH. We will continue to ask ANDAs to include this PR information to be the same as the RLD. However, we do not need to ask the ANDA holder to confirm that they are registered with this organization for the PR." • **Assessment**: **SATISFACTORY** (ANDAs proposed labeling **includes PR information above** and is **consistent with RLD labeling**) C3/C4 **Antiepileptic drug pregnancy registry (PR)_North American Antiepileptic Drugs (NAAED) PR** (posted 3/30/2016) Brief Description Update 12/2/2022: • Pregnancy Registry (PR) is a third party's PR o Add comment for Cycle 1 or if the PR is new in the NDA labeling o If ANDA included the PR in labeling, we should comment for the ANDA applicant to reach out to third party and verify that the data for the generic product will be accepted as part of the PR (data might be collected for some generic products but not others). If it is verified that the data for the generic product will be accepted, the ANDA applicant can continue to include the PR in labeling. If data for the generic product will not be accepted, the ANDA applicant should remove the PR in labeling. ▪ Example comment to include in SCD: *The reference listed drug (RLD) for your drug product contains third party pregnancy registry information in its labeling. Please reach out to the third party to verify if the data for your generic drug product will be accepted as part of their pregnancy registry. If it is verified that the data for your generic drug product will be accepted by the third party, you can continue including the pregnancy registry information in your labeling. If it is determined that the data for your generic drug product will not be accepted by the third party, please remove the pregnancy registry information in your labeling.* o If ANDA did not include PR in labeling, we should comment for the ANDA applicant to reach out to third party and determine if the data for the generic product will be accepted as part of the PR. If it is verified that the data for the generic product will be accepted, the ANDA applicant should include the PR in labeling. If data for the generic product will not be accepted, the ANDA applicant can continue to exclude the PR. ▪ Example comment to include in SCD: *The reference listed drug (RLD) for your drug product contains third party pregnancy registry information in its labeling. Please reach out to the third party to verify if the data for your generic drug product will be accepted as part of their pregnancy registry. If it is verified that the data for your generic drug product will be accepted by the third party, please include the pregnancy registry information in your labeling. If it is determined that the data for your generic drug product will not be accepted by the third party, you can continue excluding the pregnancy registry information in your labeling.* Assessment: Comment above is for issuance during C1 and not applicable for this review cycle. **See C1/C2 above.**
☐	☒	Is the drug product listed in the Policy Alert Tracker on **OGD's SharePoint**?

4.2 MODEL PRESCRIBING INFORMATION (C4)

Table 3: Review Model Labeling for Prescribing Information/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):** 020234 / S-047 **Supplement Approval Date:** 03/20/2018 **Proprietary Name:** Tegretol-XR **Established Name:** carbamazepine extended-release tablets **Description of Supplement:**

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
"This Prior Approval supplemental new drug application provides for changes to the labeling that were derived from a comprehensive analysis of historical information collected for Tegretol, resulting in an update to the Warnings, Precautions, Drug Interactions, Usage in Pregnancy, Adverse Reactions, and Dosage and Administration sections of the USPI." **Link:** https://analytics.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=5069056_4666186_090140af80693afe_NDA020234_3461829
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**
☒ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):** C1/C2 **Other Approved RLD Supplements (no impact on labeling)** • **S-048** (CMC submission **approved** 04/12/2018): "These "Changes Being Effected in 30 days" supplemental new drug applications provide for the addition of (b) (4) (b) (4) as an alternative quality control testing site for the drug substance carbamazepine." [**Note**: Approval Letter under NDA-016608-SUPPL-117.] • **S-049** (CMC submission **approved** 04/22/2020): "This "Changes Being Effected in 30 days" supplemental new drug application provides the addition two alternate stability testing sites (listed below) for the drug product Tegretol-XR Tablets: (b) (4) • **S-050** (CMC submission **approved** 08/20/2020): "This "Changes Being Effected in 30 days" supplemental new drug application provides for updates to the specification for the drug product Tegretol XR Tablets and the authorized generic Carbamazepine ER Tablets including changes to (b) (4) (b) (4) • **S-051** (CMC submission **approved** 08/26/2020): "These "Changes Being Effected" supplemental new drug applications provide for updates to the specification (b) (4) (b) (4) [**Note**: Approval Letter under NDA-016608-SUPPL-119.] C3 **Other RLD Supplements** Supplement-52 Manufacturing (CMC) CDER/OPQ/OPRO/DRBPMIII Approved 10/28/2022 - **IMPACTS CONTAINER LABELS ONLY** (see Section 4.5 below)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.
Reviewer Comments:		

C1: The RLDs model labeling is a combined insert but the ANDAs proposed labeling does not carve-out the tablet (chewable and conventional) and oral suspension dosage forms (**see Deficiency in Section 5.4 below**). In addition, the Applicant only provided a PDF version of the PI/MG received on 7/6/2021; however, **no notable differences were identified in the SBS comparison with the Word document received on 5/21/2021**. Thus, the PDF document received on 7/6/2021, was used for the SBS comparison with the RLD model labeling.

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES (C4)

The Orange Book was searched on 02/14/2023

Table 4 provides Orange Book patents for the Model Labeling (NDA 020234) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
	N/A						

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
	N/A					

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:

Deficiency Comments:

4.4 UNITED STATES PHARMACOPEIA (USP) (C4)

The USP was searched on 08/13/2021

Table 6: USP

	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (N/A if no monograph)**	**Packaging and Storage/Labeling Statements (N/A if no monograph)**
Currently Official	Yes		Carbamazepine Extended-Release Tablets	•Packaging and Storage: Preserve in tight containers, and store at controlled room temperature. Add the following: ▲ •Labeling: The labeling states the Dissolution test used only if Test 1 is not used.▲ (RB 1-May-2020)
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	**No Deficiency**	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.

Reviewer Comments:

C1: There are 2 Dissolution Tests in the USP monograph for the drug product (*Official as of 1-May-2020*); however, the DP and BE Reviews are pending (**see Section 5.1.1 below**). Notably, the ANDAs proposed labeling states, (b) (4) See Deficiencies in Section 5.3 below.

C2

USP Descriptor: See Section 5.3 below.

Biopharmaceutics Review (Reference #46432792, 11/3/2021): **INADEQUATE - MINOR**

Biopharmaceutics Executive Summary	
The Applicant proposed USP monograph dissolution method (Test 1) for carbamazepine ER tablets (Apparatus I at 100 rpm, 900 mL (for the 100 mg and 200 mg strengths) or 1800 mL (for the 400 mg strength) of Water). The Applicant's proposed dissolution acceptance criteria is same as USP test 1. The adequacy of the dissolution method and acceptance criteria is pending Applicant's response to the IRs.	
Has OGD deemed the drug product BE to the RLD?	Yes

C2 Biopharmaceutics Review is pending.

C3

USP Descriptor: Applicant **removed USP descriptor from header title and not product title in the FPI (see excerpt below)**; however, labeling is in non-PLR format and acceptable for the purposes of DLRs review at this time.

Excerpt below from ANDAs Revised Proposed PI

Carbamazepine Extended-Release Tablets

Sciecure Pharma Inc.

Carbamazepine Extended-Release Tablets, USP

Biopharmaceutics Review (Reference #51115774, 12/8/2022): **ADEQUATE**

Biopharmaceutics Executive Summary	
The Biopharmaceutics review focused on the assessment of proposed dissolution method, dissolution acceptance criteria, and the in-vitro in-vivo correlation (IVIVC) data. The Applicant proposed USP monograph dissolution method (Test 1) for carbamazepine ER tablets which is acceptable based on the method development report and submitted data. The proposed dissolution acceptance criteria are permissive for the drug product and not acceptable. The Applicant submitted an IVIVC report to demonstrate that revised USP dissolution acceptance criteria will be able to reject product that is not bioequivalent to the reference-target drug product. The IVIVC study, however, was deemed not acceptable because of incomplete data/justification provided. Therefore, the Agency recommended to revise the acceptance criteria based on the bio-batch data which the Applicant has accepted. The Applicant was requested to petition the USP for the revised acceptance criteria which the applicant has initiated. The submission is adequate from Biopharmaceutics perspective.	
Has OGD deemed the drug product BE to the RLD?	Yes

Deficiency Comments:

4.5 MODEL CONTAINER LABELS (C4)

Model container/carton/blister labels (Source: Various--see below. **)**

Approved (Source: S-052, FINAL received in EDR 1/4/2023, approved 10/28/2022)

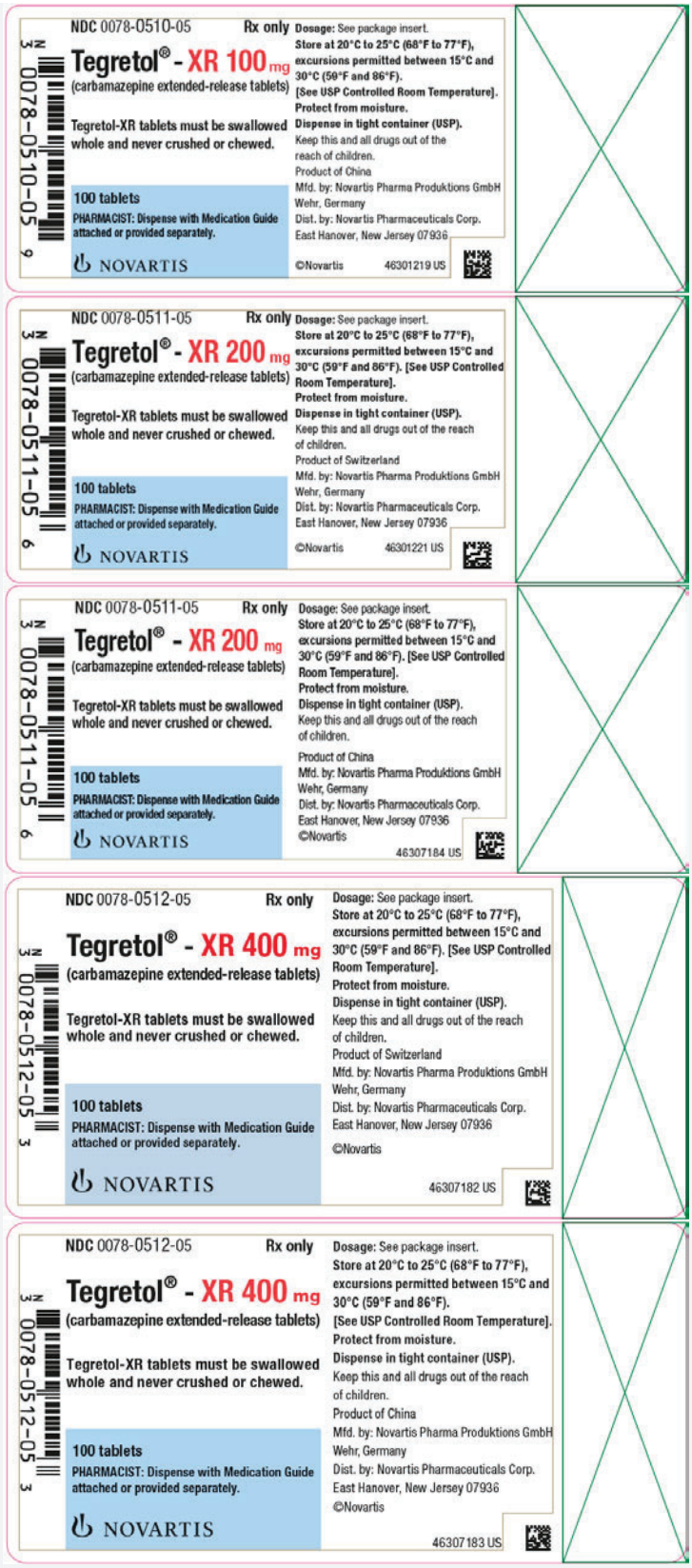
C3 Note: Only container labels were revised in S-052, which are not posted on Drugs@FDA.

C4 Note: Minor formatting differences and revised component numbers when compared to DRAFT container labels received in EDR 5/18/2022, which was used as the model labeling in C3.

Excerpt below from Approval Letter in Panorama

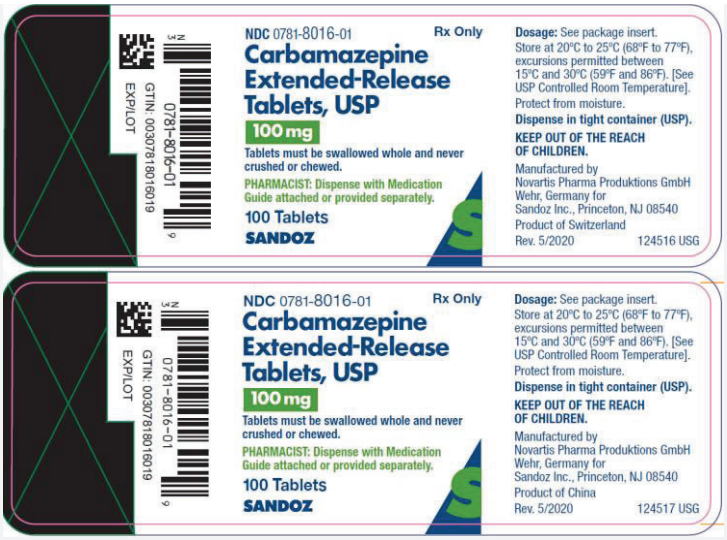
This "Changes Being Effected in 30 days" supplemental new drug application provides for multiple changes including the following:

(b) (4)



Marketed NDA Authorized Generic

Source: ANRPT-25, FINAL, 5/19/2021



Source: ANRPT-24, FINAL, 5/20/2020

5 ASSESSMENT OF ANDA LABELING AND LABELS (C4)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C4)

5.1.1 DRUG PRODUCT REVIEW (C4)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review complete

C2

DP Review (Reference #46432772)

11/8/2021: **INDADEQUATE - MINOR**

Labeling	
Description Section	
Is the information accurate?	Yes
Is the drug product subject of a USP monograph?	Yes
Does the labeling need a special USP statement in the Description?	No
How Supplied Section	
Is the information accurate?	Yes
Are the storage conditions acceptable?	Yes
Dosage and Administration Section	
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	N/A

For Solid Oral Drug Product:		
ANDA Strength	**Length(mm)**	**Imprint Code**
Carbamazepine 100mg	8	2241 on one side only
Carbamazepine 200mg	10	2242 on one side only
Carbamazepine 400mg	12	2243 on one side only
Is the imprint code consistent with the labeling?	Yes	
Any issue(s) sent to and/or received from the OGD Labeling Reviewer?	**No**	

2/18/2022
Drug Substance: **ADEQUATE**
Drug Product: **INDADEQUATE - MINOR**

Labeling	
Description Section	
Is the information accurate?	Yes
Is the drug product subject of a USP monograph?	Yes
Does the labeling need a special USP statement in the Description?	No
How Supplied Section	
Is the information accurate?	Yes
Are the storage conditions acceptable?	Yes
Dosage and Administration Section	
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	N/A

For Solid Oral Drug Product:		
ANDA Strength	**Length(mm)**	**Imprint Code**
Carbamazepine 100mg	8	2241 on one side only
Carbamazepine 200mg	10	2242 on one side only
Carbamazepine 400mg	12	2243 on one side only
Is the imprint code consistent with the labeling?	Yes	
Any issue(s) sent to and/or received from the OGD Labeling Reviewer?	**No**	

C3/C4
DP Review (Reference #51115754, uploaded 12/2/2022 and archived 1/3/2023): **ADEQUATE**

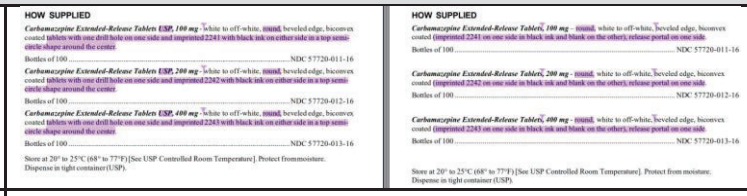
5.1.2 DESCRIPTION (C4)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	PI Tegretol-XR tablets: cellulose compounds, dextrates, iron oxides, magnesium stearate, mannitol, polyethylene glycol, sodium lauryl sulfate, titanium dioxide (200 mg tablets only). MG **What are the ingredients in TEGRETOL?** Active ingredient: carbamazepine Inactive ingredients: • **TEGRETOL-XR Tablets:** cellulose compounds, dextrates, iron oxides, magnesium stearate, mannitol, polyethylene glycol, sodium lauryl sulfate, titanium dioxide (200 mg tablets only).
Previous ANDA Labeling	PI *Inactive Ingredients:* Hypromellose, hydroxyethyl cellulose, cellulose acetate, polyethylene glycol, mannitol, dextrates, sodium lauryl sulfate, and magnesium stearate. Each tablet is printed with Opacode Black S-1-17823 ink which contains ammonium hydroxide, iron oxide black, isopropyl alcohol, n-butyl alcohol, propylene glycol and shellac. FDA approved dissolution test specifications differ from USP. MG **What are the ingredients in Carbamazepine Extended-Release Tablets?** Active ingredient: carbamazepine USP Inactive ingredients: Hypromellose, hydroxyethyl cellulose, cellulose acetate, polyethylene glycol mannitol, dextrates, sodium lauryl sulfate, magnesium stearate. Each tablet is printed with Opacode Black S-1-17823 ink which contains ammonium hydroxide, iron oxide black, isopropyl alcohol, n-butyl alcohol, propylene glycol and shellac. Assessment: **SATISFACTORY** for the PI (added dissolution statement--see Section 4.4 above) and MG (minor editorial revisions--**see below**). Excerpt below from SBS Comparison (C2 vs. C3) **What are the ingredients in Carbamazepine Extended-Release Tablets?** Active ingredient: carbamazepine, USP Inactive ingredients: Hypromellose, hydroxyethyl cellulose, cellulose acetate, polyethylene glycol mannitol, dextrates, sodium lauryl sulfate, magnesium stearate. Each tablet is printed with Opacode Black S-1-17823 ink which contains ammonium hydroxide, iron oxide black, isopropyl alcohol, n-butyl alcohol, propylene glycol and shellac. **What are the ingredients in Carbamazepine Extended-Release Tablets?** Active ingredient: carbamazepine USP Inactive ingredients: Hypromellose, hydroxyethyl cellulose, cellulose acetate, polyethylene glycol mannitol, dextrates, sodium lauryl sulfate, magnesium stearate. Each tablet is printed with Opacode Black S-1-17823 ink which contains ammonium hydroxide, iron oxide black, isopropyl alcohol, n-butyl alcohol, propylene glycol and shellac.
Current ANDA Labeling	PI *Inactive Ingredients:* Hypromellose, hydroxyethyl cellulose, cellulose acetate, polyethylene glycol, mannitol, dextrates, sodium lauryl sulfate, and magnesium stearate. Each tablet is printed with Opacode Black S-1-17823 ink which contains ammonium hydroxide, iron oxide black, isopropyl alcohol, n-butyl alcohol, propylene glycol and shellac. FDA approved dissolution test specifications differ from USP. MG **What are the ingredients in Carbamazepine Extended-Release Tablets?** Active ingredient: carbamazepine USP Inactive ingredients: Hypromellose, hydroxyethyl cellulose, cellulose acetate, polyethylene glycol mannitol, dextrates, sodium lauryl sulfate, magnesium stearate. Each tablet is printed with Opacode Black S-1-17823 ink which contains ammonium hydroxide, iron oxide black, isopropyl alcohol, n-butyl alcohol, propylene glycol and shellac. Assessment: **NO CHANGE**

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C4)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	PI

Table 8: Comparison of Model Labeling to ANDA Labeling	
	Chewable Tablets 100 mg - round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side) Bottles of 100 ..... NDC 0078-0492-05 Unit Dose (blister pack) Box of 100 (strips of 10) ..... NDC 0078-0492-35 Do not store above 30°C (86°F). *Protect from light and moisture.* *Dispense in tight, light-resistant container (USP).* *Meets USP Dissolution Test 1.* ***Tablets 200 mg*** - capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the partially scored side) Bottles of 100 ..... NDC 0078-0509-05 Bottles of 60 ..... NDC 0078-0509-20 Do not store above 30°C (86°F). *Protect from moisture.* *Dispense in tight container (USP).* *Meets USP Dissolution Test 2.* ***XR Tablets 100 mg*** - round, yellow, coated (imprinted T on one side and 100 mg on the other), release portal on one side Bottles of 100 ..... NDC 0078-0510-05 ***XR Tablets 200 mg*** - round, pink, coated (imprinted T on one side and 200 mg on the other), release portal on one side Bottles of 100 ..... NDC 0078-0511-05 ***XR Tablets 400 mg*** - round, brown, coated (imprinted T on one side and 400 mg on the other), release portal on one side Bottles of 100 ..... NDC 0078-0512-05 Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) *Protect from moisture.* *Dispense in tight container (USP).* ***Suspension 100 mg/5 mL (teaspoon)*** – yellow-orange, citrus-vanilla flavored Bottles of 450 mL ..... NDC 0078-0508-83 Shake well before using. Do not store above 30°C (86°F). *Dispense in tight, light-resistant container (USP).*| MG **How should I store TEGRETOL?** • Do not store **TEGRETOL Tablets** above 30°C (86°F). • Keep TEGRETOL Tablets dry. • Do not store **TEGRETOL Chewable Tablets** above 30°C (86°F). • Keep TEGRETOL Chewable Tablets out of the light. • Keep TEGRETOL Chewable Tablets dry. • Store **TEGRETOL-XR Tablets** at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). • Keep TEGRETOL-XR Tablets dry. • Do not store **TEGRETOL Suspension** above 30°C (86°F). • Shake well before using. • Keep TEGRETOL Suspension in a tight, light-resistant container. **Keep TEGRETOL and all medicines out of the reach of children.**
Previous ANDA Labeling	PI ***Carbamazepine Extended-Release Tablets, 100 mg*** – round, white to off-white, beveled edge, biconvex coated (imprinted 2241 on one side in black ink and blank on the other), release portal on one side. Bottles of 100 ..... NDC 57720-011-16 ***Carbamazepine Extended-Release Tablets, 200 mg*** - round, white to off-white, beveled edge, biconvex coated (imprinted 2242 on one side in black ink and blank on the other), release portal on one side. Bottles of 100 ..... NDC 57720-012-16 ***Carbamazepine Extended-Release Tablets, 400 mg*** - round, white to off-white, beveled edge, biconvex coated (imprinted 2243 on one side in black ink and blank on the other), release portal on one side. Bottles of 100 ..... NDC 57720-013-16 Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from moisture. Dispense in tight container (USP). MG **How should I store Carbamazepine Extended-Release Tablets?** • Store Carbamazepine Extended-Release Tablets at 20° to 25°C (68° to 77°F). • Keep Carbamazepine Extended-Release Tablets dry. **Keep Carbamazepine Extended-Release Tablets and all medicines out of the reach of children.** Assessment: **SATISFACTORY** for the PI (revised in alignment with the RLD--**see below** and Section 5.3 below) and **NO CHANGE** for the MG. Excerpt below from SBS Comparison (C2 vs. C3)

Table 8: Comparison of Model Labeling to ANDA Labeling	
	
Current ANDA Labeling	PI ***Carbamazepine Extended-Release Tablets, 100 mg*** – round, white to off-white, beveled edge, biconvex coated (imprinted 2241 on one side in black ink and blank on the other), release portal on one side. Bottles of 100 ..... NDC 57720-011-16 ***Carbamazepine Extended-Release Tablets, 200 mg*** - round, white to off-white, beveled edge, biconvex coated (imprinted 2242 on one side in black ink and blank on the other), release portal on one side. Bottles of 100 ..... NDC 57720-012-16 ***Carbamazepine Extended-Release Tablets, 400 mg*** - round, white to off-white, beveled edge, biconvex coated (imprinted 2243 on one side in black ink and blank on the other), release portal on one side. Bottles of 100 ..... NDC 57720-013-16 Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from moisture. Dispense in tight container (USP). MG **How should I store Carbamazepine Extended-Release Tablets?** • Store Carbamazepine Extended-Release Tablets at 20° to 25°C (68° to 77°F). • Keep Carbamazepine Extended-Release Tablets dry. **Keep Carbamazepine Extended-Release Tablets and all medicines out of the reach of children.** Assessment: **NO CHANGE**

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C4)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	Source: FORM FDA 356h, 12/7/2022 (C4) **APPLICANT INFORMATION** 2. Name of Applicant: Sciecure Pharma Inc. 3. Telephone Number *(Include country code if applicable and area code)*: 732-329-8089 (b) (6) 4. Facsi… code i… 5. Applicant Address Address 1 *(Street address, P.O. box, company name c/o)*: 11 Deer Park Drive Address 2 *(Apartment, suite, unit, building, floor, etc.)*: Unit 120 City: Monmouth Junction State/Province/Region: New Jersey Country: USA ZIP or Postal Code: 08852

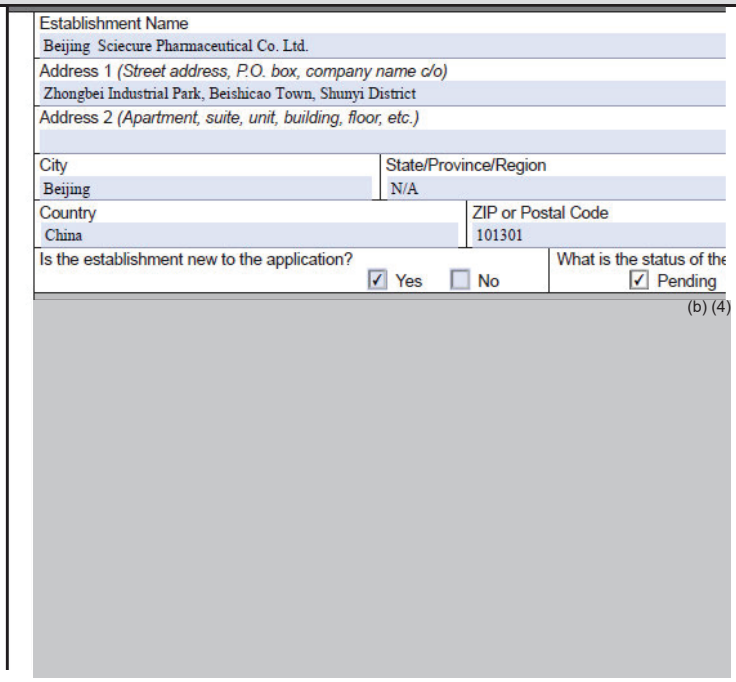
Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
	 Container Labels Manufactured by: Beijing Sciecure Pharmaceutical Co., Ltd., Shunyi District, Beijing 101301, China Manufactured for: Sciecure Pharma Inc., Monmouth Junction, NJ 08852 PI/MG **Manufactured by:** Beijing Sciecure Pharmaceutical Co., Ltd., Beijing, China **Manufactured for:** Sciecure Pharma Inc. Monmouth Junction, New Jersey 08852 Assessment: **NO CHANGE**
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Source: FORM FDA 356h, 2/3/2023 (C4)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

APPLICANT INFORMATION	2. Name of Applicant
	Sciecure Pharma Inc.

3. Telephone Number *(Include country code if applicable and area code)*	4. Facsir code i
732-329-8089 ext. (b) (6)	

5. Applicant Address

Address 1 *(Street address, P.O. box, company name c/o)*	
11 Deer Park Drive	
Address 2 *(Apartment, suite, unit, building, floor, etc.)*	
Unit 120	
City: Monmouth Junction	State/Province/Region: New Jersey
Country: USA	ZIP or Postal Code: 08852

Establishment Name		
Beijing Sciecure Pharmaceutical Co. Ltd.		
Address 1 *(Street address, P.O. box, company name c/o)*		
Zhongbei Industrial Park, Beishicao Town, Shunyi District		
Address 2 *(Apartment, suite, unit, building, floor, etc.)*		
City: Beijing	State/Province/Region: N/A	
Country: China	ZIP or Postal Code: 101301	
Is the establishment new to the application? ☑ Yes ☐ No	What is the status of the ☑ Pending	

(b) (4)

Container Labels (C3)

Manufactured by:
Beijing Sciecure Pharmaceutical Co., Ltd.,
Shunyi District, Beijing 101301, China

Manufactured for:
Sciecure Pharma Inc.,
Monmouth Junction, NJ 08852

PI/MG (C4)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
	Manufactured by: Beijing Sciecure Pharmaceutical Co., Ltd., Beijing, China **Manufactured for:** Sciecure Pharma Inc. Monmouth Junction, New Jersey 08852 Assessment: **NO CHANGE**

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		ESTABLISHED/PROPRIETARY NAME and STRENGTH:
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
		THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number:** prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
		PRODUCT DIFFERENTIATION:
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
		STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR

Deficiency	No Deficiency	
		201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
	OVERALL ASSESSMENT:	
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

(b) (4)

Description of Container Closure (Source: Module 3.2.P.7 Container Closure System, 5/21/2021)

Table 1. Summary of Packaging Configuration

Strength	100 mg	200 mg	400 mg
Count/ Bottle	100 tablets	100 tablets	100 tablets
Container	75cc HDPE bottle	75cc HDPE bottle	120cc HDPE bottle
Closure	(b) (4) CRC cap	(b) (4) CRC cap	(b) (4) CRC cap
	(b) (4)		
Dunnage	N/A	N/A	N/A

The proposed container closure system is child resistant. (b) (4)

(b) (4)

C3

ANDAs revised proposed container labels are **SATISFACTORY** (**see below**).

C4

ANDAs container labels were found **SATISFACTORY** in C3 (**see above**).

Deficiency Comments:

5.3 PRESCRIBING INFORMATION (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at end of HIGHLIGHTS section.
	DESCRIPTION/INACTIVE INGREDIENTS:	

Deficiency	No Deficiency	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐Sulfite (21 CFR 201.22) ☐Yellow #5 (Tartrazine) (21 CFR 201.20) ☐Phenylalanine/aspartame (21 CFR 201.21) ☐latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Gluten** statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	**Dosage form and route** of administration properly listed [21 CFR 201.57(c)(12)(B)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
C1

See Internal Observations in Section 5.2 above.

Internal Observations (not provided to Applicant)

Physical Description (Source: **Module 3.2.P.1** Description and Composition of the Drug Product, 5/21/2021)

3.2.P.1.1 Composition and Dosage Form

Carbamazepine Extended-Release Tablets USP, 100 mg, 200 mg and 400 mg are bi-convex coated tablets, rounded beveled edges, with one drill hole on one side and printed "2241", "2242", "2243" on either side in a top semi-circle shape around the center for 100 mg, 200 mg and 400 mg strengths, respectively.

The physical description of the tablets in the Quality submission is inconsistent with the PI (**see Section 5.1.3 above**) and it appears the Applicant has not provided images of their proposed drug product, which is a review issue. See Deficiency below.

C2

Reply to Quality DRL (Source: Module 1.12.12 SBS Comparison, 1/10/2022)

Table 1. Side by Side comparison of RLD vs. Generic Information

		Tegretol®-XR (carbamazepine extended-release tablets), 100 mg, 200 mg, and 400 mg	Carbamazepine Extended-Release Tablets, USP 100 mg, 200 mg, and 400 mg
Conditions of Use		Indicated for the treatment of pain associated with trigeminal neuralgia and therapeutic relief of epilepsy.	Indicated for the treatment of pain associated with trigeminal neuralgia and therapeutic relief of epilepsy.
Active Ingredient		Carbamazepine	Carbamazepine
Dosage Form		Tablet, extended release	Tablet, extended release
Route of Administration		Oral	Oral
Size	**100 mg**	8 mm	8 mm
	200 mg	10 mm	10 mm
	400 mg	12 mm	12 mm
Strength		100 mg, 200 mg, and 400 mg	100 mg, 200 mg, and 400 mg
Shape		Round	Round, bi-convex, beveled edges
Color	**100 mg**	Yellow	White to off-white
	200 mg	Pink	White to off-white
	400 mg	Brown	White to off-white
Weight	**100 mg**	209.6 mg	191.4 mg
	200 mg	394.6 mg	379.1 mg
	400 mg	737.2 mg	737.2 mg
Imprint	**100 mg**	T on one side / 100 mg on the other	Blank on one side / 2241 on either side in a top semi-circle shape around the center
	200 mg	T on one side / 200 mg on the other	Blank on one side / 2242 on either side in a top semi-circle shape around the center
	400 mg	T on one side / 400 mg on the other	Blank on one side / 2243 on either side in a top semi-circle shape around the center
Coating/Release portal		Coated, release portal on one side	Coated, release portal on one side
Image	**100 mg**		
	200 mg		
	400 mg		

C3
ANDAs revised propose PI is **DEFICIENT** (**see below**).

C4
ANDAs revised propose PI is **SATISFACTORY** (**see below**).

Deficiency Comments:

Deficiency # 1

Created in C3

Prescribing Information

DOSAGE AND ADMINISTRATION, **Dosage Information** table

1. Row 6-12 yr; Column Subsequent Dose, Extended-Release Tablets: Revise [redacted] (b) (4) to "Add 100 mg..." to be consistent with the RLD labeling.
2. Widen the cell to ensure the word "day" is not wrapped to the next line for better readability (see yellow highlighted text in the table below).

Dosage Information

	Initial Dose			Subsequent Dose			Maximum Daily Dose		
Indication	Tablet*	Extended-Release Tablets^	Suspension	Tablet*	Extended-Release Tablets^	Suspension	Tablet*	Extended-Release Tablets^	Suspension
Epilepsy Under 6 yr	10-20 mg/kg/day twice a day or 3 times a day		10-20 mg/kg/day 4 times a day	Increase weekly to achieve optimal clinical response, 3 times a day or 4 times a day		Increase weekly to achieve optimal clinical response, 3 times a day or 4 times a day	35 mg/kg/24 hr (see Dosage and Administration section above)		35 mg/kg/24 hr (see Dosage and Administration section above)

Response / Assessment:

1.

Response: Wording is revised according to the above comment. Revised SPL and Draft Package Insert, in PDF and Word version, are provided in Section 1.14.1.3. A side-by-side comparison of revised labeling with our last submitted labeling is provided in Section 1.14.3.1.

2.

Response: Table columns have been adjusted to ensure words are not wrapped to the next line for readability.

Assessment: **SATISFACTORY**

5.4 MEDICATION GUIDE (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Medication Guide is **up-to-date** with model labeling.
☐	☒	Medication Guide meets **content, format, and font size**.
☐	☒	**Phonetic spelling** of the established/proprietary name is present and correct.
☐	☒	Description of **child-resistant feature**(if also present in HOW SUPPLIED/STORAGE AND HANDLING).
☐	☒	**Revision date and approval statement** appear at the end of the Medication Guide correctly.
☐	☒	Applicant committed to provide a **sufficient number** of Medication Guides.
☐	☒	Applicant included the **1-800-FDA-1088** phone number.
☐	☒	Medication Guide is the same as the model labeling, except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
C3: ANDAs revised proposed MG is **SATISFACTORY** (only minor editorial revisions--**see below**).
Excerpt below from SBS Comparison (C2 vs. C3)

C4: Applicant resubmitted the same revised proposed MG ("Rev. 12/2022") received in C3 (**NO CHANGES** identified), which was found **SATISFACTORY** (**see above**).

Deficiency Comments:

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C4)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☒	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☒	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

Comments for CMC (Issue Opened 9/3/2021, **Reference #47702344**): We note the statement, "Carbamazepine extended-release tablet coating is not absorbed and is excreted in the feces; these coatings may be noticeable in the stool," in the DOSAGE AND ADMNISTRATION section of the PI (5th paragraph, last sentence). Please confirm the [accuracy] of the ANDAs proposed statement.

- Reply from CMC on 9/8/2021 (**RESOLVED**): "According to literature, “A feature of some DDS products is the phenomenon of “ghost tablets” (e.g., Tegretol XR). This occurs when the shell that houses the drug does not disintegrate or become digested, but passes out intact in the stool”. (Wheless, JW et al - A Clinician’s Guide to Oral Extended-Release Drug Delivery Systems in Epilepsy. J Pediatr Pharmacol Ther 2018;23(4):277–292). I believe that the RLD also has the same statement in their package insert on page 38 (36 of 51) of the Annotated Comparison with Listed Drug document..."

Comments for CMC (Issue Opened 2/22/2022, **Reference #49822637**): Per the Applicant's reply to the Quality DRL received on 1/10/2022 (Module 1.12.12 SBS Comparison), we intend to request the Applicant to revise the product descriptions in the HOW SUPPLLIED section for clarity. For example, revise "...one drill hole on one side and imprinted XXXX with black ink on either side in a top semi-circle shape around the center." to "...one drill hole on one side and imprinted with XXXX in black ink on the other side in a top semi-circle shape around the center." Please let us know if you concur or have additional input for consideration.

- Reply from CMC on 2/22/2022 (**RESOLVED**): "I concur with the request changes."

Deficiency Comments:

Susan Rimmel

Digitally signed by Susan Rimmel
Date: 2/17/2023 02:35:01PM
GUID: 57e14a7301fe42aa569d1859f813583c

Ellen Hwang

Digitally signed by Ellen Hwang
Date: 2/17/2023 02:43:00PM
GUID: 5256bdc00002af3bc3fa942a9512a891

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	12/09/2022
ANDA Number(s)	216235
Review Number	3
Applicant Name	Sciecure Pharma Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Carbamazepine Extended-Release Tablets USP, 100 mg, 200 mg, and 400 mg
Proposed Proprietary Name	None
Submission Received Date	May 31, 2022, December 07, 2022
Primary Labeling Reviewer	Susan Rimmel
Secondary Labeling Reviewer	Ellen Hwang

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

TABLE OF CONTENTS

1 LABELING COMMENTS (C3)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C3)

The following comments have been identified by the Division of Labeling Review (DLR) based on your submissions on May 31, 2022, and December 7, 2022. Prior to final approval, the proposed labeling should be clear and precise (grammar, spelling, and formatting) for end users, and accurately reflect the Reference Listed Drug (RLD) information to comply with FDA policies, laws, regulations (i.e., 21 CFR 314.94(a)(8)), official compendia, and relevant guidance.

1. PRESCRIBING INFORMATION
    a. DOSAGE AND ADMINISTRATION, **Dosage Information** table
        1. Row 6-12 yr; Column Subsequent Dose, Extended-Release Tablets: Revise [redacted](b) (4) to "Add 100 mg..." to be consistent with the RLD labeling.
        2. Widen the cell to ensure the word "day" is not wrapped to the next line for better readability (see yellow highlighted text in the table below).

Dosage Information

	Initial Dose			Subsequent Dose			Maximum Daily Dose		
Indication	Tablet*	Extended-Release Tablets[A]	Suspension	Tablet*	Extended-Release Tablets[A]	Suspension	Tablet*	Extended-Release Tablets[A]	Suspension
Epilepsy Under 6 yr	10-20 mg/kg/day twice a day or 3 times a day		10-20 mg/kg/day 4 times a day	Increase weekly to achieve optimal clinical response, 3 times a day or 4 times a day		Increase weekly to achieve optimal clinical response, 3 times a day or 4 times a day	35 mg/kg/24 hr (see Dosage and Administration section above)		35 mg/kg/24 hr (see Dosage and Administration section above)

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.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), 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 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C3)

1.3 POST-APPROVAL REVISIONS (C3)

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

2 INSTRUCTIONS FOR ASSESSMENT (C3)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

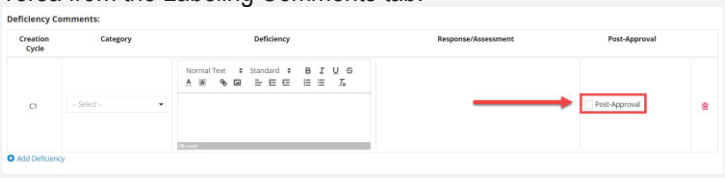
If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.



3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C3)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Draft	100 mg, 200 mg, and 400 mg: 100-count bottles	5/31/2022	Satisfactory
Blister	N/A	N/A		
Carton	N/A	N/A		

Table 2: 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	Rev. 12/2022 ; Code: PI-224	12/7/2022	Revise
Medication Guide	Draft	Rev. 12/2022 ; Code: PI-224	12/7/2022	Satisfactory
Patient Information	N/A	N/A		
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C3)

4.1 REGULATORY INFORMATION (C3)

Yes	No	
☒	☐	Are there any applicable issues in **DLR's SharePoint Drug Facts** ? C1/C2 **Antiepileptic drug pregnancy registry (PR)_North American Antiepileptic Drugs (NAAED) PR** (posted 3/30/2016): "There is a pregnancy registry established for the antiepileptic drugs -North American Antiepileptic Drug (NAAED) Pregnancy Registry. It is an independent program and was not established as a result of a PMR. But given that this pregnancy registry handled by a third party and well respected and well used, ANDAs should have the same information in insert labeling (note the website is updated to http://www.aedpregnancyregistry.org from the old one which is http://www.massgeneral.org/aed/): Patients should be encouraged to enroll in the North American Antiepileptic Drug (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 about the North American Drug Pregnancy Registry can be found at http://www.aedpregnancyregistry.org." "**Update 7/2/2019**: A meeting was held with DPMH on 6/17/2019 to discuss the NAAED and whether ANDAs should continue to include the information about the NAAED PR in their insert labeling. DPMH confirmed that this is a disease-based PR that is run by a well respected organization and has been around for a while. The NDAs are required to include this PR information in their insert labeling by DPMH. We will continue to ask ANDAs to include this PR information to be the same as the RLD. However, we do not need to ask the ANDA holder to confirm that they are registered with this organization for the PR." • **Assessment**: **SATISFACTORY** (ANDAs proposed labeling **includes PR information above** and is **consistent with RLD labeling**) C3 **Antiepileptic drug pregnancy registry (PR)_North American Antiepileptic Drugs (NAAED) PR** (posted 3/30/2016)

Yes	No	
		Brief Description Update 12/2/2022: • Pregnancy Registry (PR) is a third party's PR o Add comment for Cycle 1 or if the PR is new in the NDA labeling o If ANDA included the PR in labeling, we should comment for the ANDA applicant to reach out to third party and verify that the data for the generic product will be accepted as part of the PR (data might be collected for some generic products but not others). If it is verified that the data for the generic product will be accepted, the ANDA applicant can continue to include the PR in labeling. If data for the generic product will not be accepted, the ANDA applicant should remove the PR in labeling. ▪ Example comment to include in SCD: *The reference listed drug (RLD) for your drug product contains third party pregnancy registry information in its labeling. Please reach out to the third party to verify if the data for your generic drug product will be accepted as part of their pregnancy registry. If it is verified that the data for your generic drug product will be accepted by the third party, you can continue including the pregnancy registry information in your labeling. If it is determined that the data for your generic drug product will not be accepted by the third party, please remove the pregnancy registry information in your labeling.* o If ANDA did not include PR in labeling, we should comment for the ANDA applicant to reach out to third party and determine if the data for the generic product will be accepted as part of the PR. If it is verified that the data for the generic product will be accepted, the ANDA applicant should include the PR in labeling. If data for the generic product will not be accepted, the ANDA applicant can continue to exclude the PR. ▪ Example comment to include in SCD: *The reference listed drug (RLD) for your drug product contains third party pregnancy registry information in its labeling. Please reach out to the third party to verify if the data for your generic drug product will be accepted as part of their pregnancy registry. If it is verified that the data for your generic drug product will be accepted by the third party, please include the pregnancy registry information in your labeling. If it is determined that the data for your generic drug product will not be accepted by the third party, you can continue excluding the pregnancy registry information in your labeling.* Assessment: Comment above is for issuance during C1 and not applicable for this review cycle. **See C1/C2 above.**
☐	☒	Is the drug product listed in the Policy Alert Tracker on **OGD's SharePoint**?

4.2 MODEL PRESCRIBING INFORMATION (C3)

Table 3: Review Model Labeling for Prescribing Information/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): 020234 / S-047

Supplement Approval Date: 03/20/2018

Proprietary Name: Tegretol-XR

Established Name: carbamazepine extended-release tablets

Description of Supplement:

"This Prior Approval supplemental new drug application provides for changes to the labeling that were derived from a comprehensive analysis of historical information collected for Tegretol, resulting in an update to the Warnings, Precautions, Drug Interactions, Usage in Pregnancy, Adverse Reactions, and Dosage and Administration sections of the USPI."

Link: https://analytics.fda.gov/workspace/hubble/external/object/v0/application-placeholder-ac1a35?application_number=NDA020234

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

☒ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

C1/C2

Other Approved RLD Supplements (no impact on labeling)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)

- **S-048** (CMC submission **approved** 04/12/2018): "These "Changes Being Effected in 30 days" supplemental new drug applications provide for the addition of (b) (4) [**Note**: Approval Letter under NDA-016608-SUPPL-117.]
- **S-049** (CMC submission **approved** 04/22/2020): "This "Changes Being Effected in 30 days" supplemental new drug application provides the addition (b) (4) "
- **S-050** (CMC submission **approved** 08/20/2020): "This "Changes Being Effected in 30 days" supplemental new drug application provides for updates to the specification for the drug product Tegretol XR Tablets and the authorized generic Carbamazepine ER Tablets including changes to (b) (4)
- **S-051** (CMC submission **approved** 08/26/2020): "These "Changes Being Effected" supplemental new drug applications provide for updates (b) (4) ." [**Note**: Approval Letter under NDA-016608-SUPPL-119.]

C3

Other RLD Supplements

Supplement-52	Manufacturing (CMC)	CDER/OPQ/OPRO/DRBPMIII	Approved	10/28/2022

- **IMPACTS CONTAINER LABELS ONLY** (see Section 4.5 below)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.

Reviewer Comments:

The RLDs model labeling is a combined insert but the ANDAs proposed labeling does not carve-out the tablet (chewable and conventional) and oral suspension dosage forms (**see Deficiency in Section 5.4 below**). In addition, the Applicant only provided a PDF version of the PI/MG received on 7/6/2021; however, **no notable differences were identified in the SBS comparison with the Word document received on 5/21/2021**. Thus, the PDF document received on 7/6/2021, was used for the SBS comparison with the RLD model labeling.

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES (C3)

The Orange Book was searched on 12/09/2022

Table 4 provides Orange Book patents for the Model Labeling (NDA 020234) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**Patent Number**	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
	N/A						

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	**Exclusivity Code**	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact**
	N/A					

Reviewer Assessment:

Deficiency	**No Deficiency**	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.
Reviewer Comments: **Deficiency Comments:**		

4.4 UNITED STATES PHARMACOPEIA (USP) (C3)

The USP was searched on 08/13/2021

Table 6: USP				
	YES or NO	**Date**	**Monograph Title (N/A if no monograph)**	**Packaging and Storage/Labeling Statements (N/A if no monograph)**
Currently Official	Yes		Carbamazepine Extended-Release Tablets	•Packaging and Storage: Preserve in tight containers, and store at controlled room temperature. Add the following: ▲ •Labeling: The labeling states the Dissolution test used only if Test 1 is not used.▲ (RB 1-May-2020)

Table 6: USP				
	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☐	☒	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.

Reviewer Comments:

C1: There are 2 Dissolution Tests in the USP monograph for the drug product (*Official as of 1-May-2020*); however, the DP and BE Reviews are pending (**see Section 5.1.1 below**). Notably, the ANDAs proposed labeling states, (b) (4) See Deficiencies in Section 5.3 below.

C2

USP Descriptor: See Section 5.3 below.

Biopharmaceutics Review (Reference #46432792, 11/3/2021): **INADEQUATE - MINOR**

Biopharmaceutics Executive Summary	
The Applicant proposed USP monograph dissolution method (Test 1) for carbamazepine ER tablets (Apparatus I at 100 rpm, 900 mL (for the 100 mg and 200 mg strengths) or 1800 mL (for the 400 mg strength) of Water). The Applicant's proposed dissolution acceptance criteria is same as USP test 1. The adequacy of the dissolution method and acceptance criteria is pending Applicant's response to the IRs.	
Has OGD deemed the drug product BE to the RLD?	Yes

C2 Biopharmaceutics Review is pending.

C3

USP Descriptor: Applicant **removed USP descriptor from header title and not product title in the FPI** (**see excerpt below**); however, labeling is in non-PLR format and acceptable for the purposes of DLRs review at this time.

Excerpt below from ANDAs Revised Proposed PI

Carbamazepine Extended-Release Tablets

Sciecure Pharma Inc.

Carbamazepine Extended-Release Tablets, USP

Biopharmaceutics Review (Reference #51115774, 12/8/2022): **ADEQUATE**

Biopharmaceutics Executive Summary	
The Biopharmaceutics review focused on the assessment of proposed dissolution method, dissolution acceptance criteria, and the in-vitro in-vivo correlation (IVIVC) data. The Applicant proposed USP monograph dissolution method (Test 1) for carbamazepine ER tablets which is acceptable based on the method development report and submitted data. The proposed dissolution acceptance criteria are permissive for the drug product and not acceptable. The Applicant submitted an IVIVC report to demonstrate that revised USP dissolution acceptance criteria will be able to reject product that is not bioequivalent to the reference-target drug product. The IVIVC study, however, was deemed not acceptable because of incomplete data/justification provided. Therefore, the Agency recommended to revise the acceptance criteria based on the bio-batch data which the Applicant has accepted. The Applicant was requested to petition the USP for the revised acceptance criteria which the applicant has initiated. The submission is adequate from Biopharmaceutics perspective.	
Has OGD deemed the drug product BE to the RLD?	Yes

Deficiency Comments:

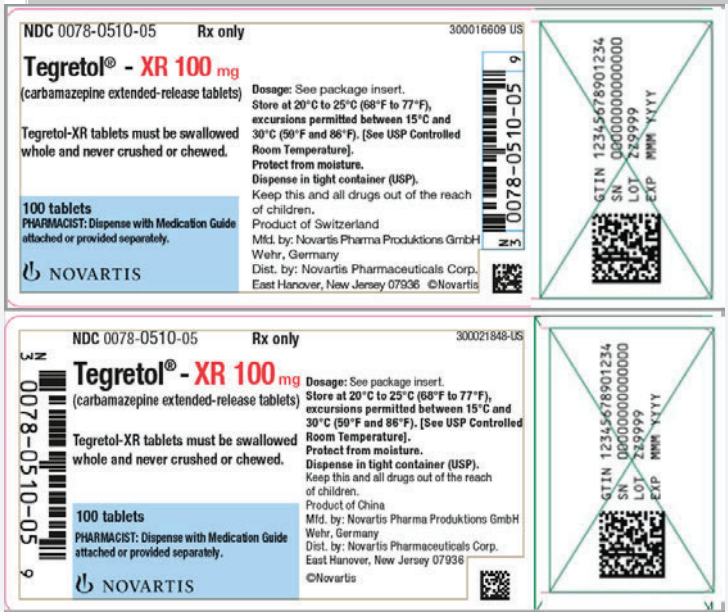
4.5 MODEL CONTAINER LABELS (C3)

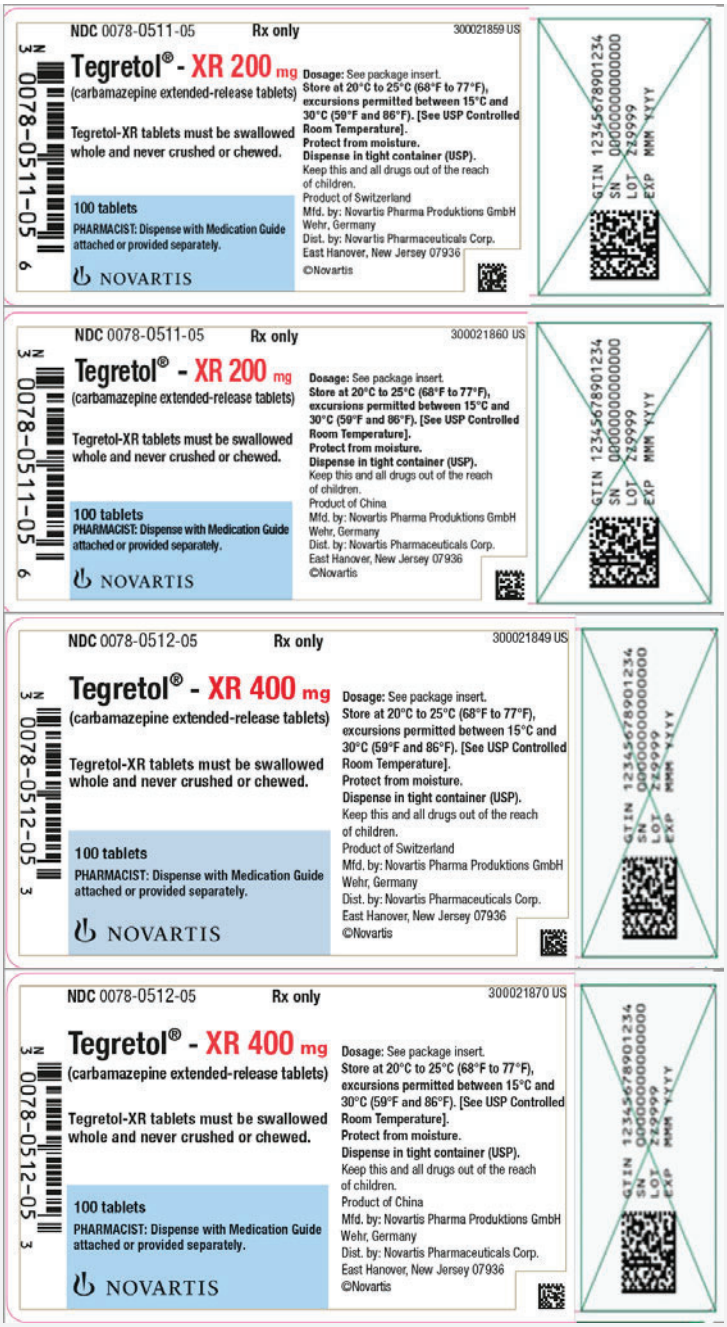
Model container/carton/blister labels (Source: Various--see below. **)**

Approved (Source: S-052, DRAFT received in EDR 5/18/2022, approved 10/28/2022)
Note: Only container labels were revised in S-052, which are not posted on Drugs@FDA.
Excerpt below from Approval Letter in Panorama

This "Changes Being Effected in 30 days" supplemental new drug application provides for multiple changes including the following:

(b) (4)





Marketed NDA Authorized Generic

Source: ANRPT-25, FINAL, 5/19/2021

Source: ANRPT-24, FINAL, 5/20/2020

5 ASSESSMENT OF ANDA LABELING AND LABELS (C3)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C3)

5.1.1 DRUG PRODUCT REVIEW (C3)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review complete

C2

DP Review (Reference #46432772)

11/8/2021: **INDADEQUATE - MINOR**

Labeling	
Description Section	
Is the information accurate?	Yes
Is the drug product subject of a USP monograph?	Yes
Does the labeling need a special USP statement in the Description?	No
How Supplied Section	
Is the information accurate?	Yes
Are the storage conditions acceptable?	Yes
Dosage and Administration Section	
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	N/A

For Solid Oral Drug Product:		
ANDA Strength	**Length(mm)**	**Imprint Code**
Carbamazepine 100mg	8	2241 on one side only
Carbamazepine 200mg	10	2242 on one side only
Carbamazepine 400mg	12	2243 on one side only
Is the imprint code consistent with the labeling?	Yes	

Any issue(s) sent to and/or received from the OGD Labeling Reviewer?	**No**

2/18/2022
Drug Substance: **ADEQUATE**
Drug Product: **INDADEQUATE - MINOR**

Labeling	
Description Section	
Is the information accurate?	Yes
Is the drug product subject of a USP monograph?	Yes
Does the labeling need a special USP statement in the Description?	No
How Supplied Section	
Is the information accurate?	Yes
Are the storage conditions acceptable?	Yes
Dosage and Administration Section	
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	N/A

For Solid Oral Drug Product:		
ANDA Strength	**Length(mm)**	**Imprint Code**
Carbamazepine 100mg	8	2241 on one side only
Carbamazepine 200mg	10	2242 on one side only
Carbamazepine 400mg	12	2243 on one side only
Is the imprint code consistent with the labeling?	Yes	

Any issue(s) sent to and/or received from the OGD Labeling Reviewer?	**No**

C3

DP Review (Reference #51115754, 12/2/2022): **ADEQUATE**

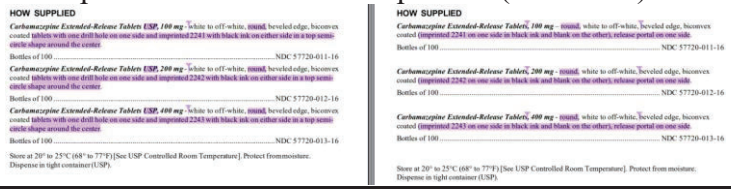
5.1.2 DESCRIPTION (C3)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	PI Tegretol-XR tablets: cellulose compounds, dextrates, iron oxides, magnesium stearate, mannitol, polyethylene glycol, sodium lauryl sulfate, titanium dioxide (200 mg tablets only). MG **What are the ingredients in TEGRETOL?** Active ingredient: carbamazepine Inactive ingredients: • **TEGRETOL-XR Tablets:** cellulose compounds, dextrates, iron oxides, magnesium stearate, mannitol, polyethylene glycol, sodium lauryl sulfate, titanium dioxide (200 mg tablets only).
Previous ANDA Labeling	PI *Inactive Ingredients:* Hypromellose, hydroxyethyl cellulose, cellulose acetate, polyethylene glycol, mannitol, dextrates, sodium lauryl sulfate, and magnesium stearate. Each tablet is printed with Opacode Black S-1-17823 ink which contains ammonium hydroxide, iron oxide black, isopropyl alcohol, n-butyl alcohol, propylene glycol and shellac. MG **What are the ingredients in Carbamazepine Extended-Release Tablets?** Active ingredient: carbamazepine, USP Inactive ingredients: Hypromellose, hydroxyethyl cellulose, cellulose acetate, polyethylene glycol mannitol, dextrates, sodium lauryl sulfate, magnesium stearate. Each tablet is printed with Opacode Black S-1-17823 ink which contains ammonium hydroxide, iron oxide black, isopropyl alcohol, n-butyl alcohol, propylene glycol and shellac. Assessment: **NO CHANGE**
Current ANDA Labeling	PI *Inactive Ingredients:* Hypromellose, hydroxyethyl cellulose, cellulose acetate, polyethylene glycol, mannitol, dextrates, sodium lauryl sulfate, and magnesium stearate. Each tablet is printed with Opacode Black S-1-17823 ink which contains ammonium hydroxide, iron oxide black, isopropyl alcohol, n-butyl alcohol, propylene glycol and shellac. FDA approved dissolution test specifications differ from USP. MG **What are the ingredients in Carbamazepine Extended-Release Tablets?** Active ingredient: carbamazepine USP Inactive ingredients: Hypromellose, hydroxyethyl cellulose, cellulose acetate, polyethylene glycol mannitol, dextrates, sodium lauryl sulfate, magnesium stearate. Each tablet is printed with Opacode Black S-1-17823 ink which contains ammonium hydroxide, iron oxide black, isopropyl alcohol, n-butyl alcohol, propylene glycol and shellac. Assessment: **SATISFACTORY** for the PI (added dissolution statement--see Section 4.4 above) and MG (minor editorial revisions--**see below**). Excerpt below from SBS Comparison (C2 vs. C3) 

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C3)

Table 8: Comparison of Model Labeling to ANDA Labeling

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	PI ***Chewable Tablets 100 mg*** **-** round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side) Bottles of 100 ..... NDC 0078-0492-05 Unit Dose (blister pack) Box of 100 (strips of 10) ..... NDC 0078-0492-35 Do not store above 30°C (86°F). *Protect from light and moisture.* *Dispense in tight, light-resistant container (USP).* *Meets USP Dissolution Test 1.* ***Tablets 200 mg*** **-** capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the partially scored side) Bottles of 100 ..... NDC 0078-0509-05 Bottles of 60 ..... NDC 0078-0509-20 Do not store above 30°C (86°F). *Protect from moisture.* *Dispense in tight container (USP).* *Meets USP Dissolution Test 2.* ***XR Tablets 100 mg*** **-** round, yellow, coated (imprinted T on one side and 100 mg on the other), release portal on one side Bottles of 100 ..... NDC 0078-0510-05 ***XR Tablets 200 mg*** **-** round, pink, coated (imprinted T on one side and 200 mg on the other), release portal on one side Bottles of 100 ..... NDC 0078-0511-05 ***XR Tablets 400 mg*** **-** round, brown, coated (imprinted T on one side and 400 mg on the other), release portal on one side Bottles of 100 ..... NDC 0078-0512-05 Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) *Protect from moisture.* *Dispense in tight container (USP).* ***Suspension 100 mg/5 mL (teaspoon)*** – yellow-orange, citrus-vanilla flavored Bottles of 450 mL ..... NDC 0078-0508-83 Shake well before using. Do not store above 30°C (86°F). *Dispense in tight, light-resistant container (USP).*| MG **How should I store TEGRETOL?** • Do not store **TEGRETOL Tablets** above 30°C (86°F). • Keep TEGRETOL Tablets dry. • Do not store **TEGRETOL Chewable Tablets** above 30°C (86°F). • Keep TEGRETOL Chewable Tablets out of the light. • Keep TEGRETOL Chewable Tablets dry. • Store **TEGRETOL-XR Tablets** at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). • Keep TEGRETOL-XR Tablets dry. • Do not store **TEGRETOL Suspension** above 30°C (86°F). • Shake well before using. • Keep TEGRETOL Suspension in a tight, light-resistant container. **Keep TEGRETOL and all medicines out of the reach of children.**
Previous ANDA Labeling	PI ***Carbamazepine Extended-Release Tablets USP, 100 mg*** **-** white to off-white, round, beveled edge, biconvex coated tablets with one drill hole on one side and imprinted 2241 with black ink on either side in a top semi-circle shape around the center. Bottles of 100 ..... NDC 57720-011-16 ***Carbamazepine Extended-Release Tablets USP, 200 mg*** **-** white to off-white, round, beveled edge, biconvex coated tablets with one drill hole on one side and imprinted 2242 with black ink on either side in a top semi-circle shape around the center. Bottles of 100 ..... NDC 57720-012-16 ***Carbamazepine Extended-Release Tablets USP, 400 mg*** **-** white to off-white, round, beveled edge, biconvex coated tablets with one drill hole on one side and imprinted 2243 with black ink on either side in a top semi-circle shape around the center. Bottles of 100 ..... NDC 57720-013-16 Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from moisture. Dispense in tight container (USP). MG **How should I store Carbamazepine Extended-Release Tablets?** • Store Carbamazepine Extended-Release Tablets at 20° to 25°C (68° to 77°F). • Keep Carbamazepine Extended-Release Tablets dry. **Keep Carbamazepine Extended-Release Tablets and all medicines out of the reach of children.** Assessment: **DEFICIENT** (revised per C1 deficiencies--see Sections 5.3 and 5.4

Table 8: Comparison of Model Labeling to ANDA Labeling	
	below--but descriptions in the PI can be improved for clarity)
Current ANDA Labeling	PI ***Carbamazepine Extended-Release Tablets, 100 mg*** – round, white to off-white, beveled edge, biconvex coated (imprinted 2241 on one side in black ink and blank on the other), release portal on one side. Bottles of 100 ..... NDC 57720-011-16 ***Carbamazepine Extended-Release Tablets, 200 mg*** - round, white to off-white, beveled edge, biconvex coated (imprinted 2242 on one side in black ink and blank on the other), release portal on one side. Bottles of 100 ..... NDC 57720-012-16 ***Carbamazepine Extended-Release Tablets, 400 mg*** - round, white to off-white, beveled edge, biconvex coated (imprinted 2243 on one side in black ink and blank on the other), release portal on one side. Bottles of 100 ..... NDC 57720-013-16 Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from moisture. Dispense in tight container (USP). MG **How should I store Carbamazepine Extended-Release Tablets?** • Store Carbamazepine Extended-Release Tablets at 20° to 25°C (68° to 77°F). • Keep Carbamazepine Extended-Release Tablets dry. **Keep Carbamazepine Extended-Release Tablets and all medicines out of the reach of children.** Assessment: **SATISFACTORY** for the PI (revised in alignment with the RLD--**see below** and Section 5.3 below) and **NO CHANGE** for the MG. Excerpt below from SBS Comparison (C2 vs. C3) 

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C3)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	Source: FORM FDA 356h, 1/10/2022 **APPLICANT INFORMATION** 2. Name of Applicant: Sciecure Pharma Inc. 3. Telephone Number (Include country code if applicable and area code): 732-329-8089 (b) (4) 4. Facsi... code i 5. Applicant Address Address 1 (Street address, P.O. box, company name c/o): 11 Deer Park Drive Address 2 (Apartment, suite, unit, building, floor, etc.): Unit 120 City: Monmouth Junction State/Province/Region: New Jersey Country: USA ZIP or Postal Code: 08852

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
	Establishment Name Beijing Sciecure Pharmaceutical Co. Ltd. Address 1 *(Street address, P.O. box, company name c/o)* Zhongbei Industrial Park, Beishicao Town, Shunyi District Address 2 *(Apartment, suite, unit, building, floor, etc.)* City: Beijing; State/Province/Region: N/A Country: China; ZIP or Postal Code: 101301 Is the establishment new to the application? ☑ Yes ☐ No; What is the status of the ☑ Pending (b) (4) [redacted] Container Labels Manufactured by: Beijing Sciecure Pharmaceutical Co., Ltd., Shunyi District, Beijing 101301, China Manufactured for: Sciecure Pharma Inc., Monmouth Junction, NJ 08852 PI/MG **Manufactured by:** Beijing Sciecure Pharmaceutical Co., Ltd., Beijing, China **Manufactured for:** Sciecure Pharma Inc. Monmouth Junction, New Jersey 08852 Assessment: **NO CHANGE**
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Source: FORM FDA 356h, 12/7/2022

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

APPLICANT INFORMATION	2. Name of Applicant
	Sciecure Pharma Inc.

3. Telephone Number *(Include country code if applicable and area code)*	4. Facsi
732-329-8089 (b) (4)	*code i*

5. Applicant Address

Address 1 *(Street address, P.O. box, company name c/o)*	
11 Deer Park Drive	
Address 2 *(Apartment, suite, unit, building, floor, etc.)*	
Unit 120	
City: Monmouth Junction	State/Province/Region: New Jersey
Country: USA	ZIP or Postal Code: 08852

Establishment Name		
Beijing Sciecure Pharmaceutical Co. Ltd.		
Address 1 *(Street address, P.O. box, company name c/o)*		
Zhongbei Industrial Park, Beishicao Town, Shunyi District		
Address 2 *(Apartment, suite, unit, building, floor, etc.)*		
City: Beijing	State/Province/Region: N/A	
Country: China	ZIP or Postal Code: 101301	
Is the establishment new to the application? ☑ Yes ☐ No	What is the status of the ☑ Pending	

(b) (4)

Container Labels

Manufactured by:
Beijing Sciecure Pharmaceutical Co., Ltd.,
Shunyi District, Beijing 101301, China

Manufactured for:
Sciecure Pharma Inc.,
Monmouth Junction, NJ 08852

PI/MG

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
	Manufactured by: Beijing Sciecure Pharmaceutical Co., Ltd., Beijing, China **Manufactured for:** Sciecure Pharma Inc. Monmouth Junction, New Jersey 08852 Assessment: **NO CHANGE**

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		ESTABLISHED/PROPRIETARY NAME and STRENGTH:
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
		THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number:** prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
		PRODUCT DIFFERENTIATION:
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
		STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR

Deficiency	No Deficiency	
		201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
OVERALL ASSESSMENT:		
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

(b) (4)

Description of Container Closure (Source: Module 3.2.P.7 Container Closure System, 5/21/2021)

Table 1. Summary of Packaging Configuration

Strength	100 mg	200 mg	400 mg
Count/ Bottle	100 tablets	100 tablets	100 tablets
Container	75cc HDPE bottle	75cc HDPE bottle	120cc HDPE bottle
Closure	(b) (4) CRC cap	(b) (4) CRC cap	(b) (4) CRC cap
	(b) (4)		
Dunnage	N/A	N/A	N/A

The proposed container closure system is child resistant.

C3

ANDAs revised proposed container label is **SATISFACTORY** (**see below**).

Deficiency Comments:

Deficiency # 1

Created in C2

Container Label

Relocate the precautionary statement, "Carbamazepine Extended-Release Tablets must be swallowed whole and never crushed or chewed.", to the principal display panel to be consistent with the Reference Listed Drug (RLD) labeling. Ensure to use a method to increase the prominence of the precautionary statement (e.g., boxing, contrasting colors, and/or some other means).

Response / Assessment:

Response:

The precautionary statement, "Carbamazepine Extended-Release Tablets must be swallowed whole and never crushed or chewed.", has been moved to the principal display panel. The precautionary statement has been boxed and bolded to increase the prominence. The revised container labels can be found in Module 1.14.1.1.

Assessment: **SATISFACTORY**

5.3 PRESCRIBING INFORMATION (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at end of HIGHLIGHTS section.
	DESCRIPTION/INACTIVE INGREDIENTS:	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐Sulfite (21 CFR 201.22) ☐Yellow #5 (Tartrazine) (21 CFR 201.20) ☐Phenylalanine/aspartame (21 CFR 201.21) ☐Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Gluten** statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	**Dosage form and route** of administration properly listed [21 CFR 201.57(c)(12)(B)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☐	☒	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☒	☐	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:
C1

See Internal Observations in Section 5.2 above.

Internal Observations (not provided to Applicant)

Physical Description (Source: **Module 3.2.P.1** Description and Composition of the Drug Product, 5/21/2021)

3.2.P.1.1 Composition and Dosage Form

Carbamazepine Extended-Release Tablets USP, 100 mg, 200 mg and 400 mg are bi-convex coated tablets, rounded beveled edges, with one drill hole on one side and printed "2241", "2242", "2243" on either side in a top semi-circle shape around the center for 100 mg, 200 mg and 400 mg strengths, respectively.

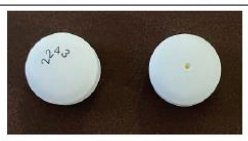
The physical description of the tablets in the Quality submission is inconsistent with the PI (**see Section 5.1.3 above**) and it appears the Applicant has not provided images of their proposed drug product, which is a review issue. See Deficiency below.

C2

Reply to Quality DRL (Source: Module 1.12.12 SBS Comparison, 1/10/2022)

Table 1. Side by Side comparison of RLD vs. Generic Information

		Tegretol®-XR (carbamazepine extended-release tablets), 100 mg, 200 mg, and 400 mg	**Carbamazepine Extended-Release Tablets, USP 100 mg, 200 mg, and 400 mg**
Conditions of Use		Indicated for the treatment of pain associated with trigeminal neuralgia and therapeutic relief of epilepsy.	Indicated for the treatment of pain associated with trigeminal neuralgia and therapeutic relief of epilepsy.
Active Ingredient		Carbamazepine	Carbamazepine
Dosage Form		Tablet, extended release	Tablet, extended release
Route of Administration		Oral	Oral
Size	**100 mg**	8 mm	8 mm
	200 mg	10 mm	10 mm
	400 mg	12 mm	12 mm
Strength		100 mg, 200 mg, and 400 mg	100 mg, 200 mg, and 400 mg
Shape		Round	Round, bi-convex, beveled edges
Color	**100 mg**	Yellow	White to off-white
	200 mg	Pink	White to off-white
	400 mg	Brown	White to off-white

Weight	**100 mg**	209.6 mg	191.4 mg
	200 mg	394.6 mg	379.1 mg
	400 mg	737.2 mg	737.2 mg
Imprint	**100 mg**	T on one side / 100 mg on the other	Blank on one side / 2241 on either side in a top semi-circle shape around the center
	200 mg	T on one side / 200 mg on the other	Blank on one side / 2242 on either side in a top semi-circle shape around the center
	400 mg	T on one side / 400 mg on the other	Blank on one side / 2243 on either side in a top semi-circle shape around the center
Coating/Release portal		Coated, release portal on one side	Coated, release portal on one side
Image	**100 mg**		
	200 mg		
	400 mg		

C3

ANDAs revised propose PI is **DEFICIENT** (**see below**).

Deficiency Comments:

Deficiency # 1

Created in C2

Prescribing Information

Response / Assessment:

Product Title: Remove the "USP" descriptor, such as "Carbamazepine Extended-Release Tablets".

Response:

a. The "USP" descriptor has been removed from the Product Title.

Assessment: **SATISFACTORY** (reference Section 4.4 above)

Deficiency # 2

Created in C2

Prescribing Information

Response / Assessment:

DESCRIPTION, 3rd paragraph, 1st sentence: Revise (b) (4) to "Each Carbamazepine Extended-Release Tablet intended for oral administration contains 100 mg, 200 mg, or 400 mg of carbamazepine." (note "and 400 mg" is revised to "or 400 mg" for clarity).

Response

b. DESCRIPTION, 3rd paragraph, 1st sentence has been revised to "Each Carbamazepine Extended-Release Tablet intended for oral administration contains 100 mg, 200 mg, or 400 mg of carbamazepine."

Assessment: **SATISFACTORY**

Deficiency # 3 Created in C2 Prescribing Information	PRECAUTIONS (note the cross-references are removed, as your revised proposed labeling removed the referenced information in the corresponding section) 1. **General**, 6th paragraph: Revise "[redacted] (b) (4) [redacted] (see DOSAGE AND ADMINISTRATION)." to "Since a given dose...unwanted side effects." 2. **Drug Interactions**, 1st paragraph, last sentence: Revise [redacted] (b) (4) [redacted] (see DOSAGE AND ADMINISTRATION)." to "Because the extent...or diluents."
Response / Assessment:	Response c. PRECAUTIONS (note the cross-references are removed, as your revised proposed labeling removed the referenced information in the corresponding section) 1. General, 6th paragraph: "(see DOSAGE AND ADMINISTRATION)." has been removed to read "Since a given dose...unwanted side effects." 2. Drug Interactions, 1st paragraph, last sentence: "(see DOSAGE AND ADMINISTRATION)." has been removed to read "Because the extent...or diluents." Assessment: **SATISFACTORY**
Deficiency # 4 Created in C2 Prescribing Information	DOSAGE AND ADMINISTRATION, **Epilepsy** 1. ***Children 6 to 12 years of age-Initial***, 1st sentence: Revise [redacted] (b) (4) [redacted] to "100 mg twice a day for Carbamazepine Extended-Release Tablets (200 mg/day)." to be consistent with the RLD labeling. 2. ***Children under 6 years of age-Initial***, 1st sentence: [redacted] (b) (4) [redacted] to "10 to 20 mg/kg/day twice a day or three times a day as tablets (chewable or conventional), or four times a day as suspension." for clarity and to minimize misuse of your proposed drug product.
Response / Assessment:	Response d. DOSAGE AND ADMINISTRATION, Epilepsy 1. Children 6 to 12 years of age-Initial, 1st sentence: has been revised to "100 mg twice a day for Carbamazepine Extended-Release Tablets (200 mg/day)." to be consistent with the RLD labeling. 2. Children under 6 years of age-Initial, 1st sentence: has been revised to "10 to 20 mg/kg/day twice a day or three times a day as tablets (chewable or conventional), or four times a day as suspension.". Assessment: **SATISFACTORY**
Deficiency # 5 Created in C2 Prescribing Information	DOSAGE AND ADMINISTRATION, **Dosage Information** table: Widen the cell(s), where applicable, to ensure words (e.g., intervals, increments, etc.) are not wrapped to the next line for better readability.
Response / Assessment:	Response

	e. DOSAGE AND ADMINISTRATION, Dosage Information table: the cell(s) were widened to ensure words (e.g., intervals, increments, etc.) are not wrapped to the next line for better readability. Assessment: **DEFICIENT** (**see below**).
Deficiency # 6 Created in C2 Prescribing Information Response / Assessment:	HOW SUPPLIED, each strength: Revise your product descriptions for clarity. For example, revise [redacted] (b) (4) to "...one drill hole on one side and imprinted with XXXX in black ink on the other side in a top semi-circle shape around the center." Response f. HOW SUPPLIED, each strength: the product descriptions has been revised for clarity. The product descriptions have been revised to read "**... (imprinted XXXX on one side in black ink and blank on the other), release portal on one side.**" Assessment: **SATISFACTORY** (revised in alignment with RLD labeling--see Section 5.1.3 above).
Deficiency # 7 Created in C3 Prescribing Information Response / Assessment:	DOSAGE AND ADMINISTRATION, **Dosage Information** table 1. Row 6-12 yr; Column Subsequent Dose, Extended-Release Tablets: Revise "[redacted] (b) (4) to "Add 100 mg..." to be consistent with the RLD labeling. 2. Widen the cell to ensure the word "day" is not wrapped to the next line for better readability (see yellow highlighted text in the table below). **Dosage Information** Initial Dose / Subsequent Dose / Maximum Daily Dose Indication | Tablet* | Extended-Release Tablets^ | Suspension | Tablet* | Extended-Release Tablets^ | Suspension | Tablet* | Extended-Release Tablets^ | Suspension Epilepsy Under 6 yr | 10-20 mg/kg/day twice a day or 3 times a day | | 10-20 mg/kg/day 4 times a day | Increase weekly to achieve optimal clinical response, 3 times a day or 4 times a day | | Increase weekly to achieve optimal clinical response, 3 times a day or 4 times a day | 35 mg/kg/24 hr (see Dosage and Administration section above) | | 35 mg/kg/24 hr (see Dosage and Administration section above)

5.4 MEDICATION GUIDE (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Medication Guide is **up-to-date** with model labeling.
☐	☒	Medication Guide meets **content, format, and font size**.
☐	☒	**Phonetic spelling** of the established/proprietary name is present and correct.
☐	☒	Description of **child-resistant feature**(if also present in HOW SUPPLIED/STORAGE AND HANDLING).
☐	☒	**Revision date and approval statement** appear at the end of the Medication Guide correctly.
☐	☒	Applicant committed to provide a **sufficient number** of Medication Guides.
☐	☒	Applicant included the **1-800-FDA-1088** phone number.
☐	☒	Medication Guide is the same as the model labeling, except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments:		

C3: ANDAs revised proposed MG is **SATISFACTORY** (only minor editorial revisions--**see below**).
Excerpt below from SBS Comparison (C2 vs. C3)

Deficiency Comments:

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C3)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☒	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☒	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

Comments for CMC (Issue Opened 9/3/2021, **Reference #47702344**): We note the statement, "Carbamazepine extended-release tablet coating is not absorbed and is excreted in the feces; these coatings may be noticeable in the stool," in the DOSAGE AND ADMNISTRATION section of the PI (5th paragraph, last sentence). Please confirm the [accuracy] of the ANDAs proposed statement.

- Reply from CMC on 9/8/2021 (**RESOLVED**): "According to literature, “A feature of some DDS products is the phenomenon of “ghost tablets” (e.g., Tegretol XR). This occurs when the shell that houses the drug does not disintegrate or become digested, but passes out intact in the stool”. (Wheless, JW et al - A Clinician’s Guide to Oral Extended-Release Drug Delivery Systems in Epilepsy. J Pediatr Pharmacol Ther 2018;23(4):277–292). I believe that the RLD also has the same statement in their package insert on page 38 (36 of 51) of the Annotated Comparison with Listed Drug document..."

Comments for CMC (Issue Opened 2/22/2022, **Reference #49822637**): Per the Applicant's reply to the Quality DRL received on 1/10/2022 (Module 1.12.12 SBS Comparison), we intend to request the Applicant to revise the product descriptions in the HOW SUPPLLIED section for clarity. For example, revise "...one drill hole on one side and imprinted XXXX with black ink on either side in a top semi-circle shape around the center." to "...one drill hole on one side and imprinted with XXXX in black ink on the other side in a top semi-circle shape around the center." Please let us know if you concur or have additional input for consideration.

- Reply from CMC on 2/22/2022 (**RESOLVED**): "I concur with the request changes."

Deficiency Comments:

Susan Rimmel

Digitally signed by Susan Rimmel
Date: 12/20/2022 03:53:12PM
GUID: 57e14a7301fe42aa569d1859f813583c

Ellen Hwang

Digitally signed by Ellen Hwang
Date: 12/20/2022 03:54:25PM
GUID: 5256bdc00002af3bc3fa942a9512a891

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	02/03/2022
ANDA Number(s)	216235
Review Number	2
Applicant Name	Sciecure Pharma Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Carbamazepine Extended-Release Tablets USP, 100 mg, 200 mg, and 400 mg
Proposed Proprietary Name	None
Submission Received Date	September 28, 2021
Primary Labeling Reviewer	Susan Rimmel
Secondary Labeling Reviewer	Ellen Hwang

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

TABLE OF CONTENTS

1 LABELING COMMENTS (C2)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C2)

Labeling deficiencies based on your submission received September 28, 2021:

1. CONTAINER LABEL
    a. Relocate the precautionary statement, "Carbamazepine Extended-Release Tablets must be swallowed whole and never crushed or chewed.", to the principal display panel to be consistent with the Reference Listed Drug (RLD) labeling. Ensure to use a method to increase the prominence of the precautionary statement (e.g., boxing, contrasting colors, and/or some other means).
2. PRESCRIBING INFORMATION
    a. Product Title: Remove the (b) (4) descriptor, such as "Carbamazepine Extended-Release Tablets".
    b. DESCRIPTION, 3rd paragraph, 1st sentence: Revise (b) (4) to "Each Carbamazepine Extended-Release Tablet intended for oral administration contains 100 mg, 200 mg, or 400 mg of carbamazepine." (note "and 400 mg" is revised to "or 400 mg" for clarity).
    c. PRECAUTIONS (note the cross-references are removed, as your revised proposed labeling removed the referenced information in the corresponding section)
        1. **General**, 6th paragraph: Revise "(b) (4) (see DOSAGE AND ADMINISTRATION)." to "Since a given dose...unwanted side effects."
        2. **Drug Interactions**, 1st paragraph, last sentence: Revise (b) (4) (see DOSAGE AND ADMINISTRATION)." to "Because the extent...or diluents."
    d. DOSAGE AND ADMINISTRATION, **Epilepsy**
        1. ***Children 6 to 12 years of age-Initial***, 1st sentence: Revise (b) (4) to "100 mg twice a day for Carbamazepine Extended-Release Tablets (200 mg/day)." to be consistent with the RLD labeling.
        2. ***Children under 6 years of age-Initial***, 1st sentence: (b) (4) to "10 to 20 mg/kg/day twice a day or three times a day as tablets (chewable or conventional), or four times a day as suspension." for clarity and to minimize misuse of your proposed drug product.
    e. DOSAGE AND ADMINISTRATION, **Dosage Information** table: Widen the cell(s), where applicable, to ensure words (e.g., intervals, increments, etc.) are not wrapped to the next line for better readability.
    f. HOW SUPPLIED, each strength: Revise your product descriptions for clarity. For example, revise (b) (4) to "...one drill hole on one side and imprinted with XXXX in black ink on the other side in a top semi-circle shape around the center."

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.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), 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 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C2)

1.3 POST-APPROVAL REVISIONS (C2)

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

2 INSTRUCTIONS FOR ASSESSMENT (C2)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

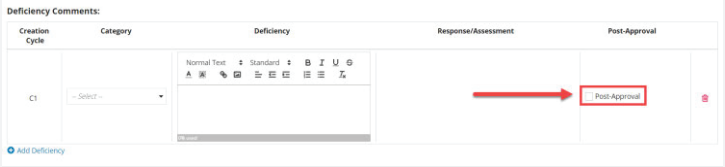
If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has **expired** and the applicant needs to revise labeling.

Reviewer Comments:
Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the DLR Standardized Comments SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.



3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C2)

Table 1: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Draft	100 mg, 200 mg, and 400 mg: 100-count bottles	9/28/2021	Revise
Blister	N/A	N/A		
Carton	N/A	N/A		

Table 2: 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	Rev. 09/2021 ; Code: PI-224	9/28/2021	Revise
Medication Guide	Draft	Rev. 09/2021 ; Code: PI-224	9/28/2021	Satisfactory
Patient Information	N/A	N/A		
Instructions for Use	N/A	N/A		
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C2)

4.1 REGULATORY INFORMATION (C2)

Yes	No	
☒	☐	Are there any applicable issues in **DLR's SharePoint Drug Facts** ? C1 **Antiepileptic drug pregnancy registry (PR)_North American Antiepileptic Drugs (NAAED) PR** (posted 3/30/2016): "There is a pregnancy registry established for the antiepileptic drugs -North American Antiepileptic Drug (NAAED) Pregnancy Registry. It is an independent program and was not established as a result of a PMR. But given that this pregnancy registry handled by a third party and well respected and well used, ANDAs should have the same information in insert labeling (note the website is updated to http://www.aedpregnancyregistry.org from the old one which is http://www.massgeneral.org/aed/): Patients should be encouraged to enroll in the North American Antiepileptic Drug (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 about the North American Drug Pregnancy Registry can be found at http://www.aedpregnancyregistry.org." "**Update 7/2/2019**: A meeting was held with DPMH on 6/17/2019 to discuss the NAAED and whether ANDAs should continue to include the information about the NAAED PR in their insert labeling. DPMH confirmed that this is a disease-based PR that is run by a well respected organization and has been around for a while. The NDAs are required to include this PR information in their insert labeling by DPMH. We will continue to ask ANDAs to include this PR information to be the same as the RLD. However, we do not need to ask the ANDA holder to confirm that they are registered with this organization for the PR." • **Assessment**: SATISFACTORY (ANDAs proposed labeling **includes PR**

Yes	No	
		information above and is **consistent with RLD labeling**) C2: Same as above.
☐	☒	Is the drug product listed in the Policy Alert Tracker on **OGD's SharePoint**?

4.2 MODEL PRESCRIBING INFORMATION (C2)

Table 3: Review Model Labeling for Prescribing Information/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): 020234 / S-047

Supplement Approval Date: 03/20/2018

Proprietary Name: Tegretol-XR

Established Name: carbamazepine extended-release tablets

Description of Supplement:

"This Prior Approval supplemental new drug application provides for changes to the labeling that were derived from a comprehensive analysis of historical information collected for Tegretol, resulting in an update to the Warnings, Precautions, Drug Interactions, Usage in Pregnancy, Adverse Reactions, and Dosage and Administration sections of the USPI."

Link: https://palantir.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4236702_3815326_090140af8048a91d_NDA020234_2653085

☐ MOST RECENTLY APPROVED ANDA MODEL LABELING

☒ OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):

Other Approved RLD Supplements (no impact on labeling)

- **S-048** (CMC submission **approved** 04/12/2018): "These "Changes Being Effected in 30 days" supplemental new drug applications provide for the addition of (b) (4) [**Note**: Approval Letter under NDA-016608-SUPPL-117.]
- **S-049** (CMC submission **approved** 04/22/2020): "This "Changes Being Effected in 30 days" supplemental new drug application provides (b) (4)
- **S-050** (CMC submission **approved** 08/20/2020): "This "Changes Being Effected in 30 days" supplemental new drug application provides for updates to the specification for the drug product Tegretol XR Tablets and the authorized generic Carbamazepine ER Tablets including changes to (b) (4)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling)
(b) (4)
• **S-051** (CMC submission **approved** 08/26/2020): "These "Changes Being Effected" supplemental new drug applications provide for updates to (b) (4) [**Note**: Approval Letter under NDA-016608-SUPPL-119.]

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is **up-to-date** with the RLD/Model labeling.

Reviewer Comments:

The RLDs model labeling is a combined insert but the ANDAs proposed labeling does not carve-out the tablet (chewable and conventional) and oral suspension dosage forms (**see Deficiency in Section 5.4 below**). In addition, the Applicant only provided a PDF version of the PI/MG received on 7/6/2021; however, **no notable differences were identified in the SBS comparison with the Word document received on 5/21/2021**. Thus, the PDF document received on 7/6/2021, was used for the SBS comparison with the RLD model labeling.

Deficiency Comments:

4.3 PATENTS AND EXCLUSIVITIES (C2)

The Orange Book was searched on 02/03/2022

Table 4 provides Orange Book patents for the Model Labeling (NDA 020234) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling							
Strengths	**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						

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	**Exclusivity Code**	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact (enter Carve-out or None)**
	N/A					

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has **expired** and the applicant needs to revise labeling.
Reviewer Comments: **Deficiency Comments:**		

4.4 UNITED STATES PHARMACOPEIA (USP) (C2)

The USP was searched on 08/13/2021

Table 6: USP

	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	Yes		Carbamazepine Extended-Release Tablets	•Packaging and Storage: Preserve in tight containers, and store at controlled room temperature. Add the following: ▲ •Labeling: The labeling states the Dissolution test used only if Test 1 is not used.▲ (RB 1-May-2020)
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	**Established name** is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary **name is different from USP** established name.
☒	☐	**USP descriptor** is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	**DISSOLUTION**: The applicant's dissolution statement is appropriate.
☐	☒	**ORGANIC IMPURITIES**: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	**ASSAY**: Drug product meets USP acceptance criteria for assay.

Reviewer Comments:

C1: There are 2 Dissolution Tests in the USP monograph for the drug product (*Official as of 1-May-2020*); however, the DP and BE Reviews are pending (**see Section 5.1.1 below**). Notably, the ANDAs proposed labeling states, "Meets USP Dissolution Test 1". See Deficiencies in Section 5.3 below.

C2

USP Descriptor: See Section 5.3 below.

Biopharmaceutics Review (Reference #46432792, 11/3/2021): **INADEQUATE - MINOR**

Biopharmaceutics Executive Summary	
The Applicant proposed USP monograph dissolution method (Test 1) for carbamazepine ER tablets (Apparatus I at 100 rpm, 900 mL (for the 100 mg and 200 mg strengths) or 1800 mL (for the 400 mg strength) of Water). The Applicant's proposed dissolution acceptance criteria is same as USP test 1. The adequacy of the dissolution method and acceptance criteria is pending Applicant's response to the IRs.	
Has OGD deemed the drug product BE to the RLD?	Yes

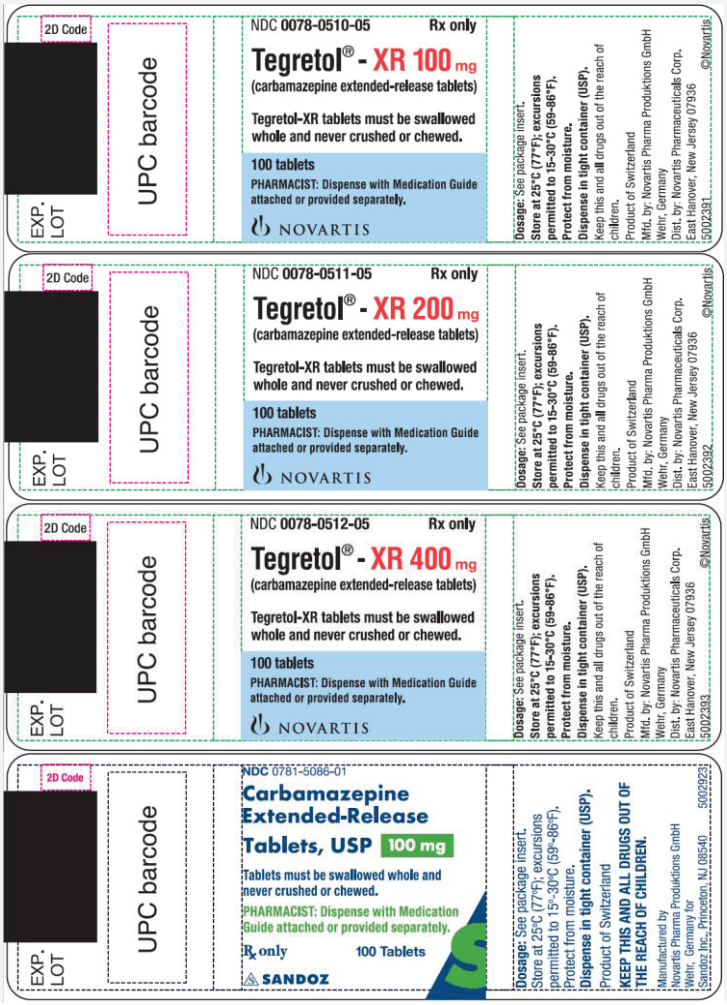
C2 Biopharmaceutics Review is pending.

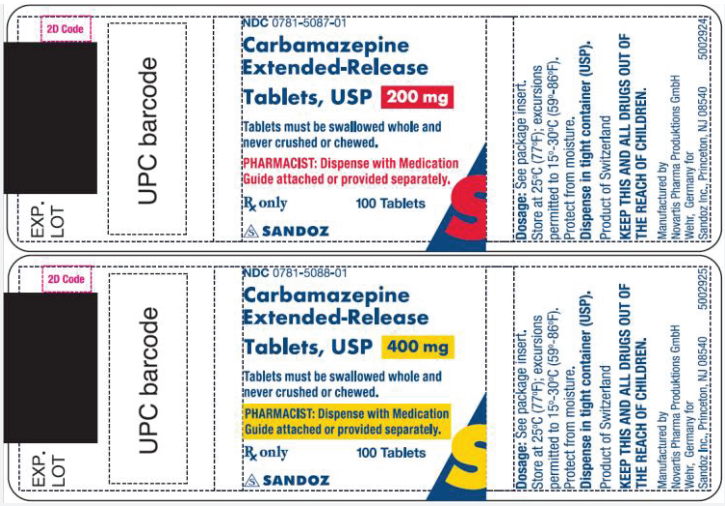
Deficiency Comments:

4.5 MODEL CONTAINER LABELS (C2)

Model container/carton/blister labels (Source: Various--see below. **)**

Approved, Trade & NDA Authorized Generic (Source: **S-031 and S-033**, FINAL received in EDR 12/23/2010, approved 3/3/2011)



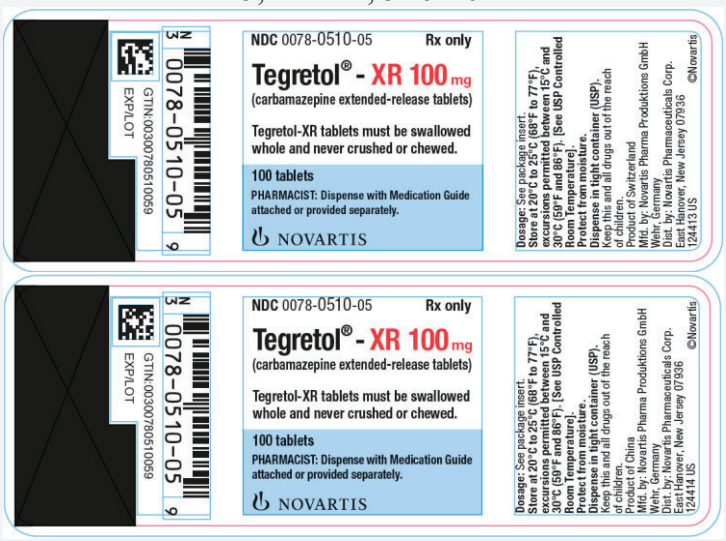


Marketed

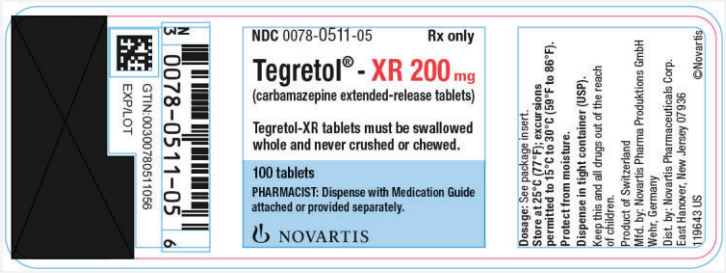
Trade

- Notable differences: revised font of NDC numbers

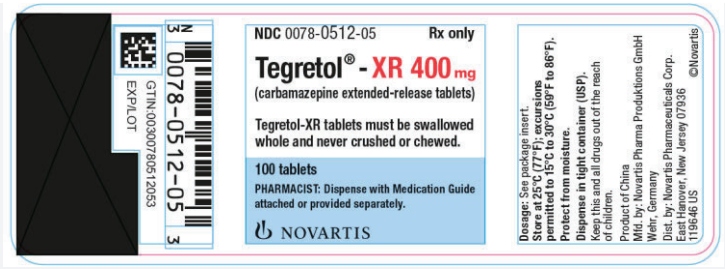
Source: ANRPT-25, FINAL, 5/19/2021



Source: ANRPT-24, FINAL, 5/20/2020



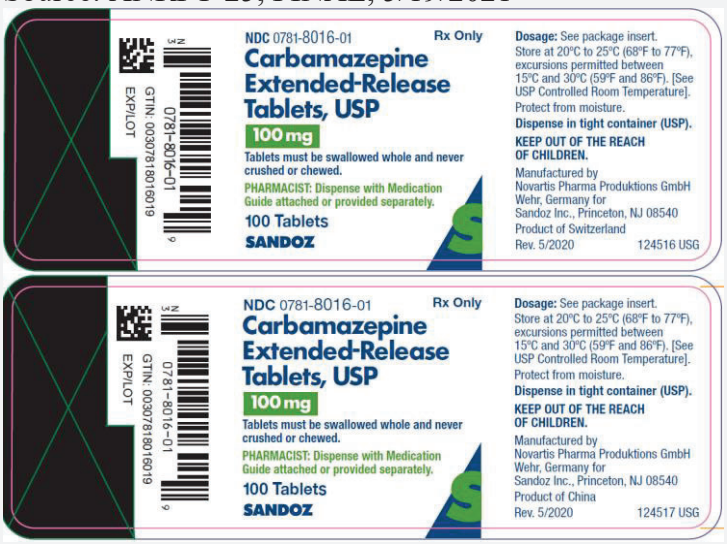
Source: ANRPT-23, FINAL, 5/20/2019



NDA Authorized Generic

- Notable differences: revised font of NDC numbers and rearranged formatting of PDP and side panel information

Source: ANRPT-25, FINAL, 5/19/2021



Source: ANRPT-24, FINAL, 5/20/2020

5 ASSESSMENT OF ANDA LABELING AND LABELS (C2)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C2)

5.1.1 DRUG PRODUCT REVIEW (C2)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review complete

C2

DP Review (Reference #46432772)

11/8/2021: **INDADEQUATE - MINOR**

Labeling	
Description Section	
Is the information accurate?	Yes
Is the drug product subject of a USP monograph?	Yes
Does the labeling need a special USP statement in the Description?	No
How Supplied Section	
Is the information accurate?	Yes
Are the storage conditions acceptable?	Yes
Dosage and Administration Section	
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	N/A

For Solid Oral Drug Product:		
ANDA Strength	**Length(mm)**	**Imprint Code**
Carbamazepine 100mg	8	2241 on one side only
Carbamazepine 200mg	10	2242 on one side only
Carbamazepine 400mg	12	2243 on one side only
Is the imprint code consistent with the labeling?	Yes	

Any issue(s) sent to and/or received from the OGD Labeling Reviewer?	**No**

2/18/2022
Drug Substance: **ADEQUATE**
Drug Product: **INDADEQUATE - MINOR**

Labeling	
Description Section	
Is the information accurate?	Yes
Is the drug product subject of a USP monograph?	Yes
Does the labeling need a special USP statement in the Description?	No
How Supplied Section	
Is the information accurate?	Yes
Are the storage conditions acceptable?	Yes
Dosage and Administration Section	
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	N/A

For Solid Oral Drug Product:		
ANDA Strength	**Length(mm)**	**Imprint Code**
Carbamazepine 100mg	8	2241 on one side only
Carbamazepine 200mg	10	2242 on one side only
Carbamazepine 400mg	12	2243 on one side only
Is the imprint code consistent with the labeling?	Yes	

Any issue(s) sent to and/or received from the OGD Labeling Reviewer?	**No**

5.1.2 DESCRIPTION (C2)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	PI Tegretol-XR tablets: cellulose compounds, dextrates, iron oxides, magnesium stearate, mannitol, polyethylene glycol, sodium lauryl sulfate, titanium dioxide (200 mg tablets only). MG **What are the ingredients in TEGRETOL?** Active ingredient: carbamazepine Inactive ingredients: • **TEGRETOL-XR Tablets:** cellulose compounds, dextrates, iron oxides, magnesium stearate, mannitol, polyethylene glycol, sodium lauryl sulfate, titanium dioxide (200 mg tablets only).
Previous ANDA Labeling	PI Hypromellose, hydroxyethyl cellulose, cellulose acetate, polyethylene glycol, mannitol, dextrates, sodium lauryl sulfate, and magnesium stearate. Each tablet is printed with Opacode Black S-1-17823 ink which contains ammonium hydroxide, iron oxide black, isopropyl alcohol, n-butyl alcohol, propylene glycol and shellac. MG **What are the ingredients in Carbamazepine Extended-Release Tablets?** Active ingredient: carbamazepine, USP Inactive ingredients: Hypromellose, hydroxyethyl cellulose, cellulose acetate, polyethylene glycol mannitol, dextrates, sodium lauryl sulfate, magnesium stearate. Each tablet is printed with Opacode Black S-1-17823 ink which contains ammonium hydroxide, iron oxide black, isopropyl alcohol, n-butyl alcohol, propylene glycol and shellac.
Current ANDA Labeling	PI *Inactive Ingredients:* Hypromellose, hydroxyethyl cellulose, cellulose acetate, polyethylene glycol, mannitol, dextrates, sodium lauryl sulfate, and magnesium stearate. Each tablet is printed with Opacode Black S-1-17823 ink which contains ammonium hydroxide, iron oxide black, isopropyl alcohol, n-butyl alcohol, propylene glycol and shellac. MG **What are the ingredients in Carbamazepine Extended-Release Tablets?** Active ingredient: carbamazepine, USP Inactive ingredients: Hypromellose, hydroxyethyl cellulose, cellulose acetate, polyethylene glycol mannitol, dextrates, sodium lauryl sulfate, magnesium stearate. Each tablet is printed with Opacode Black S-1-17823 ink which contains ammonium hydroxide, iron oxide black, isopropyl alcohol, n-butyl alcohol, propylene glycol and shellac. Assessment: **NO CHANGE**

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C2)

Table 8: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	PI

Table 8: Comparison of Model Labeling to ANDA Labeling	
	Chewable Tablets 100 mg - round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side) Bottles of 100 ..... NDC 0078-0492-05 Unit Dose (blister pack) Box of 100 (strips of 10) ..... NDC 0078-0492-35 Do not store above 30°C (86°F). *Protect from light and moisture.* *Dispense in tight, light-resistant container (USP).* *Meets USP Dissolution Test 1.* ***Tablets 200 mg*** - capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the partially scored side) Bottles of 100 ..... NDC 0078-0509-05 Bottles of 60 ..... NDC 0078-0509-20 Do not store above 30°C (86°F). *Protect from moisture.* *Dispense in tight container (USP).* *Meets USP Dissolution Test 2.* ***XR Tablets 100 mg*** - round, yellow, coated (imprinted T on one side and 100 mg on the other), release portal on one side Bottles of 100 ..... NDC 0078-0510-05 ***XR Tablets 200 mg*** - round, pink, coated (imprinted T on one side and 200 mg on the other), release portal on one side Bottles of 100 ..... NDC 0078-0511-05 ***XR Tablets 400 mg*** - round, brown, coated (imprinted T on one side and 400 mg on the other), release portal on one side Bottles of 100 ..... NDC 0078-0512-05 Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) *Protect from moisture.* *Dispense in tight container (USP).* ***Suspension 100 mg/5 mL (teaspoon)*** – yellow-orange, citrus-vanilla flavored Bottles of 450 mL ..... NDC 0078-0508-83 Shake well before using. Do not store above 30°C (86°F). *Dispense in tight, light-resistant container (USP).*| MG **How should I store TEGRETOL?** • Do not store **TEGRETOL Tablets** above 30°C (86°F). • Keep TEGRETOL Tablets dry. • Do not store **TEGRETOL Chewable Tablets** above 30°C (86°F). • Keep TEGRETOL Chewable Tablets out of the light. • Keep TEGRETOL Chewable Tablets dry. • Store **TEGRETOL-XR Tablets** at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). • Keep TEGRETOL-XR Tablets dry. • Do not store **TEGRETOL Suspension** above 30°C (86°F). • Shake well before using. • Keep TEGRETOL Suspension in a tight, light-resistant container. **Keep TEGRETOL and all medicines out of the reach of children.**
Previous ANDA Labeling	PI ***Carbamazepine Extended-Release Tablets, USP 100 mg*** - white to off-white, round, beveled edge, biconvex coated tablets with release portal and imprinted 2241 with black ink on either side. Bottles of 100 ..... NDC 57720-011-16 ***Carbamazepine Extended-Release Tablets, USP 200 mg*** - white to off-white, round, beveled edge, biconvex coated tablets with release portal and imprinted 2242 with black ink on either side. Bottles of 100 ..... NDC 57720-012-16 ***Carbamazepine Extended-Release Tablets, USP 400 mg*** - white to off-white, round, beveled edge, biconvex coated tablets with release portal and imprinted 2243 with black ink on either side. Bottles of 100 ..... NDC 57720-013-16 Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from moisture. Dispense in tight container (USP). MG **How should I store Carbamazepine Extended-Release Tablets?** • Store Carbamazepine Extended-Release Tablets at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from Moisture • Keep carbamazepine extended-release tablets dry. **Keep Carbamazepine Extended-Release Tablets and all medicines out of the reach of children.**
Current ANDA Labeling	PI

Table 8: Comparison of Model Labeling to ANDA Labeling	
	Carbamazepine Extended-Release Tablets USP, 100 mg - white to off-white, round, beveled edge, biconvex coated tablets with one drill hole on one side and imprinted 2241 with black ink on either side in a top semi-circle shape around the center. Bottles of 100 ..... NDC 57720-011-16 ***Carbamazepine Extended-Release Tablets USP, 200 mg*** - white to off-white, round, beveled edge, biconvex coated tablets with one drill hole on one side and imprinted 2242 with black ink on either side in a top semi-circle shape around the center. Bottles of 100 ..... NDC 57720-012-16 ***Carbamazepine Extended-Release Tablets USP, 400 mg*** - white to off-white, round, beveled edge, biconvex coated tablets with one drill hole on one side and imprinted 2243 with black ink on either side in a top semi-circle shape around the center. Bottles of 100 ..... NDC 57720-013-16 Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from moisture. Dispense in tight container (USP). MG **How should I store Carbamazepine Extended-Release Tablets?** • Store Carbamazepine Extended-Release Tablets at 20° to 25°C (68° to 77°F). • Keep Carbamazepine Extended-Release Tablets dry. **Keep Carbamazepine Extended-Release Tablets and all medicines out of the reach of children.** Assessment: **DEFICIENT** (revised per C1 deficiencies--see Sections 5.3 and 5.4 below--but descriptions in the PI can be improved for clarity)

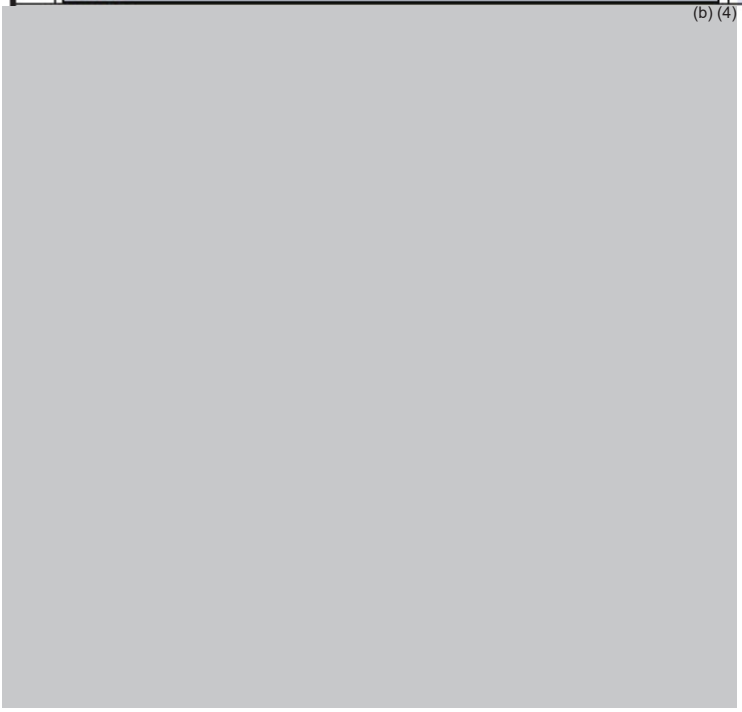
5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C2)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Previous ANDA Labeling	
Name and Address on ANDA Prescribing Information	(b) (4) [redacted] Name and Address on ANDA Container/Carton: Manufactured by: Beijing Sciecure Pharmaceutical Co., Ltd., Shunyi District, Beijing 101301, China Manufactured for: Sciecure Pharma Inc., Monmouth Junction, NJ 08852 PI/MG **Manufactured by:** Beijing Sciecure Pharmaceutical Co., Ltd., Beijing, China **Manufactured for:** Sciecure Pharma Inc. Monmouth Junction, New Jersey 08852
Current ANDA Labeling	
Name and Address on ANDA Prescribing Information	Source: FORM FDA 356h, 1/10/2022

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

APPLICANT INFORMATION	2. Name of Applicant
	Sciecure Pharma Inc.
3. Telephone Number *(Include country code if applicable and area code)*	4. Facsi… *code i*
732-329-8089 (b) (4)	
5. Applicant Address	
Address 1 *(Street address, P.O. box, company name c/o)*	
11 Deer Park Drive	
Address 2 *(Apartment, suite, unit, building, floor, etc.)*	
Unit 120	
City	State/Province/Region
Monmouth Junction	New Jersey
Country	ZIP or Postal Code
USA	08852

(b) (4)



Container Labels

Manufactured by:
Beijing Sciecure Pharmaceutical Co., Ltd.,
Shunyi District, Beijing 101301, China

Manufactured for:
Sciecure Pharma Inc.,
Monmouth Junction, NJ 08852

PI/MG

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
	Manufactured by: Beijing Sciecure Pharmaceutical Co., Ltd., Beijing, China **Manufactured for:** Sciecure Pharma Inc. Monmouth Junction, New Jersey 08852 Assessment: **NO CHANGE**

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements			
Manufactured by	**Manufactured for**	**Distributed by**	**Distributed for**

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the **too small exemption** [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
		ESTABLISHED/PROPRIETARY NAME and STRENGTH:
☐	☒	**Tall Man** lettering complies with recommendations found on FDA webpage.
☐	☒	Established/proprietary **name and strength are the most prominent** information on the Principal Display Panel.
☐	☒	No **intervening text**(written, printed, or graphic matter) between established name and strength.
		THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:
☐	☒	**Net quantity** statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Dosage** statement.
☐	☒	**NDC number:** prominence, linear bar code, and its orientation.
☐	☒	**Expiration date and lot number** (or placeholder).
☐	☒	**Equivalency statement** (product strength).
☐	☒	**Medication Guide** Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	**Image of drug product** represents the true size, color, and imprint.
☐	☒	**Yellow #5** (tartrazine) warning statement is properly displayed.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Latex** warning statement is properly displayed [21 CFR 801.437.].
		PRODUCT DIFFERENTIATION:
☐	☒	ANDA is the **same color** as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple **strengths are differentiated** by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from **related products**.
		STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:
☐	☒	**Storage/dispensing** statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].

Deficiency	No Deficiency	
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe **container closure**, cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
	OVERALL ASSESSMENT:	
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

(b) (4)

[redacted]

Description of Container Closure (Source: Module 3.2.P.7 Container Closure System, 5/21/2021)

Table 1. Summary of Packaging Configuration

Strength	100 mg	200 mg	400 mg
Count/ Bottle	100 tablets	100 tablets	100 tablets
Container	75cc HDPE bottle	75cc HDPE bottle	120cc HDPE bottle
Closure	(b) (4) CRC cap	(b) (4) CRC cap	(b) (4) CRC cap
Dunnage	N/A	N/A	N/A

(b) (4)

The proposed container closure system is child resistant. [redacted]

Deficiency Comments:

Deficiency # 1 Created in C2 Container Label Response / Assessment:	Relocate the precautionary statement, "Carbamazepine Extended-Release Tablets must be swallowed whole and never crushed or chewed.", to the principal display panel to be consistent with the Reference Listed Drug (RLD) labeling. Ensure to use a method to increase the prominence of the precautionary statement (e.g., boxing, contrasting colors, and/or some other means).
Deficiency # 2 Created in C1 Container Label Response / Assessment:	Relocate the net quantity statement (**100 Tablets**) to the bottom of the PDP or decrease the prominence, so that it does not compete with the most critical information (e.g., established name and strength) on the PDP. Response 2: Revised container label is provided in the **Module 1.14.1.1.** Comparison of revised container label with our last submitted container label is provided in the **Module 1.14.1.2.**

	Assessment: **SATISFACTORY**
Deficiency # 3 Created in C1 Container Label Response / Assessment:	Ensure that you complete the National Drug Code (NDC) number in a linear bar code prior to the submission of the final printed labeling per 21 CFR 201.25(c). Response 3: Linear bar code of NDC number has been added to the revised container label. Assessment: **SATISFACTORY**
Deficiency # 4 Created in C1 Container Label Response / Assessment:	Use a method to increase the prominence of the precautionary statement, "Carbamazepine Extended-Release Tablets must be swallowed whole and never crushed or chewed.", on the PDP (e.g., boxing, contrasting colors, and/or some other means). Response 4: A dash-line box has been added around the precautionary statement in the revised container label. Assessment: **DEFICIENT** (precautionary statement is not on the PDP, which inconsistent with the RLD labeling and all other approved ANDAs; thus, the deficiency is reissued below)

5.3 PRESCRIBING INFORMATION (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
	HIGHLIGHTS:	
☐	☒	**Contact information** for applicant and FDA are listed correctly.
☐	☒	**Revision date** appears at end of HIGHLIGHTS section.
	DESCRIPTION/INACTIVE INGREDIENTS:	
☐	☒	Appropriate **warning/precaution** statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☐Sulfite (21 CFR 201.22) ☐Yellow #5 (Tartrazine) (21 CFR 201.20) ☐Phenylalanine/aspartame (21 CFR 201.21) ☐Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Alcohol** is properly listed [21 CFR 201.10(d)(2)].
☐	☒	**Gluten** statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Sterile** product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	**Dosage form and route** of administration properly listed [21 CFR 201.57(c)(12)(B)].
	HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:	
☐	☒	All **submitted labels** and labeling are consistent with the HOW SUPPLIED section.
☒	☐	**Physical description** (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	**NDC** numbers are present.
☐	☒	Drug product is the **same color** as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	**Storage or dispensing** statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Deficiency	No Deficiency	
☐	☒	**"Discard unused portion"** for single-dose products.
☐	☒	**Manufacturer/Distributor/Packager** statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the **Antiretroviral Pregnancy Registry** (APR) upon full approval.
☐	☒	**Pregnancy registry** information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	**Patent/exclusivity** carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

C1

See Internal Observations in Section 5.2 above.

Internal Observations (not provided to Applicant)

Physical Description (Source: **Module 3.2.P.1** Description and Composition of the Drug Product, 5/21/2021)

3.2.P.1.1 Composition and Dosage Form

Carbamazepine Extended-Release Tablets USP, 100 mg, 200 mg and 400 mg are bi-convex coated tablets, rounded beveled edges, with one drill hole on one side and printed "2241", "2242", "2243" on either side in a top semi-circle shape around the center for 100 mg, 200 mg and 400 mg strengths, respectively.

The physical description of the tablets in the Quality submission is inconsistent with the PI (**see Section 5.1.3 above**) and it appears the Applicant has not provided images of their proposed drug product, which is a review issue. See Deficiency below.

C2

Reply to Quality DRL (Source: Module 1.12.12 SBS Comparison, 1/10/2022)

Table 1. Side by Side comparison of RLD vs. Generic Information

		Tegretol®-XR (carbamazepine extended-release tablets), 100 mg, 200 mg, and 400 mg	Carbamazepine Extended-Release Tablets, USP 100 mg, 200 mg, and 400 mg
Conditions of Use		Indicated for the treatment of pain associated with trigeminal neuralgia and therapeutic relief of epilepsy.	Indicated for the treatment of pain associated with trigeminal neuralgia and therapeutic relief of epilepsy.
Active Ingredient		Carbamazepine	Carbamazepine
Dosage Form		Tablet, extended release	Tablet, extended release
Route of Administration		Oral	Oral
Size	**100 mg**	8 mm	8 mm
	200 mg	10 mm	10 mm
	400 mg	12 mm	12 mm
Strength		100 mg, 200 mg, and 400 mg	100 mg, 200 mg, and 400 mg
Shape		Round	Round, bi-convex, beveled edges
Color	**100 mg**	Yellow	White to off-white
	200 mg	Pink	White to off-white
	400 mg	Brown	White to off-white
Weight	**100 mg**	209.6 mg	191.4 mg
	200 mg	394.6 mg	379.1 mg
	400 mg	737.2 mg	737.2 mg
Imprint	**100 mg**	T on one side / 100 mg on the other	Blank on one side / 2241 on either side in a top semi-circle shape around the center
	200 mg	T on one side / 200 mg on the other	Blank on one side / 2242 on either side in a top semi-circle shape around the center
	400 mg	T on one side / 400 mg on the other	Blank on one side / 2243 on either side in a top semi-circle shape around the center
Coating/Release portal		Coated, release portal on one side	Coated, release portal on one side
Image	**100 mg**		
	200 mg		
	400 mg		

Deficiency Comments:

Deficiency # 1

Product Title: Remove the (b) (4) descriptor, such as "Carbamazepine Extended-Release Tablets".

Created in C2 Prescribing Information Response / Assessment:	
Deficiency # 2 Created in C2 Prescribing Information Response / Assessment:	DESCRIPTION, 3rd paragraph, 1st sentence: Revise (b) (4) to "Each Carbamazepine Extended-Release Tablet intended for oral administration contains 100 mg, 200 mg, or 400 mg of carbamazepine." (note "and 400 mg" is revised to "or 400 mg" for clarity).
Deficiency # 3 Created in C2 Prescribing Information Response / Assessment:	PRECAUTIONS (note the cross-references are removed, as your revised proposed labeling removed the referenced information in the corresponding section) 1. **General**, 6th paragraph: Revise (b) (4) (see DOSAGE AND ADMINISTRATION)." to "Since a given dose...unwanted side effects." 2. **Drug Interactions**, 1st paragraph, last sentence: Revise (b) (4) (see DOSAGE AND ADMINISTRATION)." to "Because the extent...or diluents."
Deficiency # 4 Created in C2 Prescribing Information Response / Assessment:	DOSAGE AND ADMINISTRATION, **Epilepsy** 1. ***Children 6 to 12 years of age-Initial***, 1st sentence: Revise (b) (4) to "100 mg twice a day for Carbamazepine Extended-Release Tablets (200 mg/day)." to be consistent with the RLD labeling. 2. ***Children under 6 years of age-Initial***, 1st sentence: (b) (4) to "10 to 20 mg/kg/day twice a day or three times a day as tablets (chewable or conventional), or four times a day as suspension." for clarity and to minimize misuse of your proposed drug product.
Deficiency # 5 Created in C2 Prescribing Information Response / Assessment:	DOSAGE AND ADMINISTRATION, **Dosage Information** table: Widen the cell(s), where applicable, to ensure words (e.g., intervals, increments, etc.) are not wrapped to the next line for better readability.
Deficiency # 6	HOW SUPPLIED, each strength: Revise your product descriptions for clarity. For example, revise (b) (4)

Created in C2 Prescribing Information Response / Assessment:	(b) (4) [redacted] " to "...one drill hole on one side and imprinted with XXXX in black ink on the other side in a top semi-circle shape around the center."
Deficiency # 7 Created in C1 General Comments Response / Assessment:	Ensure to provide your revised Prescribing Information and Medication Guide in an editable Word document. Response 1: • Revised Prescribing Information and Medication Guide in editable **Word** document and **PDF** document with bookmarks are provided in Module 1.14.1.3. • A **Side-by-Side Comparison** with our last submitted Prescribing Information and Medication Guide is provided in Module 1.14.3.1. Assessment: **SATISFACTORY**
Deficiency # 8 Created in C1 Prescribing Information Response / Assessment:	Revise your established name in accordance with the USP monograph for your drug product titled "Carbamazepine Extended-Release Tablets". Response 5: Revised the established name to "Carbamazepine Extended-Release Tablets USP". (#2 of Side-by-Side Comparison) Assessment: **SATISFACTORY**
Deficiency # 9 Created in C1 Prescribing Information Response / Assessment:	Limit the use of the "USP" descriptor to the Quality sections of the Prescribing Information (DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED). Response 6: The use of the "USP" descriptor has been limited to the Quality sections of the Prescribing Information in the revised Prescribing Information and Medication Guide document in the Module 1.14.1.3. Assessment: **DEFICIENT** (product title still includes the USP descriptor; thus, a deficiency is issued below)
Deficiency # 10 Created in C1 Prescribing Information Response / Assessment:	Ensure references to the drug substance (carbamazepine) and drug product (Carbamazepine Extended-Release Tablets) are consistent throughout the Prescribing Information. Ensure to use the established name, carbamazepine extended-release tablets (i.e., dosage form included), when referring to the drug product. Response 7: Corrected the name of drug product to "Carbamazepine Extended-Release Tablets". (#5 of Side-by-Side Comparison) Assessment: **SATISFACTORY**
Deficiency # 11 Created in C1 Prescribing Information	Conduct editorial revisions throughout your Prescribing Information for punctuation and spacing errors. For example (note: not inclusive of all the necessary revisions), 1. Boxed Warning, last paragraph and sentence: Add punctuation at the end of the last sentence, such as "...BONE MARROW

	DEPRESSION DEVELOPS." 2. CLINICAL PHARMACOLOGY: Extra spacing between words throughout this section.
Response / Assessment:	Response 8: Punctuation has been added to the end of the last sentence in the revised document. (#4 of Side-by-Side Comparison) Response 9: Extra spacing between words throughout the entire document have been corrected in the revised document. (#3 of Side-by-Side Comparison) Assessment: **SATISFACTORY**
Deficiency # 12 Created in C1 Prescribing Information	DESCRIPTION 1. 3rd paragraph, second sentence: Revise the dosage form from [redacted] to "extended-release tablet". For example, revise [redacted] to "In addition, each extended-release tablet contains..." 2. Last sentence: Remove the last sentence, [redacted] as a statement is required only if [redacted]
Response / Assessment:	Response 10: The dosage form has been revised from "tablet" to "extended-release tablet" in the revised document. (#6 of Side-by-Side Comparison) Response 11: The sentence '[redacted]." has been removed in the revised document. (#7 of Side-by-Side Comparison) Assessment: **SATISFACTORY**
Deficiency # 13 Created in C1 Prescribing Information	DOSAGE AND ADMINISTRATION: Carve out the tablet (chewable and conventional) and oral suspension dosage form information, as your proposed labeling is only for the extended-release tablets.
Response / Assessment:	Response 12: • The first and third paragraphs have been removed in the section "DOSAGE AND ADMINISTRATION". (#9 of Side-by-Side Comparison) • Information related to tablet and oral suspension form for Adults and Children 6 to 12 have been removed in the section "Epilepsy (SEE INDICATIONS AND USAGE)". (#11 of Side-by-Side Comparison). Assessment: **DEFICIENT** (revised proposed carve-out is not in alignment with other areas of the proposed labeling; thus, deficiencies are issued below)
Deficiency # 14 Created in C1 Prescribing Information	DOSAGE AND ADMINISTRATION, Table (Dosage Information) 1. Expand the columns and/or rows so that all the text in each cell is visible to the reader to ensure important information is easily accessible. 2. Header row, 2nd column: Revise "Subsequent" to "Subsequent Dose" to be consistent with the RLD labeling. 3. 1st column, last row: Widen the cell so the words "Trigeminal

Neuralgia" are not wrapped to the next line for better readability.

Response / Assessment:

Response 13:
Fixed table cells to ensure all information is visible to the reader. (#12 of Side-by-Side Comparison)

Response 14:
Revised '(b) (4)o "Subsequent Dose". (#13 of Side-by-Side Comparison)

Response 15:
Fixed table cell so the words "Trigeminal Neuralgia" are not wrapped to the next line. (#14 of Side-by-Side Comparison)

Assessment: **SATISFACTORY**

Deficiency # 15

Created in C1

HOW SUPPLIED: Comment and/or revise your product description (e.g., shape, color, scoring, coating, and imprint code) to be in accordance with the information in your submission, as required per 21 CFR 201.57(c)(17).

Prescribing Information
Response / Assessment:

Response 16:
Added text "in a top semi-circle shape around the center." to be consistent with submitted information. (#16 of Side-by-Side Comparison)

Assessment: **DEFICIENT** (product descriptions can be improved for clarity per the images provided in the Quality submission; thus, the deficiency is reissued below)

5.4 MEDICATION GUIDE (C2)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Medication Guide is **up-to-date** with model labeling.
☐	☒	Medication Guide meets **content, format, and font size**.
☐	☒	**Phonetic spelling** of the established/proprietary name is present and correct.
☐	☒	Description of **child-resistant feature**(if also present in HOW SUPPLIED/STORAGE AND HANDLING).
☐	☒	**Revision date and approval statement** appear at the end of the Medication Guide correctly.
☐	☒	Applicant committed to provide a **sufficient number** of Medication Guides.
☐	☒	Applicant included the **1-800-FDA-1088** phone number.
☐	☒	Medication Guide is the same as the model labeling, except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Deficiency Comments:

Deficiency # 1

Created in C1

Ensure a sufficient number of Medication Guides is available for dispensing and distribution to patients receiving a prescription for your drug product per 21 CFR 208.24.

Medication Guide
Response / Assessment:

Response 17:
Extra Medication Guide will be available for dispensing and distribution to patients using our product.

Assessment: **SATISFACTORY**

Deficiency # 2 Created in C1 Medication Guide Response / Assessment:	Revise your proposed pronunciation of the non-proprietary name to conform to the phonetic pronunciation in the current USP Dictionary of USAN and International Drug Names. For example, "(kar" ba maz' e peen)". Response 18: Revised the pronunciation of the non-proprietary name of Carbamazepine to **(kar" ba maz' e peen)**. (#18 of Side-by-Side Comparison) Assessment: **SATISFACTORY**
Deficiency # 3 Created in C1 Medication Guide Response / Assessment:	Remove the USP descriptor in the title of your established name. Response 19: USP descriptor has been removed in the title section. (#19 of Side-by-Side Comparison) Assessment: **SATISFACTORY**
Deficiency # 4 Created in C1 Medication Guide Response / Assessment:	**What is the most important information I should know about Carbamazepine Extended-Release Tablets?**: Revise and increase the indenting of the subsections and bullets throughout this section for better readability and to be consistent with the RLD labeling. Response 20: Increased the indenting of subsections and bullets in this section to be consistent with the RLD labeling. (#20 of Side-by-Side Comparison) Assessment: **SATISFACTORY**
Deficiency # 5 Created in C1 Medication Guide Response / Assessment:	**What are Carbamazepine Extended-Release Tablets?**, 2nd bullet, last sentence: Relocate the last sentence ("Carbamazepine extended-release tablets are not a regular pain medicine and should not be used for aches or pains.") to the next line to be consistent with the RLD labeling. Response 21: Moved the last sentence to the next line to be consistent with the RLD labeling. (#21 of Side-by-Side Comparison) Assessment: **SATISFACTORY**
Deficiency # 6 Created in C1 Medication Guide Response / Assessment:	**Do not take Carbamazepine Extended-Release Tablets if you:**, 2nd bullet, 1st sentence: Reference the drug substance in the first instance of this sentence to be consistent with the RLD labeling. For example, revise [redacted] (b) (4) to "are allergic to carbamazepine or any of the ingredients in carbamazepine extended-release tablets." Response 22: Revised the sentence to refer to the drug substance as instructed in Comment F. (#22 of Side-by-Side Comparison) Assessment: **SATISFACTORY**
Deficiency # 7 Created in C1	**What should I tell my healthcare provider before taking Carbamazepine Extended-Release Tablets?**: Reference the drug substance in the instances specified below.

Medication Guide	1. 11th bullet, 2nd sentence: Revise "Carbamazepine extended-release tablets may harm your unborn baby." to "Carbamazepine may harm your unborn baby." 2. last bullet, 2nd sentence: Revise "Carbamazepine extended-release tablets passes into breast milk." to "Carbamazepine passes into breast milk."
Response / Assessment:	Response 23: Revised '(b) (4)to "Carbamazepine". (#23 of Side-by-Side Comparison) Response 24: Revised (b) (4)to "Carbamazepine". (#23 of Side-by-Side Comparison) Assessment: **SATISFACTORY**
Deficiency # 8 Created in C1 Medication Guide Response / Assessment:	**How should I take Carbamazepine Extended-Release Tablets?** (5th, 6th, and 7th bullets): Bold the text of the 5th bullet and increase the indenting of the 6th and 7th bullets to be consistent with the RLD labeling. Response 25: Bold the text and increase the indenting of subsections to be consistent with the RLD. (#24 of Side-by-Side Comparison) Assessment: **SATISFACTORY**
Deficiency # 9 Created in C1 Medication Guide Response / Assessment:	**How should I store Carbamazepine Extended-Release Tablets?**, 1st bullet: Remove "[See USP Controlled Room Temperature]. Protect from Moisture" to be consistent with the RLD labeling. Response 26: • Removed "[See USP Controlled Room Temperature]. Protect from Moisture". • Increased the indenting of subsection to be consistent with RLD. (#25 of Side-by-Side Comparison) Assessment: **SATISFACTORY**
Deficiency # 10 Created in C1 Medication Guide Response / Assessment:	**General Information about Carbamazepine Extended-Release Tablets**, last sentence: Resolve the hyperlink error in your PDF document (received on July 6, 2021). Note that your Word document (received on May 21, 2021) does not include a hyperlink. Response 27: Hyperlink has been removed in the revised Medication Guide. Assessment: **SATISFACTORY**

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C2)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber

☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☒	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☒	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

Comments for CMC (Issue Opened 9/3/2021, **Reference #47702344**): We note the statement, "Carbamazepine extended-release tablet coating is not absorbed and is excreted in the feces; these coatings may be noticeable in the stool," in the DOSAGE AND ADMNISTRATION section of the PI (5th paragraph, last sentence). Please confirm the [accuracy] of the ANDAs proposed statement.

- Reply from CMC on 9/8/2021 (**RESOLVED**): "According to literature, “A feature of some DDS products is the phenomenon of “ghost tablets” (e.g., Tegretol XR). This occurs when the shell that houses the drug does not disintegrate or become digested, but passes out intact in the stool”. (Wheless, JW et al - A Clinician’s Guide to Oral Extended-Release Drug Delivery Systems in Epilepsy. J Pediatr Pharmacol Ther 2018;23(4):277–292). I believe that the RLD also has the same statement in their package insert on page 38 (36 of 51) of the Annotated Comparison with Listed Drug document..."

Comments for CMC (Issue Opened 2/22/2022, **Reference #49822637**): Per the Applicant's reply to the Quality DRL received on 1/10/2022 (Module 1.12.12 SBS Comparison), we intend to request the Applicant to revise the product descriptions in the HOW SUPPLLIED section for clarity. For example, revise "...one drill hole on one side and imprinted XXXX with black ink on either side in a top semi-circle shape around the center." to "...one drill hole on one side and imprinted with XXXX in black ink on the other side in a top semi-circle shape around the center." Please let us know if you concur or have additional input for consideration.

- Reply from CMC on 2/22/2022 (**RESOLVED**): "I concur with the request changes."

Deficiency Comments:

Susan Rimmel

Digitally signed by Susan Rimmel
Date: 2/24/2022 03:56:30PM
GUID: 57e14a7301fe42aa569d1859f813583c

Ellen Hwang

Digitally signed by Ellen Hwang
Date: 2/24/2022 04:00:12PM
GUID: 5256bdc00002af3bc3fa942a9512a891

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA216235Orig1s000

BIOEQUIVALENCE REVIEW(s)

Knowledge-Aided Assessment and Structured Application Biopharmaceutics Assessment

Overview

ANDA Basic Information	
ANDA No.	216235
DP Name	CARBAMAZEPINE
RLD/RS No.	020234
Applicant	SCIECURE PHARMA INC
Dosage	Tablet ER
Route	Oral
Primary Assessor	Kalpana Paudel
Secondary Assessor	NA

Biopharmaceutics Executive Summary	
The Biopharmaceutics review focused on the assessment of proposed dissolution method, dissolution acceptance criteria, and the in-vitro in-vivo correlation (IVIVC) data. The Applicant proposed USP monograph dissolution method (Test 1) for carbamazepine ER tablets which is acceptable based on the method development report and submitted data. The proposed dissolution acceptance criteria are permissive for the drug product and not acceptable. The Applicant submitted an IVIVC report to demonstrate that revised USP dissolution acceptance criteria will be able to reject product that is not bioequivalent to the reference-target drug product. The IVIVC study, however, was deemed not acceptable because of incomplete data/justification provided. Therefore, the Agency recommended to revise the acceptance criteria based on the bio-batch data which the Applicant has accepted. The Applicant was requested to petition the USP for the revised acceptance criteria which the applicant has initiated. The submission is adequate from Biopharmaceutics perspective.	
Has OGD deemed the drug product BE to the RLD?	Yes

Drug Substance(s) and Drug Product				
	DS Name	**Strength Name (Active Moiety or Salt)**	**Therapeutic Area**	**Therapeutic Sub-Category**
1	CARBAMAZEPINE	CARBAMAZEPINE	Neurology 2	Epilepsy

DP Strength List		
	DS 1	
	mg	
Strength 1	400	
Strength 2	100	
Strength 3	200	

Review Iteration						
	Review Iteration	**Assessor Decision**	**Date Finalized**	**Submission(s) To Be Reviewed**	**Supporting Document**	**Submission Date**
1	Original Review	DRL	11/3/2021	Amendment Correspondence; Quality Form 3674; New	3 1	9/10/2021 5/21/2021
2	DRL Response	Inadequate Minor	3/2/2022	Amendment Correspondence; Quality	6	1/10/2022

3	CR Response	Adequate	12/8/2022	Amendment Correspondence; Labeling; Quality; Resubmission	7	5/31/2022

In Vitro Release Specification						
CARBAMAZEPINE - Tablet ER						
Strength		**Apparatus**	**Rotation Speed**	**Temperature**	**Medium / Volume (ml)**	**Acceptance Criteria**
1	100mg,200mg	1-Basket	100	37	Water (Degassed) - Volume: 900 ml	3 hr; Range - 18-38% 6 hr; Range - 46-66% 12 hr; Range - 70-90% 24 hr; NLT - 80%
2	400mg	1-Basket	100	37	Water (Degassed) - Volume: 1800 ml	3 hr; Range - 18-38% 6 hr; Range - 46-66% 12 hr; Range - 70-90% 24 hr; NLT - 80%

Reference Biopharmaceutics Properties

RLD Basic Information	
NDA No.	020234
Non-proprietary DP Name	CARBAMAZEPINE
Proprietary DP Name	TEGRETOL-XR

RLD Reference Information	
Dosage and Administration	Please see the label below for details.
Equilibrium Solubility	NA
pKa	NA
Bioavailability	The relative bioavailability of the product is 89 % compared to oral suspension.
Pharmacokinetics	Carbamazepine is 76% bound to the plasma proteins in blood. Plasma levels of Carbamazepine are variable and may range from 0.5 µg/mL to 25 µg/mL, with no apparent relationship to the daily intake of the drug. Carbamazepine is metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of Carbamazepine-10, 11-epoxide from Carbamazepine.
BCS Classification	The BCS classification of the RLD is not provided in the submission.
DS/DP Characterization	The RLD product was designed as an osmotic delivery system.
Other Relevant Biopharm Information	NA

Reference Documents		
URL Description	**URL**	**Init. Page**
Description and composition of the RLD drug product (page 4)	\\CDSESUB1\evsprod\nda020234\0087\m3\32-body-data\32p-drug-prod\tegretol-xr extended-release-tablets-01\32p1-desc-comp\description-and-composition.pdf	4

RLD Drug Substance(s) and Drug Product		
	DS Name	**Strength Name (Active Moiety or Salt)**
1	CARBAMAZEPINE	Carbamazepine

RLD DP Strength List		
	DS 1	
	mg	
Strength 1	100	
Strength 2	200	
Strength 3	400	

Pilot BE Studies

Are there any submitted pilot studies evaluating the BE of several formulation variants for the test product?	Yes
Has an IVIVC or IVIVR (e.g. physiological based model with virtual BE) been established?	No
Pertinent BE / Clinical Evaluations Perspective	The data are not adequate to build a safe space
Reviewer Evaluation	The applicant conducted an IVIVC study using the dissolution data generated by the selected dissolution method and pharmacokinetics data from a pilot bioequivalence study. The IVIVC data was submitted to demonstrate that revised acceptance criteria for the dissolution method will reject product that is not bioequivalent to the reference-target drug product. The IVIVC study is deemed not acceptable at this time. Please refer to the IVIVC section below for details.

Drug Substance Information

CARBAMAZEPINE (ER)	
Drug Substance Information	
High Risk drug substance	Yes
BCS Solubility	Low
BCS Class Reported by Applicant	II
(b) (4)	
Reviewer Evaluation	The complete release (i.e., >80% dissolution) of carbamazepine tablets occurs in about 24 hours.; Dissolution profiles of biobatch and exhibit batches in QC and multi media
Are there supportive BE studies (i.e. pilot BE studies evaluating formulation variants) to support the in vivo relevance of the dissolution test?	Yes
Reviewer Evaluation	The applicant submitted IVIVC data from Pilot BE studies to propose a revised acceptance criteria that will reject product that is not bioequivalent to the reference-target drug product.

Initial Risk Assessment

CARBAMAZEPINE (ER) / BCS Solubility: Low	
Is in vitro dissolution independent of test condition (e.g., medium pH, rotation speed)?	No
Could Critical Bioavailability Attribute(s) be clearly identified, detected and controlled?	Yes
Initial Risk Ranking	Medium

Mitigation Strategies

CARBAMAZEPINE (ER) / BCS Solubility: Low / Initial Risk: Medium	
Recommended Biopharmaceutics Mitigation Strategies (Pertinent Critical Bioavailability Attribute(s) CBAs)	
(b) (4)	
Mitigated Biopharmaceutics Risk Level	**Reviewer Evaluation**
Low	Adequate

Drug Substance Dissolution Methods and Acceptance Criteria

CARBAMAZEPINE (Tablet ER)						
Proposed Dissolution Methods and Acceptance Criteria						
Strength	**Apparatus**	**Rotation Speed**	**Temp (°C)**	**Medium/Volume (mL)**	**Acceptance Criteria**	**Adequate**
100mg; 200mg	1-Basket	100 rpm	37	Water (Degassed) - Volume: 900 ml	3 hr, Range - 18-38%; 6 hr, Range - 46-66%; 12 hr, Range - 70-90%; 24 hr, NLT - 80%	Yes
400mg	1-Basket	100 rpm	37	Water (Degassed) - Volume: 1800 ml	3 hr, Range - 18-38%; 6 hr, Range - 46-66%; 12 hr, Range - 70-90%; 24 hr, NLT - 80%	Yes

Reviewer Evaluation	The Biopharmaceutics review focused on the dissolution method development, dissolution data, dissolution acceptance criteria, and IVIVC data. The parameters of the proposed dissolution method for the routine QC testing of the proposed generic drug product are the same as those specified in the USP Monograph of the carbamazepine extended-release tablets with the exception of the use of a 10-mesh size of the basket. Note that the FDA Dissolution Methods Database refers to USP. For the study, one tablet is placed into basket with hole side facing down, and then a cage sinker is loaded into basket to cover the tablet. The Applicant's proposed dissolution acceptance criteria is same as USP test 1. Based on the submitted in vitro dissolution profile data, the proposed in vitro dissolution acceptance criteria are permissive and not acceptable. Applicant's submitted IVIVC study also does not support the proposed acceptance criteria as the model is deemed inadequate. Therefore, applicant will be requested to revise the acceptance criteria based on the bio-batch data. If the proposed dissolution method is ultimately deemed to be adequate for QC testing purposes, the Applicant should be reminded to submit a USP petition to request incorporation of their approved dissolution method and (if applicable) acceptance criteria in the drug product's official monograph. IVIVC study: The applicant also submitted an IVIVC study using the dissolution data generated by the selected dissolution method and pharmacokinetics data from a pilot bioequivalence study to propose that a revised dissolution acceptance criteria (mentioned below) will be able to reject product that is not bioequivalent to the reference-target drug product with the USP dissolution specification. However, the IVIVC study is deemed not acceptable at this time because of the incomplete data and justifications submitted. Please refer to the IVIVC IR for details. 3 hr (b) (4) % 6 hr (b) (4) % 12 hr (b) (4) % 24 hr (b) (4) % ; IVIVC report
Unique Situations	
Any unique situations not covered by KASA?	No
Adequate	Yes
Reviewer Evaluation	
Proposed Dissolution Testing	
FDA Dissolution Database	
Is the dissolution analytical quantification method acceptable to OLDP assessors?	Yes
Reviewer Evaluation	
Description of Links for Dissolution Methods	**URL Link**
Dissolution method validation	\\CDSESUB1\evsprod\anda216235\0001\m3\32-body-data\32p-drug-prod\beij-carb-abl\32p5-contr-drug-prod\32p53-val-analyt-proc\tmvr-03-an1-2016-37-dissolution.pdf
Dissolution method validation	\\CDSESUB1\evsprod\anda216235\0001\m3\32-body-data\32p-drug-prod\beij-carb-abl\32p5-contr-drug-prod\32p53-val-analyt-proc\tmvr-03-an1-2016-37-a1-dissolution-addendum.pdf
Variability in the dissolution results meet the recommendations (e.g. %CV < 20% at early time points (<15 minutes) and <10% at other time points)	Yes
Reviewer Evaluation	
Number of units tested meets the requirements (e.g. 12 units)	Yes

Reviewer Evaluation	
Source of Dissolution Test Method	USP Monograph
Does the proposed drug product meet the USP Monograph standards?	No
Actions requested of the Applicant	Initiate USP Monograph revision
Reviewer Evaluation	

Deficiencies

Proposed Dissolution Methods and Acceptance Criteria

Iteration	Status	ID	[Issue Topic]
Original Review	Solved	1	Method development report and justification for the selection of 10-mesh basket
			[Deficiency/IR]
			Provide in vitro dissolution method development report supporting the selection of the proposed dissolution test conditions including the justification for the selection of 10-mesh basket.
			[Summary of the applicant's response and reviewer comment]
			In the Response to the Biopharmaceutics Information, the Applicant reported that the final phase of the dissolution was greatly impacted by the mesh size of the basket used in the method. The method using baskets with larger opening (i.e., 10 mesh) produced > 80% dissolution while the method using baskets with smaller opening (b) (4)) produced incomplete release (b) (4)) at 24 hour timepoint. Note that the Applicant did not provide data with (b) (4) basket which is the standard size for basket. For the study, one tablet is placed into basket with hole side facing down and then a cage sinker is placed in the basket to cover the tablet. In the method validation report, the applicant noted that original test process (without cage sinker) and the new test process (with cage sinker) had equivalent detection capabilities. The Applicant explored other dissolution conditions such as by varying the basket rotation speed, the pH of the media and surfactant. The agitation speed from 50 rpm, 100 rpm, and 150 rpm produced similar dissolution profiles and therefore has no impact on dissolution profiles. Similar dissolution profiles were observed at pH 1.2 and pH 4.5 media to that of Water while pH 6.8 medium produced slower and incomplete dissolution profile at 24 hour timepoint. Similarly, addition of different amount of the surfactant (SDS) at 0.5, 1, and 2% level (1800 mL) did not improve the drug release. Rather, the drug release rate decreased with increasing SDS concentration. ; IR response
Iteration	**Status**	**ID**	**[Issue Topic]**
DRL Response	Solved	2	method development report with the bio-batch
			[Deficiency/IR]
			In your response letter dated September 10, 2021, we noted that you have explored all the dissolution method conditions and discriminating ability with RLD as the target drug product. You should explore the dissolution method conditions with your proposed drug product. Accordingly, we request that you submit data obtained with the proposed product. In addition, for discriminating ability testing, your reference batch should be reference target product (e.g., bio-batch).
			[Summary of the applicant's response and reviewer comment]
			It is noted that the applicant explored all the dissolution method conditions with RLD. The applicant will be recommended to explore all the method conditions with the applicant's proposed product.
CR Response	Solved	2	**[Summary of the applicant's response and reviewer comment]**
			The Applicant submitted data exploring the dissolution method conditions with their proposed drug product. In addition, the applicant provided data for discriminating ability comparing with the bio-batch. The selected dissolution method was able to detect changes in the cellulose acetate grade ratio of the coating changes based on the f2 values. The Applicant's response is acceptable. ; Dissolution method development
			[Deficiency/IR Previous Iteration]
Iteration	**Status**	**ID**	**[Issue Topic]**
Original Review	Solved	3	List of CMAs, CPPs, and formulation variables
			[Deficiency/IR]
			Provide a list of the critical material attributes (CMAs), critical formulation variables and critical process attributes (CPAs) affecting dissolution.
			[Summary of the applicant's response and reviewer comment]
			The Applicant provided the requested information.
Iteration	**Status**	**ID**	**[Issue Topic]**
Original	Solved	4	Discriminating ability

Review			**[Deficiency/IR]**
			Provide data supporting the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations in the most relevant critical material attributes, critical formulation variables, and critical process parameters (i.e., ± 10-20% change to the specification-ranges of these variables). Submit the dissolution profile data and similarity testing results obtained with appropriate statistical test (e.g., f2 values) comparing the test and reference drug products. In addition, if available, submit data showing that the selected dissolution method is able to reject product that is not bioequivalent to the reference-target drug product.
			[Summary of the applicant's response and reviewer comment]
			In response to the Biopharmaceutics Information Request (see the link above), the Applicant provided data to show that the USP method is discriminating (b) (4) Not only were the dissolution profiles of two batches different compared to the target, but the profiles among the batches were also different based on similarity factor (f2). The applicant will be requested to provide all the dataset in excel format to verify the f2 calculations.
Iteration	**Status**	**ID**	**[Issue Topic]**
DRL Response	Solved	5	IVIVC issues
			[Deficiency/IR]
			You submitted an in-vitro in-vivo correlation (IVIVC) study to support that revised USP acceptance criteria for the selected dissolution method will be able to reject product that is not bioequivalent to the reference-target drug product. However, your IVIVC study is deemed not acceptable at this time because of the insufficient data/justification provided. As outlined in the FDA Guidance for Industry Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations three or more formulations with different release rates are recommended to define an IVIVC. Exceptions to this may be considered for formulations for which in vitro dissolution is independent of the dissolution test conditions (e.g., medium, agitation, pH, volume). Please submit the following information/data to aid in the regulatory decision making in terms of the acceptability of the proposed IVIVC model, if you still want to pursue the model: a. A modeling summary report, which provides an overview of the modeling strategy and details of the modeling procedures, including model development, model verification/modification, and model application in a step-by-step process. Inclusion of a flow chart, decision tree, or other similar representation is preferred for clarity. b. Demonstrate that the dissolution of the proposed drug product is dependent or independent of dissolution conditions. c. As part of the validation steps, follow the “leave-one out” cross validation approach in the construction and validation of your model to challenge its robustness. d. Provide side by side comparative formulation composition for all batches used in the model development and external predictions. e. Submit the executable project files (e.g., .phxproj, .xlsx or .xls, .sas) for the IVIVC model development and internal/external validation. Provide all relevant input including complete in vitro and in vivo data (i.e., individual, mean, % CV, profiles, in .csv, .xlsx or .xls, or .xpt format) and output files used in the construction and validation of the IVIVC model. f. Provide definition file(s) listing all input and output files, and the use or purpose of each of this files in an appropriate format (e.g., .pdf, .xpt, .xls). In addition, provide the hyperlinks for each data file and instructions for extracting these files. g. Provide the IVIVC predictions including the output files and summary table supporting your revised dissolution acceptance criteria, if any. Note that the FDA’s final decision regarding the acceptability of the IVIVC model will be made based on the totality of the supportive data and relevant information provided in the submission, which should include demonstration of a robust model predictability.
			[Summary of the applicant's response and reviewer comment]
CR Response	Solved	5	**[Summary of the applicant's response and reviewer comment]**
			The Applicant chose not to pursue the IVIVC model and adapt the dissolution acceptance criteria recommended by the Agency.
			[Deficiency/IR Previous Iteration]
Iteration	**Status**	**ID**	**[Issue Topic]**
Original	Solved	6	Dissolution profile data for all exhibit data in excel format

Review			**[Deficiency/IR]**
			Provide the complete dissolution profile data (n=12, individual data, range, mean, % CV, and mean dissolution profiles) for all exhibit batches of 100 mg, 200 mg, and 400 mg strengths of your proposed drug product in Microsoft Excel ".xls or .xlsx" format. Also provide the details on manufacturing date, site, size and the dissolution test date.
			[Summary of the applicant's response and reviewer comment]
			The Applicant provided the requested information.
Iteration	**Status**	**ID**	**[Issue Topic]**
DRL Response	Solved	7	Revise dissolution acceptance criteria based on the bio-batch
			[Deficiency/IR]
			Based on the submitted in vitro dissolution profile data, your proposed in vitro dissolution acceptance criteria are permissive for your drug product and not acceptable. Note that per the current Agency's guideline for proper setting of the dissolution specification, drug product acceptance criteria are set primarily based on the performance of the bio-batch/exhibit batches at release. In addition, selection of the in vitro drug dissolution acceptance criteria ranges is based on mean target value ±10% and >80% for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved IVIVC model, physiologically based absorption and pharmacokinetic model, safe space etc. Since your submitted IVIVC model is not acceptable at this time, we recommend the following acceptance criteria for the proposed generic drug product based on the bio-batch data: 3 hr 18-38% 6 hr 46-66% 12 hr 70-90% 24 hr NLT 80% We request that you acknowledge your acceptance of the recommended acceptance criteria for all the strengths of your drug product at release and on stability and update your drug product release and stability specifications accordingly. In addition, please be advised that all proposed exhibit batches are expected to meet the revised dissolution specification in your stability program through your proposed expiry period. Be reminded that if stability failure occurs at Level 1 (L1), Level 2 (L2) testing and Level 3 (L3) testing should be conducted. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.
			[Summary of the applicant's response and reviewer comment]
CR Response	Solved	7	**[Summary of the applicant's response and reviewer comment]**
			The Applicant accepted Agency's recommended dissolution acceptance criteria for all the strengths of drug product at release and on stability.
			[Deficiency/IR Previous Iteration]

Recommended Dissolution Acceptance Criteria

Iteration	**Status**	**ID**	**[Issue Topic]**
CR Response	Solved	1	Petition the USP
			[Deficiency/IR]
			[Summary of the applicant's response and reviewer comment]
			The applicant noted in the response that they have initiated the revision process to the official USP monograph for carbamazepine tablets following the USP Pending Monograph Process.

Drug Product Exhibit Batch Dissolution Testing

Commercial batch size is within a factor of ten times the size of the biobatch	Yes
Reviewer Evaluation	
Testing was conducted using unexpired and/or fresh lots	Yes
Reviewer Evaluation	
Is the RLD drug product scored?	No

Deficiencies

No deficiencies to display

Kalpana Paudel

Digitally signed by Kalpana Paudel
Date: 12/08/2022 06:54:07PM
GUID: 562e1e15002f200f35c6ccac959cdb34

Knowledge-Aided Assessment and Structured Application Biopharmaceutics Assessment

Overview

ANDA Basic Information	
ANDA No.	216235
DP Name	CARBAMAZEPINE
RLD/RS No.	020234
Applicant	SCIECURE PHARMA INC
Dosage	Tablet ER
Route	Oral
Primary Assessor	Kalpana Paudel
Secondary Assessor	Vidula Kolhatkar

Biopharmaceutics Executive Summary	
The Biopharmaceutics review focused on the assessment of proposed dissolution method, dissolution acceptance criteria, and in-vitro in-vivo correlation (IVIVC) data. The Applicant proposed USP monograph dissolution method (Test 1) for carbamazepine ER tablets. The proposed dissolution acceptance criteria are same as USP test 1. The Applicant also submitted IVIVC data to demonstrate that revised USP dissolution acceptance criteria will be able to reject product that is not bioequivalent to the reference-target drug product. However, the IVIVC study is deemed not acceptable because of incomplete data/justification provided. The proposed dissolution method and acceptance criteria are not acceptable pending applicant's response to the IRs.	
Has OGD deemed the drug product BE to the RLD?	Yes
Drug Substance	**The method in USP**
CARBAMAZEPINE (Tablet ER)	Method 1

Drug Substance(s) and Drug Product				
	DS Name	**Strength Name (Active Moiety or Salt)**	**Therapeutic Area**	**Therapeutic Sub-Category**
1	CARBAMAZEPINE	CARBAMAZEPINE	Neurology 2	Epilepsy

DP Strength List		
	DS 1	
	mg	
Strength 1	400	
Strength 2	100	
Strength 3	200	

Review Iteration						
	Review Iteration	**Assessor Decision**	**Date Finalized**	**Submission(s) To Be Reviewed**	**Supporting Document**	**Submission Date**
1	Original Review	DRL	11/3/2021	Amendment Correspondence; Quality Form 3674; New	3 1	9/10/2021 5/21/2021
2	DRL Response	Inadequate Minor		Amendment Correspondence; Quality	6	1/10/2022

Reference Biopharmaceutics Properties

RLD Basic Information	
NDA No.	020234
Non-proprietary DP Name	CARBAMAZEPINE
Proprietary DP Name	TEGRETOL-XR

RLD Reference Information	
Dosage and Administration	Please see the label below for details.
Equilibrium Solubility	NA
pKa	NA
Bioavailability	The relative bioavailability of the product is 89 % compared to oral suspension.
Pharmacokinetics	Carbamazepine is 76% bound to the plasma proteins in blood. Plasma levels of Carbamazepine are variable and may range from 0.5 µg/mL to 25 µg/mL, with no apparent relationship to the daily intake of the drug. Carbamazepine is metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of Carbamazepine-10, 11-epoxide from Carbamazepine.
BCS Classification	The BCS classification of the RLD is not provided in the submission.
DS/DP Characterization	The RLD product was designed as an osmotic delivery system.
Other Relevant Biopharm Information	NA

Reference Documents		
URL Description	**URL**	**Init. Page**
Description and composition of the RLD drug product (page 4)	\\CDSESUB1\evsprod\nda020234\0087\m3\32-body-data\32p-drug-prod\tegretol-xr extended-release-tablets-01\32p1-desc-comp\description-and-composition.pdf	4

RLD Drug Substance(s) and Drug Product		
DS Name		**Strength Name (Active Moiety or Salt)**
1	CARBAMAZEPINE	Carbamazepine

RLD DP Strength List	
	DS 1
	mg
Strength 1	100
Strength 2	200
Strength 3	400

Pilot BE Studies

Are there any submitted pilot studies evaluating the BE of several formulation variants for the test product?	Yes
Has an IVIVC or IVIVR (e.g. physiological based model with virtual BE) been established?	No
Pertinent BE / Clinical Evaluations Perspective	The data are not adequate to build a safe space
Reviewer Evaluation	The applicant conducted an IVIVC study using the dissolution data generated by the selected dissolution method and pharmacokinetics data from a pilot bioequivalence study. The IVIVC data was submitted to demonstrate that revised acceptance criteria for the dissolution method will reject product that is not bioequivalent to the reference-target drug product. The IVIVC study is deemed not acceptable at this time. Please refer to the IVIVC section below for details.

Drug Substance Information

CARBAMAZEPINE (ER)	
Drug Substance Information	
High Risk drug substance	Yes
BCS Solubility	Low
BCS Class Reported by Applicant	II
(b) (4)	
Reviewer Evaluation	The complete release (i.e., >80% dissolution) of carbamazepine tablets occurs in about 24 hours.; Dissolution profiles of biobatch and exhibit batches in QC and multi media
Are there supportive BE studies (i.e. pilot BE studies evaluating formulation variants) to support the in vivo relevance of the dissolution test?	Yes
Reviewer Evaluation	The applicant submitted IVIVC data from Pilot BE studies to propose revised acceptance criteria that will reject product that is not bioequivalent to the reference-target drug product.

Initial Risk Assessment

CARBAMAZEPINE (ER) / BCS Solubility: Low	
Is in vitro dissolution independent of test condition (e.g., medium pH, rotation speed)?	No
Could Critical Bioavailability Attribute(s) be clearly identified, detected and controlled?	Yes
Initial Risk Ranking	Medium

Mitigation Strategies

CARBAMAZEPINE (ER) / BCS Solubility: Low / Initial Risk: Medium	
(b) (4)	
Mitigated Biopharmaceutics Risk Level	**Reviewer Evaluation**
Low	Adequate

Drug Substance Dissolution Methods and Acceptance Criteria

CARBAMAZEPINE (Tablet ER)		
Proposed Dissolution Methods and Acceptance Criteria		
(b) (4)		**Adequate**
		No
		No

Reviewer Evaluation	The Biopharmaceutics review focused on the dissolution method development, dissolution data, dissolution acceptance criteria, and IVIVC data. The parameters of the proposed dissolution method for the routine QC testing of the proposed generic drug product are the same as those specified in the USP Monograph of the carbamazepine extended-release tablets with the exception of the use of a 10-mesh size of the basket. Note that the FDA Dissolution Methods Database refers to USP. For the study, one tablet is placed into basket with hole side facing down, and then a cage sinker is loaded into basket to cover the tablet. The Applicant's proposed dissolution acceptance criteria is same as USP test 1. Based on the submitted in vitro dissolution profile data, the proposed in vitro dissolution acceptance criteria are permissive and not acceptable. Applicants submitted IVIVC study also does not support the proposed acceptance criteria as the model is deemed inadequate. Therefore, applicant will be requested to revise the acceptance criteria based on the bio-batch data. If the proposed dissolution method is ultimately deemed to be adequate for QC testing purposes, the Applicant should be reminded to submit a USP petition to request incorporation of their approved dissolution method and (if applicable) acceptance criteria in the drug product's official monograph. IVIVC study The applicant submitted an IVIVC study using the dissolution data generated by the selected dissolution method and pharmacokinetics data from a pilot bioequivalence study to propose revised dissolution acceptance criteria that will be able to reject product that is not bioequivalent to the reference-target drug product with the USP dissolution specification. However, the IVIVC study is deemed not acceptable at this time because of the incomplete data and justifications submitted. Please refer to the IVIVC IR for details. IVIVC report
Unique Situations	
Any unique situations not covered by KASA?	No
Adequate	No
Reviewer Evaluation	The assessment of dissolution method is pending Applicant's response to the IRs.
Proposed Dissolution Testing	
FDA Dissolution Database	
Is the dissolution analytical quantification method acceptable to OLDP assessors?	Yes
Reviewer Evaluation	
Description of Links for Dissolution Methods	**URL Link**
Dissolution method validation	\\CDSESUB1\evsprod\anda216235\0001\m3\32-body-data\32p-drug-prod\beij-carb-abl\32p5-contr-drug-prod\32p53-val-analyt-proc\tmvr-03-an1-2016-37-dissolution.pdf
Dissolution method validation	\\CDSESUB1\evsprod\anda216235\0001\m3\32-body-data\32p-drug-prod\beij-carb-abl\32p5-contr-drug-prod\32p53-val-analyt-proc\tmvr-03-an1-2016-37-a1-dissolution-addendum.pdf
Variability in the dissolution results meet the recommendations (e.g. %CV < 20% at early time points (<15 minutes) and <10% at other time points)	Yes

Reviewer Evaluation	
Number of units tested meets the requirements (e.g. 12 units)	Yes
Reviewer Evaluation	
Source of Dissolution Test Method	USP Monograph
Does the proposed drug product meet the USP Monograph standards?	Yes
The Test in USP	Method 1
Reviewer Evaluation	The assessment of dissolution method is pending Applicant's response to the IRs.

Deficiencies

Proposed Dissolution Methods and Acceptance Criteria

Iteration	Status	ID	[Issue Topic]
Original Review	Solved	1	Method development report and justification for the selection of 10-mesh basket
			[Deficiency/IR]
			Provide in vitro dissolution method development report supporting the selection of the proposed dissolution test conditions including the justification for the selection of 10-mesh basket.
			[Summary of the applicant's response and reviewer comment]
			In the Response to the Biopharmaceutics Information, the Applicant reported that the final phase of the dissolution was greatly impacted by the mesh size of the basket used in the method. The method using baskets with larger opening (i.e., 10 mesh) produced > 80% dissolution while the method using baskets with smaller opening (i.e., 20 mesh) produced incomplete release (65%) at 24 hour timepoint. Note that the Applicant did not provide data with 40-mesh basket which is the standard size for basket. For the study, one tablet is placed into basket with hole side facing down and then a cage sinker is placed in the basket to cover the tablet. In the method validation report, the applicant noted that original test process (without cage sinker) and the new test process (with cage sinker) had equivalent detection capabilities. The Applicant explored other dissolution conditions such as by varying the basket rotation speed, the pH of the media and surfactant. The agitation speed from 50 rpm, 100 rpm, and 150 rpm produced similar dissolution profiles and therefore has no impact on dissolution profiles. Similar dissolution profiles were observed at pH 1.2 and pH 4.5 media to that of Water while pH 6.8 medium produced slower and incomplete dissolution profile at 24 hour timepoint. Similarly, addition of different amount of the surfactant (SDS) at 0.5, 1, and 2% level (1800 mL) did not improve the drug release. Rather, the drug release rate decreased with increasing SDS concentration. It is noted that the applicant explored all the dissolution method conditions with RLD. The applicant will be recommended to explore the method conditions with the applicant's proposed product. ; IR response
Iteration	**Status**	**ID**	**[Issue Topic]**
DRL Response	Pending	2	method development report with the bio-batch
			[Deficiency/IR]
			In your response letter dated September 10, 2021, we noted that you have explored all the dissolution method conditions and discriminating ability with RLD as the target drug product. You should explore the dissolution method conditions with your proposed drug product. Accordingly, we request that you submit data obtained with the proposed product. In addition, for discriminating ability testing, your reference batch should be reference target product (e.g., bio-batch).
			[Summary of the applicant's response and reviewer comment]
			It is noted that the applicant explored all the dissolution method conditions with RLD. The applicant will be recommended to explore all the method conditions with the applicant's proposed product.
Iteration	**Status**	**ID**	**[Issue Topic]**
Original Review	Solved	3	List of CMAs, CPPs, and formulation variables
			[Deficiency/IR]
			Provide a list of the critical material attributes (CMAs), critical formulation variables and critical process attributes (CPAs) affecting dissolution.
			[Summary of the applicant's response and reviewer comment]
			The Applicant provided the requested information.
Iteration	**Status**	**ID**	**[Issue Topic]**
Original Review	Solved	4	Discriminating ability
			[Deficiency/IR]

			Provide data supporting the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations in the most relevant critical material attributes, critical formulation variables, and critical process parameters (i.e., ± 10-20% change to the specification-ranges of these variables). Submit the dissolution profile data and similarity testing results obtained with appropriate statistical test (e.g., f2 values) comparing the test and reference drug products. In addition, if available, submit data showing that the selected dissolution method is able to reject product that is not bioequivalent to the reference-target drug product.
			[Summary of the applicant's response and reviewer comment]
			In response to the Biopharmaceutics Information Request (see the link above), the Applicant provided data to show that the USP method is discriminating (b) (4) . The applicant will be requested to provide all the dataset in excel format to verify the f2 calculations.
Iteration	**Status**	**ID**	**[Issue Topic]**
DRL Response	Pending	5	IVIVC issues
			[Deficiency/IR]
			You submitted an in-vitro in-vivo correlation (IVIVC) study to support that revised USP acceptance criteria for the selected dissolution method will be able to reject product that is not bioequivalent to the reference-target drug product. However, your IVIVC study is deemed not acceptable at this time because of the insufficient data/justification provided. As outlined in the FDA Guidance for Industry Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations three or more formulations with different release rates are recommended to define an IVIVC. Exceptions to this may be considered for formulations for which in vitro dissolution is independent of the dissolution test conditions (e.g., medium, agitation, pH, volume). Please submit the following information/data to aid in the regulatory decision making in terms of the acceptability of the proposed IVIVC model, if you still want to pursue the model: a. A modeling summary report, which provides an overview of the modeling strategy and details of the modeling procedures, including model development, model verification/modification, and model application in a step-by-step process. Inclusion of a flow chart, decision tree, or other similar representation is preferred for clarity. b. Demonstrate that the dissolution of the proposed drug product is dependent or independent of dissolution conditions. c. As part of the validation steps, follow the “leave-one out” cross validation approach in the construction and validation of your model to challenge its robustness. d. Provide side by side comparative formulation composition for all batches used in the model development and external predictions. e. Submit the executable project files (e.g., .phxproj, .xlsx or .xls, .sas) for the IVIVC model development and internal/external validation. Provide all relevant input including complete in vitro and in vivo data (i.e., individual, mean, % CV, profiles, in .csv, .xlsx or .xls, or .xpt format) and output files used in the construction and validation of the IVIVC model. f. Provide definition file(s) listing all input and output files, and the use or purpose of each of this files in an appropriate format (e.g., .pdf, .xpt, .xls). In addition, provide the hyperlinks for each data file and instructions for extracting these files. g. Provide the IVIVC predictions including the output files and summary table supporting your revised dissolution acceptance criteria, if any. Note that the FDA’s final decision regarding the acceptability of the IVIVC model will be made based on the totality of the supportive data and relevant information provided in the submission, which should include demonstration of a robust model predictability.
			[Summary of the applicant's response and reviewer comment]
Iteration	**Status**	**ID**	**[Issue Topic]**
Original Review	Solved	6	Dissolution profile data for all exhibit data in excel format
			[Deficiency/IR]
			Provide the complete dissolution profile data (n=12, individual data, range, mean, % CV, and mean dissolution profiles) for all exhibit batches of 100 mg, 200 mg, and 400 mg strengths of your proposed drug product in Microsoft Excel “.xls or .xlsx” format. Also provide the details on manufacturing date, site, size and the dissolution test date.
			[Summary of the applicant's response and reviewer comment]
			The Applicant provided the requested information.

Iteration	Status	ID	[Issue Topic]
DRL Response	Pending	7	Revise dissolution acceptance criteria based on the bio-batch
			[Deficiency/IR]
			Based on the submitted in vitro dissolution profile data, your proposed in vitro dissolution acceptance criteria are permissive for your drug product and not acceptable. Note that per the current Agency's guideline for proper setting of the dissolution specification, drug product acceptance criteria are set primarily based on the performance of the bio-batch/exhibit batches at release. In addition, selection of the in vitro drug dissolution acceptance criteria ranges is based on mean target value ±10% and >80% for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved IVIVC model, physiologically based absorption and pharmacokinetic model, safe space etc. Since your submitted IVIVC model is not acceptable at this time, we recommend the following acceptance criteria for the proposed generic drug product based on the bio-batch data: 3 hr 18-38% 6 hr 46-66% 12 hr 70-90% 24 hr NLT 80% We request that you acknowledge your acceptance of the recommended acceptance criteria for all the strengths of your drug product at release and on stability and update your drug product release and stability specifications accordingly. In addition, please be advised that all proposed exhibit batches are expected to meet the revised dissolution specification in your stability program through your proposed expiry period. Be reminded that if stability failure occurs at Level 1 (L1), Level 2 (L2) testing and Level 3 (L3) testing should be conducted. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.
			[Summary of the applicant's response and reviewer comment]

Recommended Dissolution Acceptance Criteria

Iteration	Status	ID	[Issue Topic]
Original Review	Solved	1	Excel sheet data for discriminating ability
			[Deficiency/IR]
			We acknowledge your response (dated September 10, 2021) to Biopharmaceutics questions. Please provide all the dissolution data from Tables 1-4, and Tables 8-14 in Microsoft Excel ".xls or .xlsx" format.
			[Summary of the applicant's response and reviewer comment]
			The Applicant submitted requested data.

Drug Product Exhibit Batch Dissolution Testing

Commercial batch size is within a factor of ten times the size of the biobatch	Yes
Reviewer Evaluation	
Testing was conducted using unexpired and/or fresh lots	Yes
Reviewer Evaluation	
Is the RLD drug product scored?	No

Deficiencies

1. In your response letter dated September 10, 2021, we noted that you have explored all the dissolution method conditions and discriminating ability with RLD as the target drug product. You should explore the dissolution method conditions with your proposed drug product. Accordingly, we request that you submit data obtained with the proposed product. In addition, for discriminating ability testing, your reference batch should be reference target product (e.g., bio-batch).

2. You submitted an in-vitro in-vivo correlation (IVIVC) study to support that revised USP acceptance criteria for the selected dissolution method will be able to reject product that is not bioequivalent to the reference-target drug product. However, your IVIVC study is deemed not acceptable at this time because of the insufficient data/justification provided.
   As outlined in the FDA Guidance for Industry Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations three or more formulations with different release rates are recommended to define an IVIVC. Exceptions to this may be considered for formulations for which in vitro dissolution is independent of the dissolution test conditions (e.g., medium, agitation, pH, volume).
   Please submit the following information/data to aid in the regulatory decision making in terms of the acceptability of the proposed IVIVC model, if you still want to pursue the model:

   a. A modeling summary report, which provides an overview of the modeling strategy and details of the modeling procedures, including model development, model verification/modification, and model application in a step-by-step process. Inclusion of a flow chart, decision tree, or other similar representation is preferred for clarity.
   b. Demonstrate that the dissolution of the proposed drug product is dependent or independent of dissolution conditions.
   c. As part of the validation steps, follow the “leave-one out” cross validation approach in the construction and validation of your model to challenge its robustness.
   d. Provide side by side comparative formulation composition for all batches used in the model development and external predictions.
   e. Submit the executable project files (e.g., .phxproj, .xlsx or .xls, .sas) for the IVIVC model development and internal/external validation. Provide all relevant input including complete in vitro and in vivo data (i.e., individual, mean, % CV, profiles, in .csv, .xlsx or .xls, or .xpt format) and output files used in the construction and validation of the IVIVC model.
   f. Provide definition file(s) listing all input and output files, and the use or purpose of each of this files in an appropriate format (e.g., .pdf, .xpt, .xls). In addition, provide the hyperlinks for each data file and instructions for extracting these files.
   g. Provide the IVIVC predictions including the output files and summary table supporting your revised dissolution acceptance criteria, if any.

   Note that the FDA’s final decision regarding the acceptability of the IVIVC model will be made based on the totality of the supportive data and relevant information provided in the submission, which should include demonstration of a robust model predictability.

3. Based on the submitted in vitro dissolution profile data, your proposed in vitro dissolution acceptance criteria are permissive for your drug product and not acceptable. Note that per the current Agency’s guideline for proper setting of the dissolution specification, drug product acceptance criteria are set primarily based on the performance of the bio-batch/exhibit batches at release. In addition, selection of the in vitro drug dissolution acceptance criteria ranges is based on mean target value ±10% and >80% for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved IVIVC model, physiologically based absorption and pharmacokinetic model, safe space etc. Since your submitted IVIVC model is not acceptable at this time, we recommend the following acceptance criteria for the proposed generic drug product based on the bio-batch data:

3 hr	18-38%
6 hr	46-66%
12 hr	70-90%
24 hr	NLT 80%

   We request that you acknowledge your acceptance of the recommended acceptance criteria for all the strengths of your drug product at release and on stability and update your drug product release and stability specifications accordingly. In addition, please be advised that all proposed exhibit batches are expected to meet the revised dissolution specification in your stability program through your proposed expiry period. Be reminded that if stability failure occurs at Level 1 (L1), Level 2 (L2) testing and Level 3 (L3) testing should be conducted. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

Kalpana Paudel

Digitally signed by Kalpana Paudel
Date: 2/22/2022 03:38:24PM
GUID: 562e1e15002f200f35c6ccac959cdb34

Vidula Kolhatkar

Digitally signed by Vidula Kolhatkar
Date: 2/23/2022 08:01:09AM
GUID: 5424aeae00c3274f93e50573f7ca407e

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	216235		
Drug Product Name	Carbamazepine Extended-Release Tablets USP		
Strength(s)	100 mg, 200 mg, and 400 mg		
Applicant Name	Sciecure Pharma Inc.		
Applicant Address	11 Deer Park Drive, Unit 120 Monmouth Junction, NJ 08852		
US Contact Name and US Mailing Address	Nuo Wang Sciecure Pharma Inc. 11 Deer Park Drive, Unit 120 Monmouth Junction, NJ 08852 nuo.wang@sciecurepharma.com		
US Contact Telephone Number	(b) (4)		
US Contact Fax Number	732-823-1696		
Original Submission Date(s)	05/21/21		
Submission Date(s) of Amendment(s) Under Review	N/A		
Primary Assessor	Santhosh K. Pabba, Ph.D., R.Ph.		
Secondary Assessor	Fang Lu, Ph.D.		
Tertiary Assessor	Qing Liu, Ph.D.		
Study Number(s)	ARL/17/124	ARL/17/125	
Study Type(s)	Fasting	Fed	
Strength(s)	400 mg	400 mg	
Clinical Site	Accutest Research Laboratories (I) Pvt. Ltd.		
Clinical Site Address	1st & 2nd Floor, Synergy Square Complex, Krishna Industrial Estate, BIDC, Gorwa, Vadodara – 390016, India.		
Analytical Site	(b) (4)		
Analytical Site Address			
Office of Study Integrity and Surveillance (OSIS) status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete**	**Post October 1, 2014 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☒ **Complete**	

	☐ N/A (Waiver/Deem Bioequivalent) [1]	☐ N/A (Waiver/Deem Bioequivalent)[1]
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:** March 2015 **RLD Number:** NDA 020234 ☐ 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
1	Fasting	400 mg	☒ Adequate ☐ Inadequate
1	Fed	400 mg	☒ Adequate ☐ Inadequate
1	Waiver	100 mg and 200 mg	☒ Adequate ☐ Inadequate

[1] Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product, Sciecure Pharma Inc.'s Carbamazepine Extended-Release (ER) Tablets, USP, 400 mg, to the corresponding reference product, Novartis Pharmaceuticals Corp.'s TEGRETOL-XR® (carbamazepine) ER Tablets, 400 mg. Each of the BE studies was designed as a single-dose, two-treatment, four-period, two-sequence, fully replicated crossover study in healthy male subjects. Carbamazepine ER Tablets is a **Narrow Therapeutic Index (NTI)** drug. The study designs of the fasting and fed BE studies are in line with the study designs recommended in the current Product Specific Guidance (PSG) for Carbamazepine ER Tablets.[2] The applicant's fasting and fed BE studies meet the BE criteria, as specified in the PSG for this drug product. The results, as calculated by the assessor, are summarized in the tables below.

Fasting Study

Carbamazepine Extended-Release Tablets USP 1 × 400 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study No. ARL/17/124 – NTI drug product							
Parameter	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC_{0-72} (ng*hr/mL)	186527.3	105	187098.1	106	1.00	94.69	104.97
C_{max} (ng/mL)	3829.71	105	3805.51	106	1.01	95.94	105.57

Parameter	Unscaled Lower 90% CI	Unscaled Upper 90% CI	Point Estimate	sWT	sWR	sWT sWR ratio	sWT sWR Lower 90% CI	sWT sWR Upper 90% CI (≤ 2.5)
LAUCT (ng*hr/mL)	94.69	104.97	0.99	0.2900946	0.1758032	1.6501097	1.30	2.09
LCMAX (ng/mL)	95.94	105.57	1.00	0.2670923	0.1761646	1.5161517	1.20	1.92

Unscaled	sWT sWR ratio	95% Upper Confidence Bound	OUTCOME
PASS	PASS	-0.025497	PASS
PASS	PASS	-0.025757	PASS

[2] https://www.accessdata.fda.gov/drugsatfda_docs/psg/Carbamazepine_ER%20tab_020234_RV03-15.pdf (*Recommended Feb 2008; Revised Mar 2015*), last accessed 10/13/2021.

Fed Study

Carbamazepine Extended-Release Tablets USP 1 × 400 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study No. ARL/17/125							
Parameter	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC_{0-72} (ng*hr/mL)	220811.6	99	228838.0	95	0.96	94.48	98.55
C_{max} (ng/mL)	4319.80	99	4469.38	95	0.97	94.72	98.62

Parameter	Unscaled Lower 90% CI	Unscaled Upper 90% CI	Point Estimate	sWT	sWR	sWT sWR ratio	sWT/ sWR Lower 90% CI	sWT/ sWR Upper 90% CI (≤ 2.5)
LAUCT (ng*hr/mL)	94.48	98.55	0.96	0.0870073	0.0930533	0.9350258	0.73	1.20
LCMAX (ng/mL)	94.72	98.62	0.97	0.0763201	0.0923483	0.8264374	0.64	1.06

Unscaled	sWT sWR ratio	95% Upper Confidence Bound	OUTCOME
PASS	PASS	-0.004426	PASS
PASS	PASS	-0.005095	PASS

For both the fasting and fed BE study, the AUC was truncated at 72 hours. The current PSG for this drug product does not mention truncation of AUC at 72 hours. Nevertheless, the truncation of AUC at 72 hours is acceptable, as (i) based on the reported carbamazepine half-life of 25–65 hours after initial dose (RLD label), carbamazepine is a long half-life drug, and (ii) the Divisions of Bioequivalence have precedence of accepting the truncation of AUC at 72 hours for the same drug product ((b) (4) (b) (4) 213311 for Carbamazepine ER Tablets).[3] For the current ANDA, the concentration values at the later points are near flat (minimal slope), which is in agreement with the RLD label and the other approved (b) (4) 213311. The assessor considers truncation of AUC at 72 hrs and without AUCi for the current ANDA acceptable and in agreement with the precedence set in the previous approved ANDAs.

(b) (4)

Per the PSG for Warfarin Sodium Tablets,[4] for an NTI test product to be considered bioequivalent to the RLD, the test product must pass the following three (3) criteria when conducting statistical analysis using the reference-scaled average bioequivalence approach for NTI drugs:

1. The 90% CIs of test/reference geometric mean ratio must fall within the limits of 80-125% using average BE approach.
2. A 95% upper confidence bound must be less than or equal to 0 using reference-scaled average BE approach for NTI drugs.
3. The upper limits of 90% CIs of S_{WT}/S_{WR} are less than a standard value of 2.5.

The test product met all three criteria for both the fasting and fed BE studies. The fasting and fed BE studies are acceptable.

Test formulation

Per the PSG, in vivo BE studies for the 100 mg and 200 mg strengths may not be needed based on (i) acceptable BE studies for the 400 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths. All inactive ingredients utilized in the test formulation (for all strengths) are below the listed IIG levels for orally administered drug products. The test formulation of lower strengths – 100 mg and 200 mg are deemed compositionally proportional to that of the bio strength, 400 mg of the test product as per the SUPAC-MR guidance. The formulations of the test product for all strengths are acceptable.

Dissolution Testing:

The applicant conducted dissolution testing using the USP dissolution method [900 mL (for the 100 mg and 200 mg strengths) or 1800 mL (for the 400 mg strength) of Water using USP Apparatus I (basket) at 100 rpm].[5] The applicant's Quality Control (QC) dissolution method and data have been assessed separately by the Biopharmaceutics assessment team (at the time of current BE assessment, per GDRP, biopharmaceutics sent out an information request[6] (IR) to the applicant for asking the applicant for justification of selection of using 10 mesh basket and asked for discriminating ability of the selected dissolution method. The standard mesh size is 40 for basket**.**

Dissolution data in the QC media (water), the f2 values comparing the lower strengths of the test product (100 mg and 200 mg) to the bio-strength (400 mg) are greater than 50, indicating that the dissolution profiles for the 100 mg and 200 mg strengths are comparable to that for the bio-strength, 400 mg in the QC media. The applicant also conducted comparative multimedia dissolution testing using USP Apparatus I at 100 rpm

[4] https://www.accessdata.fda.gov/drugsatfda_docs/psg/Warfarin_Sodium_tab_09218_RC12-12.pdf (Recommended Dec 2012), accessed on 5/29/2019.
[5] USP41-NF36, search: carbamazepine.
[6] GDRP: 216235; https://panorama.fda.gov/project/view?ID=60aba3bc00a137245f8c5679a6384f82; document name: A216235BioPharm_IR.pdf

in three (3) media: pH 1.2 Hydrochloric Acid, pH 4.5 Acetate Buffer, and pH 6.8 Phosphate Buffer for all strengths of the test and reference products as per PSG. The results demonstrated that the dissolution profiles for the 100 mg and 200 mg strengths are comparable to that for the bio-strength, 400 mg in pH 1.2 Hydrochloric Acid, pH 4.5 Acetate Buffer, and pH 6.8 Phosphate Buffer.

Additionally, the applicant conducted *in vitro* alcohol dose dumping (ADD) study in 900 mL (for 100 mg and 200 mg strengths) and 1800 mL (for 400 mg strength) of 0.1N HCl containing 0%, 5%, 20% and 40% alcohol using USP apparatus I at 100 rpm. The current PSG does not recommend the applicant to conduct alcohol dose dumping study for the product. Assessor assessed those data for information only. For each strengths of the test product, the percent dissolved of carbamazepine at 120 minutes in 0.1 N HCl containing 0%, 5%, 20%, and 40% alcohol are comparable to those of the reference product. Therefore, the applicant's *in vitro* alcohol dose dumping study is acceptable.

The dissolution data are **adequate** with respect to the requests under 21 CFR 320.24 (b) (6) for the lower modified-release strengths (100 mg and 200 mg) of the test product. The Division of Bioequivalence I (DBI) deems the following strengths (100 mg and 200 mg) of the test product to be bioequivalent to the corresponding strengths of the reference product under 21 CFR § 320.24 (b) (6).

Per GDRP, Office of Study Integrity and Surveillance (OSIS) inspected the analytical site (b) (4) for other four ANDAs in November 2018 and the final classification was No Action Indicated (NAI).[7] Therefore, an inspection at the analytical site is not warranted at this time. Per the EIR, the inspection at the clinical site [Accutest Research Laboratories (I) Pvt. Ltd.] [8] was classified as NAI for an inspection in May 2019 for ANDA 212883 (b) (4). Therefore, an inspection at the clinical site is not warranted at this time. In addition, the studies submitted in the current ANDA do not indicate any conduct issues and no data integrity deficiencies were identified by the Assessor. The OSIS inspection status of the current ANDA is complete.

The application is **adequate**.

(b) (4)

[8] GDRP, ANDA-216235-ORIG-1; Clinical Site, Decline to Inspect_NAI_Memo_ANDA_216235_Accutest Research_Clinical.pdf, dated 8/12/2021.
https://panorama.fda.gov/task/view?ID=60ad44460084b4a3552ae5f23bfeeaaa

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Drug Product and Strength(s)	Carbamazepine Extended-Release Tablets, USP, 100 mg, 200 mg, and 400 mg
Reference Standard (RS) and Strength(s)	TEGRETOL-XR® (carbamazepine) Extended-Release Tablets, 400 mg
RS Holder; NDA/ANDA Number; Approval Date[9]	Novartis Pharmaceuticals Corp. NDA 020234 Approved 03/25/1996
Reference Listed Drug (RLD) and Strength(s)	TEGRETOL-XR® (carbamazepine) Extended-Release Tablets, 100 mg, 200 mg, and 400 mg
RLD Holder; NDA/ANDA Number; Approval Date[9]	Novartis Pharmaceuticals Corp. NDA 020234 Approved 03/25/1996

3.2 PK/PD Information[10]

Most recent RLD label Please check if an NG/G/J tube study is needed.	Label for Tegretol-XR_0320201{ NG/G/J tube study is not needed.
Indication	**Epilepsy** Tegretol is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of Tegretol as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types: 1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types. 2. Generalized tonic-clonic seizures (grand mal). 3. Mixed seizure patterns which include the above, or other partial or generalized seizures. Absence seizures (petit mal) do not appear to be controlled by Tegretol. **Trigeminal Neuralgia** Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia.

[9] Online Orange Book, search: carbamazepine, accessed on 10/13/2021. https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=020234#20142

[10] Drugs@FDA, search:20234, accessed on 10/13/2021, label updated 3/20/2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/016608s115_018281_s058_018927s055_020234_s047.pdf

	Beneficial results have also been reported in glossopharyngeal neuralgia. This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.
Black Box	**WARNINGS** Serious dermatologic reactions and hla-b*1502 allele Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (ten) and stevens-johnson syndrome (sjs), have been reported during treatment with tegretol. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly caucasian populations, but the risk in some asian countries is estimated to be about 10 times higher. Studies in patients of chinese ancestry have found a strong association between the risk of developing sjs/ten and the presence of hla-b*1502, an inherited allelic variant of the hla-b gene. Hla-b*1502 is found almost exclusively in patients with ancestry across broad areas of asia. Patients with ancestry in genetically at-risk populations should be screened for the presence of hla-b*1502 prior to initiating treatment with tegretol. Patients testing positive for the allele should not be treated with tegretol unless the benefit clearly outweighs the risk (see warnings and precautions, laboratory tests). <u>APLASTIC ANEMIA AND AGRANULOCYTOSIS</u> Aplastic anemia and agranulocytosis have been reported in association with the use of tegretol. Data from a population-based case control study demonstrate that the risk of developing these reactions is 5 to 8 times greater than in the general population. However, the overall risk of these reactions in the untreated general population is low, approximately six patients per one million population per year for agranulocytosis and two patients per one million population per year for aplastic anemia. Although reports of transient or persistent decreased platelet or white blood cell counts are not uncommon in association with the use of tegretol data are not available to estimate accurately their incidence or outcome. However, the vast majority of the cases of leukopenia have not progressed to the more serious conditions of aplastic anemia or agranulocytosis. Because of the very low incidence of agranulocytosis and aplastic anemia, the vast majority of minor hematologic changes observed in monitoring of patients on tegretol are unlikely to signal the occurrence of either abnormality. Nonetheless, complete pretreatment hematological testing should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Bioavailability	The bioavailability of Tegretol-XR tablet was 89% compared to suspension. Following a twice a day dosage regimen, Tegretol-XR tablets afford steady-state plasma levels comparable to conventional Tegretol tablets given four times a day, when administered at the same total mg daily dose. Tegretol in blood is 76% bound to plasma proteins. Plasma levels of Tegretol are variable and may range from 0.5 to 25 mcg/mL, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 mcg/mL.
Food Effect	Take TEGRETOL with food.
Tmax	3 to 12 hours after administration of Tegretol-XR tablets.
Metabolism	Tegretol is metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10,11-epoxide from Tegretol. Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine10,11 epoxide.
Excretion	After oral administration of ^{14}C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol.
Half-life	Because Tegretol induces its own metabolism, the half-life is also variable. Autoinduction is completed after 3 to 5 weeks of a fixed dosing regimen. Initial half-life values range from 25 to 65 hours, decreasing to 12 to 17 hours on repeated doses.
Maximum Daily Dose[11]	1200 mg (>15 years old); 1600 mg (adults, in rare instances)

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance	 PSG for Carbamazepine ERT_N *(Recommended Feb 2008; Revised Mar 2015)*	
Summary of OGD or DB History	Approved ANDAs:	Yes, See table below.  Orange Book Approved Drug Proc

[11] https://www.clinicalkey.com/pharmacology/monograph/90?sec=monindi&n=Tegretol -XR#dosage-limits

	Pending ANDAs:	Yes, see table below.  ANDA by RLD Search (N20234 - Te
	Controls:[12]	Yes, none from the current applicant (CSPC). CC #45618 is Memo for PSG revision (March 2015).[13]
	Protocols:[14]	Yes, none from the current applicant (CSPC).
	Pending Citizen Petitions and other legal and regulatory issues:[15] If yes, please comment.	☐ Yes ☒ No as of 10/04/2021

[12] GDRP and Mercado, search: carbamazepine, link: https://panorama.fda.gov/search?objCode=ALL&allowRedirect=false&query=carbamazepine+extended&showResultsPage=false#?facets=%5B%7B%22fieldName%22:%22categoryID%22,%22filters%22:%5B%22categoryID_s:537669e800073f720fcf8b8f349f8fd9%22%5D%7D%5D&size=%22All%22

[13] GDRP, Guidance Revision #45618, Carbamazepine ER Tablets RLD 020234 Guidance Revision, Carbamazepine_45618_revision_memo.doc, dated 2/28/2015. http://panorama.fda.gov/task/view?ID=5491cfa30023ae8b72ebc99504f460bf

[14] OGD-DB Protocols Tracking, search: carbamazepine,

[15] DLRS policy alert list modified 05/20/2019 http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/DLRS/SitePages/Home.aspx, accessed on 7/8/2019

3.4 Pre-Study Bioanalytical Method Validation

Table 4 (A) Bio-analytical Method Validation Report of Carbamazepine – Fasting

Information requested	Data	
Bio-analytical method validation report location	Module 5.3.1.4, Appendix 16.5 Bio-analytical Report of Carbamazepine, Annex 16.13, Method validation report, Pages 1 to 87	
Analyte	Carbamazepine	
Internal standard (IS)	Carbamazepine-D10	
Method description	Extraction Procedure	
	Type of Extraction	Solid Phase Extraction
	(b) (4)	
	Detector	LC-MS/MS (b) (4)

Information requested	Data	
	Diluent	Methanol: Water (60:40 v/v)
Method description	Mass to charge ratio(m/z)	Carbamazepine : Parent Ion 237.10 amu : Product Ion 194.10 amu Carbamazepine-D10 : Parent Ion 247.20 amu : Product Ion 204.20 amu
Limit of quantitation	50.008 ng/mL	
Average recovery of drug (%)	LQC: 69.45%, MQC: 64.83%, HQC: 74.14% Avg.: 69.47%	
Average recovery of IS (%)	80.35%	
Standard curve concentrations (units/mL)	500.008 ng/mL to 6000.943 ng/mL	
QC concentrations (units/mL)	LLQC: 50.018 ng/mL LQC: 149.552 ng/mL MQC: 2100.737 ng/mL HQC: 4801.684 ng/mL	
QC Intra day precision range (%)	LLQC: 8.63% LQC: 3.69% MQC: 4.44% HQC: 4.70%	
QC Intra day accuracy range (%)	LLQC: 102.28% LQC: 99.11% MQC: 98.30% HQC: 97.69%	
QC Inter day precision range (%)	LLQC: 6.34% LQC: 3.62% MQC: 3.17% HQC: 2.85%	
QC Inter day accuracy range (%)	LLQC: 104.45% LQC: 100.80% MQC: 98.91% HQC: 97.63%	
Bench-top stability (hrs)	19 Hrs at room temperature	
Stock solution stability (days)	8 days at 2ºC to 8ºC	
Processed sample stability	8 Hrs at room temperature, 33 Hrs at 10ºC	
Freeze-thaw stability (cycles)	3 cycles and 5 cycles at -70ºC±10ºC	
Long term storage stability (days)	178 days long term stability at -20°C ±5°C and -70°C ±10°C generated and data incorporated in Addendum to MV report, Addendum-08	
Dilution integrity	1/2 and 1/4 times dilution	

Information requested	Data
Selectivity	No significant interfering peaks noted at the RT of analyte and IS in blank plasma samples

Addendum-02 of Carbamazepine2 (Fasting)

Information requested	Data
Bio-analytical method validation report location	Module 5.3.1.4, Appendix 16.5 Bio-analytical Report of Carbamazepine, Annex 16.14, Addendum to Method validation report, Addendum-02, Pages 1 to 54
Analyte	Carbamazepine
Internal standard (IS)	Carbamazepine-D10
Method description	Extraction Procedure
	Note: All frozen plasma samples were thawed before analysis. Each plasma sample was vortexed to ensure complete mixing of contents.
	Type of Extraction | Solid Phase Extraction
	(b) (4) [redacted]

Information requested	Data	
	(b) (4) [redacted]	
	Diluent	Methanol: Water (60:40 v/v)
	Mass to charge ratio(m/z)	Carbamazepine : Parent Ion 237.200 Da : Product Ion 194.100 Da Carbamazepine-D10 : Parent Ion 247.200 Da : Product Ion 204.200 Da
Limit of quantitation	50.038 ng/mL	
Average recovery of drug (%)	NA	
Average recovery of IS (%)	NA	
Standard curve concentrations (units/mL)	50.038 ng/mL to 5994.608 ng/mL	
QC concentrations (units/mL)	LLQC: 50.049 ng/mL LQC: 149.646 ng/mL MQC: 2102.048 ng/mL HQC: 4804.681 ng/mL DQC: 24004.201 ng/mL	
QC Intra day precision range (%)	LLQC: 2.66 % to 5.11% LQC: 2.25% to 4.01% MQC: 2.79% to 5.27% HQC: 1.97% to 2.86% DQC: 1.80% to 3.40%	

Information requested	Data
QC Intra day accuracy range (%)	LLQC: 98.28% to 102.51% LQC: 98.08% to 100.41% MQC: 98.72% to 99.62% HQC: 101.07% to 102.18% DQC: 100.96% to 102.58%
QC Inter day precision range (%)	LLQC: 4.02% LQC: 3.11% MQC: 3.84% HQC: 2.39% DQC: 2.85%
QC Inter day accuracy range (%)	LLQC: 100.23% LQC: 99.52% MQC: 99.17% HQC: 101.53% DQC: 101.82%
Bench-top stability (hrs)	NA
Stock solution stability (days)	NA
Processed sample stability	NA
Freeze-thaw stability (cycles)	NA
Long term storage stability (days)	NA
Dilution integrity	Dilution QC'S were prepared using a factor of 1/5 on the concentration about 4 times of ULOQ
Selectivity	No significant interfering peaks noted at the RT of analyte and IS in blank plasma samples

Addendum-04, Addendum-05, Addendum-08, Addendum-09 and Addendum-10 of Carbamazepine2 (Fasting)

Information requested	Data
Bio-analytical method validation report location	Module 5.3.1.4, Appendix 16.5 Bio-analytical Report of Carbamazepine, Annex 16.15, Addendum to Method validation report, Addendum-04, Pages 1 to 46 Annex 16.16, Addendum to Method validation report, Addendum-05, Pages 1 to 26 Annex 16.17, Addendum to Method validation report, Addendum-08, Pages 1 to 39 (178 days long term stability) Annex 16.18, Addendum to Method validation report, Addendum-09, Pages 1 to 42 Annex 16.19, Addendum to Method validation report, Addendum-10, Pages 1 to 42
Analyte	Carbamazepine

Information requested	Data	
Internal standard (IS)	Carbamazepine-D10	
Method description	Extraction Procedure	
	Note: All frozen plasma samples were thawed before analysis. Each plasma sample was vortexed to ensure complete mixing of contents.	
	Type of Extraction	Solid Phase Extraction
	(b) (4)	
Method description		

Information requested	Data
	For Addendum to method validation report, Addendum-04, Addendum-05 and Addendum-08
	Carbamazepine at around 1.42 minutes Carbamazepine D10 at around 1.42 minutes Note: The retention time listed shall not be considered as method specification but as assay parameters. The mobile phase can be delivered as isocratic, a premixed solution using a single pump or gradient using binary pumps.
	For Addendum to method validation report, Addendum-09
	Carbamazepine at around 1.40 minutes Carbamazepine D10 at around 1.40 minutes Note: The retention time listed shall not be considered as method specification but as assay parameters. The mobile phase can be delivered as isocratic, a premixed solution using a single pump or gradient using binary pumps.

(Fed)

Information requested	Data	
Bio-analytical method validation report location	Module 5.3.1.4, Appendix 16.5 Bio-analytical Report of Carbamazepine, Annex 16.13, Method validation report, Pages 1 to 87	
Analyte	Carbamazepine	
Internal standard (IS)	Carbamazepine-D10	
Method description	Extraction Procedure	
	Type of Extraction	Solid Phase Extraction
	(b) (4)	

Information requested	Data		
Method description	Mass to charge ratio(m/z)	Carbamazepine amu amu Carbamazepine-D10 amu amu	: Parent Ion 237.10 : Product Ion 194.10 : Parent Ion 247.20 : Product Ion 204.20
Limit of quantitation	50.008 ng/mL		
Average recovery of drug (%)	LQC: 69.45%, MQC: 64.83%, HQC: 74.14% Avg.: 69.47%		
Average recovery of IS (%)	80.35%		
Standard curve concentrations (units/mL)	500.008 ng/mL to 6000.943 ng/mL		
QC concentrations (units/mL)	LLQC: 50.018 ng/mL LQC: 149.552 ng/mL MQC: 2100.737 ng/mL HQC: 4801.684 ng/mL		
QC Intra day precision range (%)	LLQC: 8.63% LQC: 3.69% MQC: 4.44% HQC: 4.70%		
QC Intra day accuracy range (%)	LLQC: 102.28% LQC: 99.11% MQC: 98.30% HQC: 97.69%		
QC Inter day precision range (%)	LLQC: 6.34% LQC: 3.62% MQC: 3.17% HQC: 2.85%		
QC Inter day accuracy range (%)	LLQC: 104.45% LQC: 100.80% MQC: 98.91% HQC: 97.63%		
Bench-top stability (hrs)	19 Hrs at room temperature		
Stock solution stability (days)	8 days at 2ºC to 8ºC		
Processed sample stability	8 Hrs at room temperature, 33 Hrs at 10ºC		
Freeze-thaw stability (cycles)	3 cycles and 5 cycles at -70ºC±10ºC		
Long term storage stability (days)	178 days long term stability at -20°C ±5°C and -70°C ±10°C generated and data incorporated in Addendum to MV report, Addendum-08		
Dilution integrity	1/2 and 1/4 times dilution		
Selectivity	No significant interfering peaks noted at the RT of analyte and IS in blank plasma samples		

Information requested	Data
Method description	For Addendum to method validation report, Addendum-10
	Carbamazepine at around 1.34 minutes Carbamazepine D10 at around 1.34 minutes Note: The retention time listed shall not be considered as method specification but as assay parameters. The mobile phase can be delivered as isocratic, a premixed solution using a single pump or gradient using binary pumps.
	Detector: LC-MS/MS (b) (4)
	Diluent: Methanol: Water (60:40 v/v)
	Mass to charge ratio(m/z)
	For Addendum to method validation report, Addendum-04, Addendum-05 and Addendum-08
	Carbamazepine : Parent Ion 237.000 Da : Product Ion 194.100 Da Carbamazepine-D10 : Parent Ion 247.000 Da : Product Ion 204.200 Da
	For Addendum to method validation report, Addendum-09
	Carbamazepine : Parent Ion 237.200 Da : Product Ion 194.100 Da Carbamazepine-D10 : Parent Ion 247.200 Da : Product Ion 204.200 Da
	For Addendum to method validation report, Addendum-10
	Carbamazepine : Parent Ion 237.100 Da : Product Ion 194.000 Da Carbamazepine-D10 : Parent Ion 247.100 Da : Product Ion 204.200 Da
Limit of quantitation	For Addendum to method validation report, Addendum-04, Addendum-05 and Addendum-08 50.033 ng/mL For Addendum to method validation report, Addendum-09 and Addendum -10 50.048 ng/mL
Average recovery of drug (%)	NA
Average recovery of IS (%)	NA
Standard curve concentrations (units/mL)	For Addendum to method validation report, Addendum-04, Addendum-05 and Addendum-08 50.033 ng/mL to 5993.997 ng/mL For Addendum to method validation report, Addendum-09 and Addendum-10 50.048 ng/mL to 5990.691 ng/mL

Information requested	Data
QC concentrations (units/mL)	For Addendum to method validation report, Addendum-04 and Addendum-08 LLQC: 50.052 ng/mL LQC: 149.904 ng/mL M1QC: 804.040 ng/mL MQC: 2110.605 ng/mL HQC: 4824.240 ng/mL DQC: 24028.943 ng/mL For Addendum to method validation report, Addendum-09 and Addendum-10 LLQC: 50.058 ng/mL LQC: 149.672 ng/mL M1QC: 800.922 ng/mL MQC: 2102.419 ng/mL HQC: 4805.530 ng/mL DQC: 23994.058 ng/mL
QC Intra day precision range (%)	For Addendum to method validation report, Addendum-04 LLQC: 1.90% LQC: 1.12% M1QC: 1.51% MQC: 2.72% HQC: 0.70% DQC: 1.74% For Addendum to method validation report, Addendum-09 LLQC: 1.75% LQC: 1.42% M1QC: 2.42% MQC: 2.02% HQC: 1.08% DQC: 1.11% For Addendum to method validation report, Addendum-10 LLQC: 3.71% LQC: 7.12% M1QC: 5.62% MQC: 3.66% HQC: 4.01% DQC: 0.55%

Information requested	Data
QC Intra day accuracy range (%)	For Addendum to method validation report, Addendum-04 LLQC: 98.48% LQC: 99.61% M1QC: 99.52% MQC: 100.53% HQC: 101.01% DQC: 100.09% For Addendum to method validation report, Addendum-09 LLQC: 101.08% LQC: 103.30% M1QC: 107.84% MQC: 104.09% HQC: 104.13% DQC: 104.17% For Addendum to method validation report, Addendum-10 LLQC: 92.24% LQC: 104.04% M1QC: 112.11% MQC: 107.71% HQC: 105.04% DQC: 107.09%
QC Inter day precision range (%)	NA
QC Inter day accuracy range (%)	NA
Bench-top stability (hrs)	NA
Stock solution stability (days)	NA
Processed sample stability	NA
Freeze-thaw stability (cycles)	NA
Long term storage stability (days)	NA
Dilution integrity	Dilution QC'S were prepared using a factor of 1/5 on the concentration about 4 times of ULOQ
Selectivity	No significant interfering peaks noted at the RT of analyte and IS in blank plasma samples

Addendum-04, Addendum-05, Addendum-08 and Addendum-11 of Carbamazepine2 (Fed)

Information requested	Data
Bio-analytical method validation report location	Module 5.3.1.4, Appendix 16.5 Bio-analytical Report of Carbamazepine, Annex 16.14, Addendum to Method validation report, Addendum-04, Pages 1 to 46 Annex 16.15, Addendum to Method validation report, Addendum-05, Pages 1 to 26 Annex 16.16, Addendum to Method validation report, Addendum-08, Pages 1 to 39 (178 days long term stability) Annex 16.17, Addendum to Method validation report, Addendum-11, Pages 1 to 43
Analyte	Carbamazepine
Internal standard (IS)	Carbamazepine-D10
Method description	Extraction Procedure
	Note: All frozen plasma samples were thawed before analysis. Each plasma sample was vortexed to ensure complete mixing of contents.
	Type of Extraction: Solid Phase Extraction
	(b) (4)
Method description	

<table>
<tr><th>Information requested</th><th>Data</th></tr>
<tr><td></td><td>(b) (4)
[redacted]
Retention time</td></tr>
<tr><td></td><td>For Addendum to method validation report, Addendum-04, Addendum-05 and Addendum-08</td></tr>
<tr><td></td><td>Carbamazepine at around 1.42 minutes
Carbamazepine D10 at around 1.42 minutes

Note: The retention time listed shall not be considered as method specification but as assay parameters. The mobile phase can be delivered as isocratic, a premixed solution using a single pump or gradient using binary pumps.</td></tr>
<tr><td></td><td>For Addendum to method validation report, Addendum-11</td></tr>
<tr><td></td><td>Carbamazepine at around 1.34 minutes
Carbamazepine D10 at around 1.34 minutes

Note: The retention time listed shall not be considered as method specification but as assay parameters. The mobile phase can be delivered as isocratic, a premixed solution using a single pump or gradient using binary pumps.</td></tr>
<tr><td></td><td>Detector | LC-MS/MS [redacted](b) (4))</td></tr>
<tr><td></td><td>Diluent | Methanol: Water (60:40 v/v)</td></tr>
<tr><td></td><td>Mass to charge ratio(m/z)</td></tr>
<tr><td></td><td>For Addendum to method validation report, Addendum-04, Addendum-05, Addendum-08 and Addendum-11</td></tr>
<tr><td></td><td>Carbamazepine : Parent Ion 237.000 Da
: Product Ion 194.100 Da
Carbamazepine-D10 : Parent Ion 247.000 Da
: Product Ion 204.200 Da</td></tr>
<tr><td>Limit of quantitation</td><td>For Addendum to method validation report, Addendum-04, Addendum-05 and Addendum-08
50.033 ng/mL
For Addendum to method validation report, Addendum-11
50.047 ng/mL</td></tr>
<tr><td>Average recovery of drug (%)</td><td>NA</td></tr>
<tr><td>Average recovery of IS (%)</td><td>NA</td></tr>
</table>

Information requested	Data
Standard curve concentrations (units/mL)	For Addendum to method validation report, Addendum-04, Addendum-05 and Addendum-08 50.033 ng/mL to 5993.997 ng/mL For Addendum to method validation report, Addendum-11 50.047 ng/mL to 5995.681 ng/mL
QC concentrations (units/mL)	For Addendum to method validation report, Addendum-04 and Addendum-08 LLQC: 50.052 ng/mL LQC: 149.904 ng/mL M1QC: 804.040 ng/mL MQC: 2110.605 ng/mL HQC: 4824.240 ng/mL DQC: 24028.943 ng/mL For Addendum to method validation report, Addendum-11 LLQC: 50.048 ng/mL LQC: 149.643 ng/mL M1QC: 800.764 ng/mL MQC: 2102.006 ng/mL HQC: 4804.584 ng/mL DQC: 23979.758 ng/mL
QC Intra day precision range (%)	For Addendum to method validation report, Addendum-04 LLQC: 1.90% LQC: 1.12% M1QC: 1.51% MQC: 2.72% HQC: 0.70% DQC: 1.74% For Addendum to method validation report, Addendum-11 LLQC: 1.47% LQC: 1.79% M1QC: 1.26% MQC: 0.75% HQC: 2.13% DQC: 1.54%

Information requested	Data
QC Intra day accuracy range (%)	For Addendum to method validation report, Addendum-04 LLQC: 98.48% LQC: 99.61% M1QC: 99.52% MQC: 100.53% HQC: 101.01% DQC: 100.09% For Addendum to method validation report, Addendum-11 LLQC: 100.44% LQC: 97.83% M1QC: 100.80% MQC: 100.94% HQC: 101.25% DQC: 102.61%
QC Inter day precision range (%)	NA
QC Inter day accuracy range (%)	NA
Bench-top stability (hrs)	NA
Stock solution stability (days)	NA
Processed sample stability	NA
Freeze-thaw stability (cycles)	NA
Long term storage stability (days)	NA
Dilution integrity	Dilution QC'S were prepared using a factor of 1/5 on the concentration about 4 times of ULOQ
Selectivity	No significant interfering peaks noted at the RT of analyte and IS 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

- A LC-MS/MS method was developed and validated for the analysis of carbamazepine. The applicant submitted the following acceptable addendums to the method validation report #ARL/REP/MI/166CBZ/00 (April 2015):

Addendum No./ Version No.	Date	Reason
ADD01	03 June 2015	Long term stability in matrix at -70°C ±10°C for 83 days incorporated.
ADD02	24 May 2017	As per addendum to Method Validation protocol, Addendum-01 (ARL/PRT/MI/166CBZ/00/ADD01) – i. Partial Method Validation will be done on (b) (4) (MI/01/020/0012) as Instrument changed from (MI/01/020/0007) to (b) (4) MI/01/020/0012). ii. Analyst software version changed from 1.4.2 to 1.5.2. iii. Injection volume changed from 2µL to 1 µL. iv. Run time changed from 2.5 min. to 3.0 min. v. Incorporated Working solution stability at LLOQ and ULOQ level.
ADD03	25 May 2017	As per addendum to Method Validation protocol, Addendum-02 (ARL/PRT/MI/166CBZ/00/ADD02) – Partial Method Validation was done on (b) (4) (MI/01/020/0014) as Instrument changed from (MI/01/020/0012) t (b) (4) (MI/01/020/0014).
ADD04	26 July 2017	As per addendum to Method Validation protocol, Addendum-03 (ARL/PRT/MI/166CBZ/00/ADD03) – 1) Instrument changed from T (b) (4) (MI/01/020/0014). To (b) (4) (MI/01/020/0020). 2) Analyst software version changed from 1.5.2 to 1.6.3. 3) Incorporated M1QC level at the 804.040 ng/mL concentration
ADD05	13 September 2017	As per addendum to Method Validation protocol, Addendum-04 (ARL/PRT/MI/166CBZ/00/ADD04) – 1) Selectivity and Selectivity in presence of Concomitant drugs (Azithromycin, Omeprazole, Norfloxacin, Tinidazole and Paracetamol) experiments was performed on instrument ID – MI/01/020/0020 (b) (4)

Addendum No./ Version No.	Date	Reason
ADD06	14 September 2017	As per Addendum to Method Validation Protocol (ARL/PRT/MI/166CBZ/00/ADD03) initial analysis of long term stability was done on Instrument ID: MI/01/020/0020 (b) (4) (b) (4) and samples were stored at -20°C ±5°C for long term stability. Long term stability in matrix at -20°C ±5°C for 32 days done on Instrument ID: MI/01/020/0020 (b) (4) (b) (4).
ADD07	14 November 2017	As per Addendum to Method Validation Protocol (ARL/PRT/MI/166CBZ/00/ADD03) initial analysis of long term stability was done on Instrument ID: MI/01/020/0020 (b) (4) (b) (4) and samples were stored at -20°C ±5°C and -70°C ±10°C for long term stability. Long term stability in matrix at -20°C ±5°C and -70°C ±10°C for 123 days done on Instrument ID: MI/01/020/0020 (b) (4) (b) (4).
ADD08	30 December 2017	As per Addendum to Method Validation Protocol (ARL/PRT/MI/166CBZ/00/ADD03) initial analysis of long term stability was done on Instrument ID: MI/01/020/0020 (b) (4) (b) (4) and samples were stored at -20°C ±5°C and -70°C ±10°C for long term stability. Long term stability in matrix at -20°C ±5°C and -70°C ±10°C for 178 days done on Instrument ID: MI/01/020/0020 (b) (4) (b) (4).
ADD09	30 January 2018	Partial Method Validation was done as per Addendum to method Validation Protocol, Addendum-05 (ARL/PRT/MI/166CBZ/00/ADD05) 1. Instrument changed from (b) (4) (MI/01/020/0020). to (b) (4) (MI/01/020/0012). 2. Analyst software version changed from 1.6.3 to 1.5.2. 3. Incorporated M1QC level at the 800 ng/mL concentration

Addendum No./ Version No.	Date	Reason
ADD10	30 January 2018	Partial Method Validation was done as per Addendum to method Validation Protocol, Addendum-06 (ARL/PRT/MI/166CBZ/00/ADD06) 4. Instrument changed from (b) (4) (MI/01/020/0012) to (b) (4) (MI/01/020/0014).
ADD11	30 January 2018	Partial Method Validation was done as per Addendum to method Validation Protocol, Addendum-07 (ARL/PRT/MI/166CBZ/00/ADD07) 1. Partial Method Validation was done on (b) (4) (MI/01/020/0013) as Instrument changed from (MI/01/020/0014) to (b) (4) (MI/01/020/0013).

- K2EDTA was used as the anticoagulant for the method validation and during the sample collection.

- The average percent recovery was 69.47% for Carbamazepine. The recovery was consistent across all three levels of Quality Control (QC) samples, ranging from 69.45% to 74.14%. The concentrations: LQC: 149.552 ng/mL; MQC: 2100.737 ng/mL; HQC: 4801.684 ng/mL (shown below). The average recovery of Internal Standard (IS) 80.35%.

Average recovery of drug (%)	LQC: 69.45%, MQC: 64.83%, HQC: 74.14% Avg.: 69.47%
Average recovery of IS (%)	80.35%
Standard curve concentrations (units/mL)	500.008 ng/mL to 6000.943 ng/mL
QC concentrations (units/mL)	LLQC: 50.018 ng/mL LQC: 149.552 ng/mL MQC: 2100.737 ng/mL HQC: 4801.684 ng/mL

- The applicant demonstrated adequate long term storage stability (LTSS) studies for carbamazepine. The LTSS data is sufficient to cover the storage periods of fasting and fed studies.

- Dilution integrity was established at 1/5 dilution (%CV: 1.06) for DQC: 23994 ng/mL during the fasting BE study. Please see complete details in Section: Reanalysis of Study sample for the fasting and fed BE studies of the current assessment. The Cmax values for the fasting and fed BE studies are shown below:

Fasting

		Test				Reference				Ratio
Parameter	**Unit**	**Mean**	**CV%**	**Min**	**Max**	**Mean**	**CV%**	**Min**	**Max**	**(T/R)**
CMAX	ng/mL	4351.267	12.72	3080.68	5648.78	4504.365	13.16	3291.61	5970.62	0.97

Fed

		Test				Reference				Ratio
Parameter	**Unit**	**Mean**	**CV%**	**Min**	**Max**	**Mean**	**CV%**	**Min**	**Max**	**(T/R)**
CMAX	ng/mL	4351.267	12.72	3080.68	5648.78	4504.365	13.16	3291.61	5970.62	0.97

- The pre-study method validation is adequate.

3.5 In Vivo Studies

ARL/17/124 - Fasting Study

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters			Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-72} (ng*hr/mL)	
ARL/17/124	Primary objective was to demonstrate the bioequivalence between Test Product (T): Carbamazepine Extended-Release Tablets, 400 mg and Reference Product (R): Tegretol®-XR (carbamazepine extended-release tablets) 400 mg in normal, healthy, adult, Male and/ or Female human subjects, under fasting conditions. Secondary objective was to monitor the safety and tolerability of a single oral dose of investigational medicinal products (IMPs).	A randomized, open label, balanced, two treatment, two sequence, four period, single dose, fully replicated, crossover, study.	Test product (T) 01 Tablet, Carbamazepine Extended Release Tablets 400 mg Oral, 17030031 [Batch No.]	54 Male normal, healthy, adult, human subjects 33.39 (22 - 44)	3955.972 ± 885.234 (22.377)	20.000 (3.000 - 36.000)	194956.017 ± 50173.811 (25.736)	Refer Appendix 5.3.1.2
			Reference product (R) 01 Tablet, Tegretol®-XR 400 mg (carbamazepine extended-release tablets) Oral, F1156		3889.795 ± 784.326 (20.164)	24.000 (4.500 - 28.020)	192028.018 ± 40838.903 (21.267)	

			[Lot No.]					

Fed – ARL/17/125

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters			Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-72} (ng*hr/ mL)	
ARL/17/125	Primary objective was to demonstrate the bioequivalence between Test Product (T): Carbamazepine Extended-Release Tablets, 400 mg and Reference Product (R): Tegretol®-XR (carbamazepine extended-release tablets) 400 mg in normal, healthy, adult, Male and/ or Female	A randomized, open label, balanced, two treatment, two sequence, four period, single dose, fully replicated,	Test product (T) 01 Tablet, Carbamazepine Extended Release Tablets 400 mg Oral, 17030031 [Batch No.]	50 Male normal, healthy, adult, human subjects 30.86 (19 - 44)	4351.267 ± 553.657 (12.724)	24.000 (9.000 - 36.000)	222790.477 ± 33582.363 (15.074)	Refer Appendix 5.3.1.2

	human subjects, under fed conditions. Secondary objective was to monitor the safety and tolerability of a single oral dose of investigational medicinal products (IMPs).	crossover, study.	Reference product (R) 01 Tablet, Tegretol®-XR 400 mg (carbamazepine extended-release tablets) Oral, F1156 [Lot No.]		4504.365 ± 592.851 (13.162)	20.000 (7.500 - 48.000)	230685.632 ± 31760.082 (13.768)	

3.6 OSIS Status

Refer to comments in the Executive Summary.

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

4.1.1.1.1 Study Information

Study Number	ARL/17/124
Study Title	A Randomized, Balanced, Open Label, Two Treatment, Two Sequence, Four Period, Single Dose, Fully Replicated, Crossover, Bioequivalence Study of Test Product Carbamazepine Extended-Release Tablets, 400 mg of Sciecure Pharma Inc, with Reference Product Tegretol®-XR (carbamazepine extended-release tablets) 400 mg of Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936., in Normal, Healthy, Adult, Male and/ or Female Human Subjects under Fasting Conditions.
Study Type	√ In Vivo BE ☐ In Vitro BE ☐ Permeability ☐ Other
Submission Location:	
Study Report	5.3.1.2
Validation Report	5.3.1.4
Bioanalytical Report	5.3.1.4
Clinical Site (Name, Address, Phone #, Fax #)	Accutest Research Laboratories (I) Pvt. Ltd. 1st & 2nd Floor, Synergy Square Complex, Krishna Industrial Estate, BIDC, Gorwa, Vadodara – 390016, India. Tel.: +91 265-2280161,62,63 Fax: +91 265-2280164
Principal Clinical Investigator (Name, Email)	Dr. Tushar Shah, M.B.B.S. Tushar.shah@accutestglobal.com
Analytical Site (Name, Address, Phone #, Fax #)	(b) (4)
Principal Analytical Investigator (Name, Email)	
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) 128 Days (b) -70ºC ±10ºC

Long-Term Storage Stability Coverage (no. days @ temp ºC)	178 days @ -20ºC ±5ºC and @ -70ºC ±10ºC
LTSS Data Location	In module 5.3.1.4, (5314-bioanal-report) refer annex 16.17 of Bio-analytical report of Clinical study report (Addendum to MV report no: ARL/REP/MI/166CBZ/00/ADD08, Section No. 13.1, Page No. 29 to 37 of 39)

4.1.1.1.2 Product (Bio-batch) Information

Product	Test	Reference
Treatment ID	T	R
f Product/ Brand Name	Carbamazepine Extended Release Tablets 400 mg [Name of IMP]	Tegretol®-XR 400 mg (carbamazepine extended-release tablets) [Brand Name]
Manufacturer	Manufactured By: Beijing Sciecure Pharmaceutical Co., Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301, PR China Manufactured for: Sciecure Pharma Inc 11 Deer Park Dr Suite 120 Monmouth Junction NJ 08852	Manufactured By: Novartis Pharma Production GmbH wehr, Germany Manufactured for: Novartis Pharmaceuticals Core-East Hanover, New Jersey 07936
Batch No. /Lot No.	17030031	F1156
Manufacture Date	04 March 2017	NA
Expiration Date	February-2019	March-2019
Strength	400 mg	400 mg
Dosage Form	Extended Release Tablet	Extended Release Tablet
Bio-batch Size	(b) (4)	NA
Production Batch Size		NA
Potency	98.6%	N/A
Uniformity of Dosage Units (AV ≤ 15)	1.3	N/A
Dose Administered	01 Tablet	01 Tablet
Route of Administration	Oral	Oral

NA = Not Available

Are the test and reference products expired at the time of study? **If Yes, please comment.**	☐ Yes ☒ No **Fasting study:** Period-I: 11 September 2017 – 15 September 2017 Period-II: 02 October 2017 – 06 October 2017

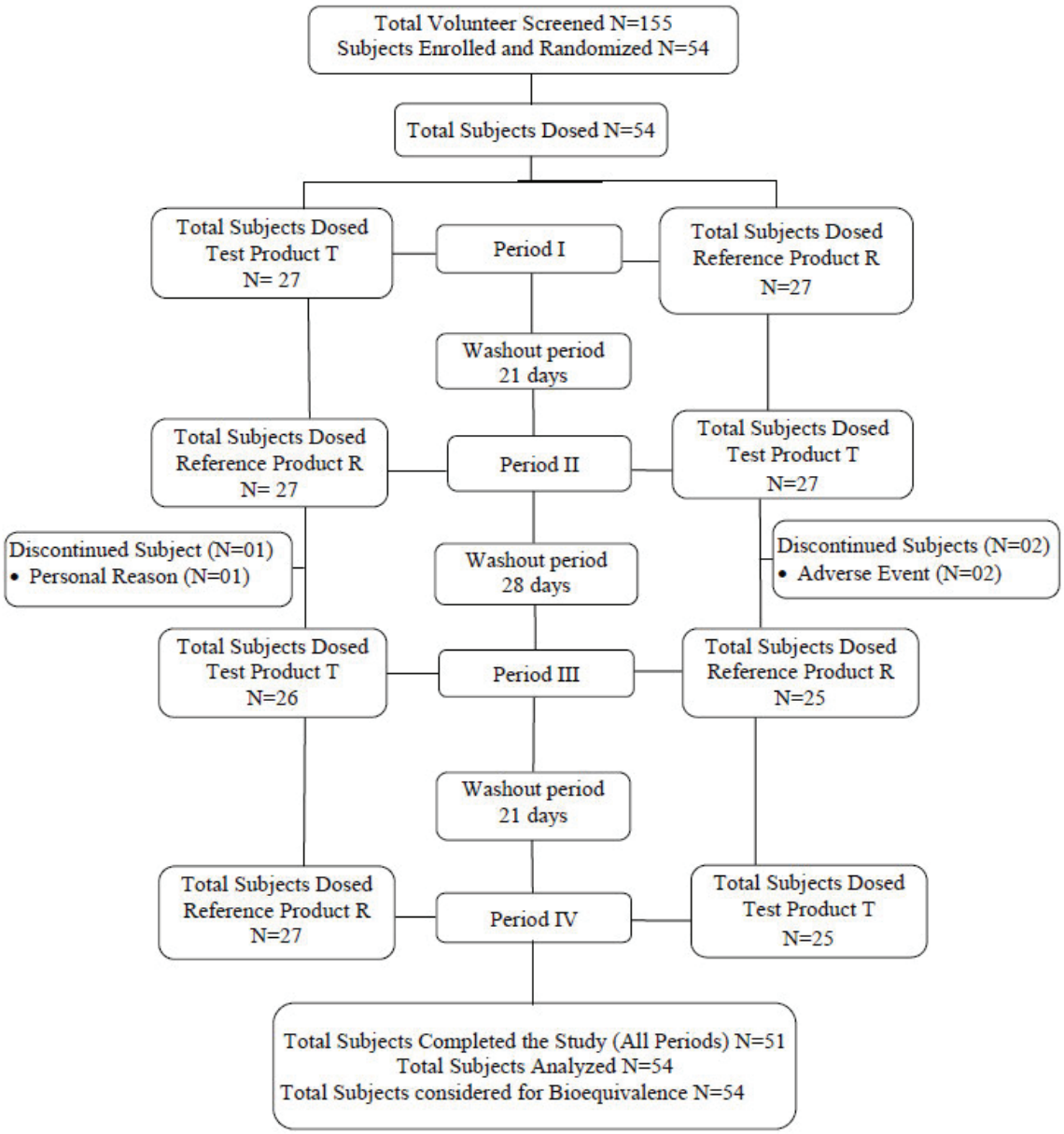
	Period-III: 30 October 2017 – 03 November 2017 Period-IV: 20 November 2017 – 24 November 2017 Clinical Completion Date: 24 November 2017 **Fed Study:** Period-I: 18 September 2017 – 22 September 2017 Period-II: 13 October 2017 – 17 October 2017 Period-III: 03 November 2017 – 07 November 2017 Period-IV: 24 November 2017 – 28 November 2017 Clinical Completion Date: 28 November 2017 Test manufactured date: March 4, 2017 RLD expired date: March 2019
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
Is difference of the potency values for the Test and RLD within 5%? **If No, please comment.**	☒ Yes ☐ No

Assessor note: the applicant has conducted QC dissolution testing on 3 batches (including the bio-batch) for each strength of the test product. However, the applicant conducted multi-media and alcohol dose dumping (not required per PSG) on only one batch of the test product. The test batch (Lot# 201803091) of 400 mg bio-strength on which the multi-media and alcohol dose-dumping studies were conducted is not a bio-batch (Lot# 17030031). The applicant did not provide justification for it. However, the assessor found that the QC dissolution data for the 3 batches (Lot# 201803091, Lot# 17030041, and Lot# 17030031) of 400 mg bio-strength are comparable at each time point.

4.1.1.1.3 Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 54 Dosed: Period I: 54 Period II: 54 Period III: 51 Period IV: 52 Completed all 4 periods: 51 Samples Analyzed: 54 Statistical Data Analyzed: 54 Please see the details below.
No. of Sequences	2
No. of Periods	4
No. of Treatments	2
No. of Groups	1
Washout Period	21 days
Randomization	☒ Yes ☐ No
Blood Sampling Times	0.00 (pre-dose) and 1.50, 3.00, 4.50, 6.00, 7.50, 9.00, 10.50, 12.00, 13.00, 14.00, 15.00, 16.00, 18.00, 20.00, 24.00, 26.00, 28.00, 36.00, 48.00 and 72.00hours post-dose in each study period.
IRB Approval	☒ Yes ☐ No Final version: approved August 12, 2017
Informed Consent	☒ Yes ☐ No Final version: approved August 12, 2017
Length of Fasting	At least 10.00 hours
Length of Confinement	Subjects were confined within the facility for at least 10.50 hours prior to dosing until 72.00 hours post dose 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

10.1 DISPOSITION OF SUBJECTS



Comments on Study Design: Adequate

- The applicant conducted an open-label, single-dose, randomized, two-treatment, four-period, two-sequence, fully-replicate, crossover design study as recommended by the PSG for Carbamazepine ER Tablets.

- The washout periods (21 days) are adequate considering that the half-life for Carbamazepine ER Tablets ranges from 25 to 65 hours.

- Per fasting study protocol #ARL/17/124, the AUC was truncated at 72 hours. The current PSG for this drug product does not mention truncation of AUC at 72 hours.

Nevertheless, the truncation of AUC at 72 hours is acceptable, as (i) based on reported carbamazepine half-life of 25–65 hours after initial dose (RLD label), carbamazepine is a long half-life drug, and (ii) the DBs has precedence of accepting the truncation of AUC at 72 hours for the same drug product ((b) (4) 213311 Carbamazepine ER Tablets).[3]

- Per the applicant's fasting study protocol #ARL/17/124, inclusion of subjects for pharmacokinetic and statistical analysis will be done as per the following table:

Category	Study Period completion status	S_{wr} calculations	T vs T intra subject variability	Scaled Average BE (if Swr ≥ 0.294)	Average BE (if Swr < 0.294)	90% CI for σWT/σWR
A	All 4 study periods	Yes	Yes	Yes	Yes	Yes
B	3 study periods with Reference twice and Test once	Yes	No	No	Yes	No
C	3 study periods with Reference once and Test twice	No	Yes	No	Yes	No
D	2 study periods with Reference once and Test once	No	No	No	Yes	No
E	2 study periods with Test twice	No	Yes	No	No	No
F	2 study periods with Reference twice	Yes	No	No	No	No
G	1 study period (with any one treatment)	No	No	No	No	No

Subjects belonging to category G will not be considered for bioanalysis unless withdrawn due to adverse events.
Calculation of the within-subject SD for the test and reference product (S_{WT} & S_{WR}) will be done using the PROC MIXED procedure of SAS.

51subjects (excluding subjects (b) (6) completed all 4 periods and belong to category A.

Details:

- A total of 54 subjects were planned and enrolled in this study.
- A total of 54 subjects were dosed in period-I.

- A total of 54 subjects were dosed in period-II.
- Subject no. (b) (6) was dropped out from the study in period-III due to personal reason.
- Subject no. (b) (6) were withdrawn from the study in check in of study period-III due to adverse event.
- A total of 51 subjects were dosed in period-III.
- A total of 52 subjects were dosed in period-IV.
- A total of 51 subjects were completed the clinical phase (All the periods) of study successfully. Hence plasma samples of 54 subjects were analyzed.

- The data of 54 subjects were considered to perform pharmacokinetic analysis. The data of 52 subjects (excluding subject (b) (6) were considered for calculation within subject SD for reference products (i.e R vs R variability). The data of 51 subjects (excluding subject (b) (6) were considered for calculation within subject SD for test products (i.e T vs T variability).
- The data of 51 subjects (excluding subject (b) (6)) were considered for calculation of 95% upper bound using scaled average bioequivalence approach.
- The data of 54 subjects were considered for calculation of 90% confidence interval using average bioequivalence approach.

4.1.1.2 Clinical Results

4.1.1.2.1 Demographic Profile of Subjects

Study No. ARL/17/124			
		Treatment Groups	
		Test Product (T) N=54	Reference Product (R) N=54
Age (years)	Mean ± SD	33.39 ± 06.31	33.39 ± 06.31
	Range	22 - 44	22 - 44
Age Groups		Nil	Nil
	18 – 40	42 (77.78 %)	42 (77.78 %)
	41 – 64	12 (22.22 %)	12 (22.22 %)
	65 – 75	Nil	Nil
	> 75	Nil	Nil
Sex	Male	54 (100.00 %)	54 (100.00 %)
	Female	00 (00.00 %)	00 (00.00 %)
Race	Asian	54 (100.00 %)	54 (100.00 %)
	Black	Nil	Nil
	Caucasian	Nil	Nil
	Hispanic	Nil	Nil
	Other	Nil	Nil
BMI (kg/m^2)	Mean ± SD	21.37 ± 01.79	21.37 ± 01.79
	Range	18.50 – 24.65	18.50 – 24.65
Other Factors		-	-

[5] Provide a separate table for each Bioequivalence Study.

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No

4.1.1.2.2 Dropout Information

Study No. ARL/17/124				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
(b) (6)	Subject was dropped out from the study due to personal reason.	III	No	NA

(b) (6)	Subject was withdrawn from the study at 15:05 on 30 October 2017 due to adverse event. Treatment given was Test product T in Period-II.	III	No	NA
	Subject was withdrawn from the study at 19:13 on 30 October 2017 due to adverse event. Treatment given was Test product T in Period-II.	III	No	NA

Note: "" subject was discontinued from study in period-III only.*

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No ☐ N/A

4.1.1.2.3 Study Adverse Events

Body System / Adverse Event	**Reported Incidence by Treatment Groups**	
	Fasted Bioequivalence Study No. ARL/17/124	
	Test Product T (N=105)	**Reference Product R (N=106)**
Hemopoietic System		
High Total W.B.C. Count	01 (00.95 %)	00 (00.00 %)
Low Hemoglobin	01 (00.95 %)	00 (00.00 %)
Total	02 (01.90 %)	00 (00.00 %)

Subjects Experiencing Emesis

N/A

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 As per the RLD label
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

4.1.1.2.4 Protocol Deviations

Study No. ARL/17/124		
Type	**Subject #s (Test)**	**Subject #s (Reference)**
Blood Sample Time Point Deviation	25 Subjects [redacted] (b) (6)	28 Subjects
Blood and Urine Laboratory Test Deviation (For Subject no. 09 on Check-in of period-IV)	-	-
Statistical Analysis Plan Deviation	-	-

Note: The Assessor agrees with the applicant that the above deviations did not impact the study outcome.[16]

If the applicant used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is 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 ☐ N/A

Comments on Clinical Results: Adequate

Dropouts: There were 3 dropouts (subject [redacted] (b) (6) in the fasting study. Subject # [redacted] (b) (6) experienced AEs [redacted] (b) (6) low hemoglobin; [redacted] (b) (6) high WBC) after administration of test product in Period 2. Hence were discontinued. Subject 9 withdrew consent prior to Period 3 check-in. The applicant dropouts are acceptable and should not have an impact on the study outcome.

[16] \\CDSESUB1\evsprod\anda216235\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\arl-17-124\clinical-study-report.pdf, page 38-40 of 66.

Adverse Events:
No serious adverse events or deaths were reported in the fasting study. The adverse event profile of the test product is comparable as per the RLD label which has mentioned about hemoglobin and blood count abnormalities.

Protocol Deviations:
There were few sampling point and missing sample deviations. This should not have an impact on the study outcome as the applicant used actual sampling time points in the statistical analysis.

Concomitant Medications:
The subjects who experienced AEs withdrew their consent from the fasting BE study, (Subject (b) (6) who was given Tablet Zifi 200 (Cefixime 200 mg) Twice Daily from 30 October 2017 to 04 November 2017 and subject (b) (6) was given Tablet Livogen (Ferrous Fumarate-152 mg, Folic Acid-1500 mcg), once daily from 30 October 2017 from 13 November 2017 as a treatment of adverse event). Therefore, there is no impact of concomitant medication on the fasting BE study outcome.

4.1.1.3 Bioanalytical Results

4.1.1.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

Note: the assessor prepared the current table for applicable SOP's based on the information in the bioanalytical study report.

SOP No.	Effective Date of SOP	SOP Title
	(b) (4)	Preparation of Standard Solutions, Calibration Curve Standards and Quality Control Samples
		Bio-Analytical Method Validation
		Batch Acceptance of Subject Sample Analysis
		Chromatographic Acceptance Criteria
		Repeat Sample Analysis
		Incurred Sample Reanalysis

All necessary SOPs submitted?	☒ Yes ☐ No

4.1.1.3.2 Sample Analysis Calibration and Quality Control

Bioequivalence Study No. ARL/17/124 Carbamazepine									
Parameter	**Standard Curve Samples**								
	CS-01	**CS-02**	**CS-03**	**CS-04**	**CS-05**	**CS-06**	**CS-07**	**CS-08**	**CS-09**

Concentration (ng/mL)	50.048	100.095	300.285	600.571	1201.141	2402.282	3603.423	5104.850	5990.691
Inter day Precision (% CV)	1.03	1.90	2.40	3.42	2.55	2.17	2.49	2.41	2.80
Inter day Accuracy (% Actual)	100.58	98.79	100.13	99.79	99.64	99.97	100.59	99.61	100.57
Linearity (Range of r^2)	0.9920 to 1.0000								
Linearity Range (ng/mL)	50.048 to 5990.691								
Sensitivity/LOQ (ng/mL)	50.048								

Bioequivalence Study No. ARL/17/124 Carbamazepine					
Parameter	**Quality Control Samples**				
	LQC	**M1QC**	**MQC**	**HQC**	**DQC**
Concentration (ng/mL)	149.672	800.922	2102.419	4805.530	23994.058
Inter day Precision (% CV)	3.83	3.75	4.22	4.00	1.06
Inter day Accuracy (% Actual)	102.71	106.64	103.10	104.20	102.42

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 Assessor for additional actions	☐ Yes ☒ No See comments below.
Were 20% of chromatograms included?	☒ Yes ☐ No Subjects No. 22 to 32
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

Rejected Batches:

- Analytical run # ARL_17_124 (b) (6) batch consecutive CC points namely CS06, CS07 & CS08 not within acceptance due to poor chromatography for Analyte and IS.
- Analytical run # ARL_17_124 (b) (6) Batch was stopped after injection CARMVLQC165/211217 due to UPS power failure hence batch was rejected.
- For analytical run # ARL_17_124_ (b) (6) In this batch MQC'S not meets acceptance criteria, hence batch was rejected. Hence, this run was rejected and repeated.

- Analytical run # ARL_17_124_(b) (6) was In this batch LQC & M1QC'S not meets acceptance criteria, hence batch was rejected.
- Analytical run # RL_17_124_(b) (6)_A was stopped after injection 28/Y/T14 due to UPS power failure hence batch was rejected.

Reinjections and Reintegrations:

None.

Assessor note: The assessor verified and confirms that the above rejected runs were conducted as per the effective SOP's listed above. The data is adequate.

4.1.1.3.3 Reanalysis of Study Samples

Study No. ARL/17/124 In Module 5.3.1.4 (5314-bio-ana-rep), page no. 27 to 52 of 57 Carbamazepine								
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[8]	00	00	0.00	0.00	00	00	0.00	0.00
outside assay range (Code A)	08	02	0.18	0.05	08	02	0.18	0.05
Inconsistent internal standard area response (code B)	00	01	0.00	0.02	00	01	0.00	0.02
Power failure (Code C1)	84	84	1.90	1.90	84	84	1.90	1.90
Batch Repeat (Code E)	126	126	2.84	2.84	126	126	2.84	2.84
Positive Pre-dose (code F)	02	01	0.05	0.02	00	00	0.00	0.00
Total	220	214	4.97	4.83	218	213	4.92	4.81

Table No.11: Listing of repeat sample analysis for Carbamazepine, outside assay range (Code A)

Sr. No.	Sample ID	Initial conc. (ng/mL) (A)	Initial run ID	Repeat conc. (ng/mL) (B)	Repeat run ID	Final reported value (ng/mL)	Instrument ID
1	19/Y/T14	7539.346	ARL_17_124_(b) (6)	4441.670	ARL_17_124_SUB_REPETITION	4441.670	MI/01/020/0012
2	19/Z/T13	6596.551	ARL_17_124_	5309.514	ARL_17_124_SUB_REPETITION	5309.514	MI/01/020/0012
3	19/Z/T18	6077.482	ARL_17_124_	5246.757	ARL_17_124_SUB_REPETITION	5246.757	MI/01/020/0012
4	19/W/T13	6343.220	ARL_17_124_	4859.771	ARL_17_124_SUB_REPETITION	4859.771	MI/01/020/0012
5	19/W/T14	5997.074	ARL_17_124_	5604.245	ARL_17_124_SUB_REPETITION	5604.245	MI/01/020/0012
6	19/W/T15	6586.890	ARL_17_124_	5590.649	ARL_17_124_SUB_REPETITION	5590.649	MI/01/020/0012
7	19/W/T16	6487.375	ARL_17_124_	5596.361	ARL_17_124_SUB_REPETITION	5596.361	MI/01/020/0012
8	19/W/T17	6366.621	ARL_17_124_	5631.576	ARL_17_124_SUB_REPETITION	5631.576	MI/01/020/0012
9	19/W/T18	6252.656	ARL_17_124_	5567.917	ARL_17_124_SUB_REPETITION	5567.917	MI/01/020/0012
10	24/W/T13	6020.052	ARL_17_124_	4345.355	ARL_17_124_SUB_REPETITION	4345.355	MI/01/020/0012

Table No.12: Listing of repeat sample analysis for Carbamazepine, Inconsistent internal standard area response (Code B)

Sr. No.	Sample ID	Initial run ID	Initial conc. (ng/mL)	Repeat run ID	Repeat conc. (ng/mL)	Final reported value (ng/mL)	Instrument ID
1	21/W/T06	ARL_17_124_(b) (6)	3465.544	ARL_17_124_SUB_REPETITION	3577.748	3577.748	MI/01/020/0012

Table No.15: Listing of repeat sample analysis for Carbamazepine, Positive pre-dose (code F)

Sr. No.	Sample Code	Initial Conc. (A) (ng/mL)	Initial run ID	Repeat-1 Conc. (B) (ng/mL)	Repeat-2 Conc. (C) (ng/mL)	Repeat run ID	Mean of repeats (D) (ng/mL)	SD of repeats	% CV of repeat analysis	% Difference (D/A-1)*100	Final Reported Conc. (ng/mL)
Instrument ID – MI/01/020/0012											
1	26/Y/T01	60.510	ARL_17_124_(b) (6)	57.456	57.470	ARL_17_124_SUB_REPETITION	57.463	0.010	0.02	-5.04	60.510
Instrument ID – MI/01/020/0014											
1	39/Y/T01	75.776	ARL_17_124_(b) (6)	80.141	79.368	ARL_17_124_Repetition	79.755	0.547	0.69	5.25	75.776
2	39/W/T01	69.745	ARL_17_124_	71.131	73.099	ARL_17_124_Repetition	72.115	1.392	1.93	3.40	69.745

All the other repeated samples shown in the applicant's bioanalytical report[17] are in accordance with SOP (b) (4), "*Repeat Sample Analysis*." (criteria described below):

Code A (Outside of Assay Range): Ten samples was reanalyzed due to this reason as per the SOP (b) (4) "*Repeat Sample Analysis*.. The Assessor verified the raw data for the reanalyzed sample due to this reason. The original concentration of the above-mentioned samples repeated for the code: A was above the highest calibration curve standard concentration of 5900 ng/mL and highest QC level of 4805 ng/mL. The Assessor notes that during pre-study method validation, the applicant has conducted dilution integrity '5' factor dilution at concentration at 23944 ng/mL, diluted to 5 times (%CV: 1.06%). Upon verification of the raw data for the reanalyzed sample due to this reason, the Assessor confirms that the reanalysis is acceptable and the repeat analysis was performed in accordance with the applicants repeat analysis SOP (as shown below).

SAMPLE OUTSIDE ASSAY RANGE: CODE A

Samples with initial concentration above the highest calibration curve standard concentration will be considered for repeat analysis under Code A i.e. "sample outside assay range".

Analyst/ group leader will calculate the proposed appropriate dilution of respective sample, so that the concentrations of sample in repeat analysis will be within the assay range.

Analyst/ group leader will ensure that the appropriate dilution validation data is available.

Respective sample(s) will be diluted appropriately with interference free blank matrix. This diluted sample(s) will be analyzed in singlet. The dilution factor to be used will be mentioned in the form no.: (b) (4) 'REPEAT ANALYSIS APPROVAL' under additional comments section.

Note:

Dilution QCs will also be processed and analyzed along with all the repeated samples under Code A in the same batch as applicable.

The concentration will be calculated by applying respective dilution factor.

[17] \\CDSESUB1\evsprod\anda216235\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\arl-17-124\5314-bioanal-report.pdf,

- **Code B**: For analyte carbamazepine, as per the SOP, one (1) sample was reanalyzed due to the following reason. The Assessor checked the raw data[18] for the reanalyzed sample due to this reason. The IS peak area of the above-mentioned sample is out of the +/- 50% of the batch average internal standard response (CCs and QCs only). The applicant conducted reanalysis per their pre-established SOP and reported in repeat value in singlet. (as shown below).

INCONSISTENT INTERNAL STANDARD AREA RESPONSE: CODE B

Analyst/ group leader will calculate the mean internal standard response in the batch by considering all samples of the batch including calibration curve and quality control samples (excluding system suitability and blank samples). Analyst/ group leader will calculate the percent difference of internal standard response of individual sample in the batch with respect to the mean internal standard response in the batch.

Note: *In cases where labeled internal standards are used, if for more than 20 % but less than 50 % of samples inclusive of Calibration Curve standards and Quality Control samples, internal standard deviation is observed to be significant i.e. greater than ± 50 % of the mean response of internal standard response in batch but accuracy of calibration curve standards and quality control samples is still within acceptance as per SOP for "BATCH ACCEPTANCE OF SUBJECT SAMPLE ANALYSIS", then batch can be accepted without repetition. However individual repeats for internal standard variation from such a batch, if any, will be identified for repetition under Code B.*

[18] \\CDSESUB1\evsprod\anda216235\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\arl-17-124\result-table-remaining-sub.pdf; page # 63 of 146

INCOMPLETE ANALYSIS: CODE C

Typical reasons of incomplete analysis are as follows but not limited to:

Power failure, software error or equipment failure.

Sample loss due to vial breaking or spillage.

Power failure, software error or equipment failure: Code C1

If a batch is interrupted due to power failure, software error or equipment failure (such as auto sampler/ pump malfunctioning or drift in response), analyst/ group leader will rectify the problem by addressing the interruption to engineer(s).

Analyst/ group leader will ensure that unanalyzed samples of interrupted batch are within validated period of auto sampler stability and that reinjection reproducibility has been established during method validation. Based on stability data available, sample analysis will be carried out in following way:

Analyst/ group leader will reanalyze entire interrupted batches which are not within validated period of auto sampler stability under Code C1.

Analyst/ group leader will re-inject entire interrupted batches by giving extension 'R' to the acquisition batch, which are within validated period of auto sampler stability and if reinjection reproducibility has been established during method validation.

Also, if in case, some unknown sample(s) from an acquisition batch are not acquired/skipped, they will be repeated under Code C1. In such an event, if calibration curve standards or quality control samples are not acquired/ skipped, but the batch meets the acceptance criteria in terms of all predefined criteria excluding these samples, the batch will be accepted, without repeating or re-injecting them.

Sample loss due to vial breaking, extraction cartridge related issues or accidental spillage of sample: Code C2

Analyst will repeat such sample(s) in singlet, which are thus lost during analysis.

- **Code: F**: The applicant repeated 3 pre-dose (0.0hr) samples in duplicate due to positive pre-dose (code F) as per (b) (4) "Repeat Sample Analysis," Section 10.1.3.6 POSITIVE PRE-DOSE: CODE F. *Pre-dose subject samples in any period, with concentration greater than or equal to concentration of LLOQ of the analyte, will be repeated under this code; in duplicate.* For all the pre-dose

samples, the % difference between the mean of repeat values and initial value were within ± 15% of the initial value and CV (%) of the repeat values were within 20% variation. Hence, the initial values were reported for all the samples repeated under per code F. For subjects (b) (6), in Period II, III, and IV, the assessor verified and confirms that the pre-dose concentrations were all less than 5% of the respective Cmax for that subject and period. Therefore, those subjects were included in PK and statistical analysis.

BATCH REPEATS: CODE E

Batches which do not meet acceptance criteria as per SOP for 'BATCH ACCEPTANCE OF SUBJECT SAMPLE ANALYSIS' will be repeated under this code in singlet.

POSITIVE PRE-DOSE: CODE F

Pre-dose subject samples in any period, with concentration greater than or equal to concentration of LLOQ of the analyte, will be repeated under this code; in duplicate.

Note: Do not use the reanalysis results obtained simultaneously for other analyte, when the sample is repeated; refer specifically to cases of combination of drugs.

Does the Assessor agree with the reanalysis of study samples: analytical and/or PK repeat?	☒ Yes ☐ No
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

Incurred Sample Reanalysis (ISR):

To demonstrate reproducible quantitation of incurred subject samples, a total of 450 (10.16%) of the study samples for carbamazepine which were selected as per the SOP titled: Incurred Sample Reanalysis SOP, were reassayed. Samples around Cmax and later in the elimination phase were selected. The incurred sample reproducibility (ISR) values were used for comparison purposes and are included in the analytical report but not used in determining the final reported value. Incurred sample repeats were considered acceptable if the original and reassay values from two-thirds of the repeated samples had a relative percent difference of ≤ 20%. The results of the incurred sample repeats showed

that 97.78% met the acceptance criteria. The applicant's ISR analysis was consistent with the FDA's *Guidance for Industry: Bioanalytical Method Validation (September 2013)*.[19]

Comments on Bioanalytical Results: Adequate

[19] Guidance for Industry – Bioanalytical Method Validation. September 2013. https://www.fda.gov/downloads/Drugs/Guidances/ucm368107.pdf.

4.1.1.4 Pharmacokinetic Results

4.1.1.4.1 Arithmetic Mean Pharmacokinetic Parameters - Assessor Calculated

ARITHMETIC MEANS AND RATIOS - REPLICATE 1 (PERIODS 1 AND 2)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	196688.5	21.83	101601.0	267744.6	190737.9	20.23	103969.3	250682.5	1.03
CMAX	ng/mL	3985.174	18.50	2105.88	5173.53	3896.609	19.98	2183.39	5044.77	1.02
TMAX	hr	18.000	.	9.00	36.00	20.000	.	9.00	28.02	0.90

*** Tmax values are presented as median, range.**

ARITHMETIC MEANS AND RATIOS - REPLICATE 2 (PERIODS 3 AND 4)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	193121.6	29.64	38840.38	324359.6	193367.7	22.44	100477.4	306080.0	1.00
CMAX	ng/mL	3925.053	26.13	948.79	5643.37	3882.718	20.55	2170.74	5941.04	1.01
TMAX	hr	20.000	.	3.00	28.02	24.000	.	4.50	28.00	0.83

* Tmax values are presented as median, range.

ARITHMETIC MEANS AND RATIOS - ALL PERIODS (PERIODS 1, 2, 3, AND 4)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	194956.0	25.74	38840.38	324359.6	192028.0	21.27	100477.4	306080.0	1.02
CMAX	ng/mL	3955.972	22.38	948.79	5643.37	3889.795	20.16	2170.74	5941.04	1.02
TMAX	hr	20.000	.	3.00	36.00	24.000	.	4.50	28.02	0.83

Note: The Assessor-calculated arithmetic mean PK parameters are the same as those calculated by the applicant.[20]

4.1.1.4.2 Geometric Means and 90% Confidence Intervals - Applicant Calculated

Reference Scaled Average Bioequivalence Approach Used	√ **Yes** ☐ **No**
If No, then complete Table 3A only If Yes, then complete Tables 3A and 3B	
Carbamazepine Extended Release Tablets 400 mg (No of subjects completed= 54)	

[20] \\CDSESUB1\evsprod\anda216235\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\arl-17-124\clinical-study-report.pdf, page 44 of 66.

Single oral dose (1 x 400 mg Tablets) Least Squares Geometric Means, Ratio of Means and 90% Confidence Interval						
Fasting Bioequivalence Study (Study Code: ARL/17/124)						
Parameter	Test	N*	RLD	N*	Ratio	90% C.I.
AUC_{0-72} (ng*hr/mL)	186527.2582	105	187098.1302	106	99.6949	94.6866 - 104.9681
C_{max} (ng/mL)	3829.7136	105	3805.5114	106	100.6360	95.9368 - 105.5653

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	S^2_{WR}	sWR	S^2_{WT}	sWT
LAUC72 (ng*hr/mL)	99.4909	94.6866	104.9681	0.030907	0.1758	0.084155	0.2901
LCMAX (ng/mL)	100.2764	95.9368	105.5653	0.031034	0.1762	0.071338	0.2671

Parameter	sWT / sWR Ratio	90% Upper Confidence Bound of sWT / sWR Ratio	Criteria Bound	Method Used	Outcome
LAUC72 (ng*hr/mL)	1.650110	2.086913	-0.0227	ABE and SABE	Bioequivalent
LCMAX (ng/mL)	1.516152	1.917495	-0.0234	ABE and SABE	Bioequivalent

Note:
SABE= Scaled Average Bioequivalence
ABE=Average Bioequivalence

4.1.1.4.3 Geometric Means and 90% Confidence Intervals - Assessor Calculated

Carbamazepine Extended-Release Tablets USP 1 × 400 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study No. ARL/17/124 – NTI drug product							
Parameter	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC_{0-72} (ng*hr/mL)	186527.3	105	187098.1	106	1.00	94.69	104.97
C_{max} (ng/mL)	3829.71	105	3805.51	106	1.01	95.94	105.57

Parameter	Unscaled Lower 90% CI	Unscaled Upper 90% CI	Point Estimate	sWT	sWR	sWT sWR ratio	sWT sWR Lower 90% CI	sWT sWR Upper 90% CI (≤ 2.5)
LAUCT (ng*hr/mL)	94.69	104.97	0.99	0.2900946	0.1758032	1.6501097	1.30	2.09
LCMAX (ng/mL)	95.94	105.57	1.00	0.2670923	0.1761646	1.5161517	1.20	1.92

Unscaled	sWT sWR ratio	95% Upper Confidence Bound	OUTCOME
PASS	PASS	-0.025497	PASS
PASS	PASS	-0.025757	PASS

Assessor's Note:

- The Assessor-calculated geometric least square mean PK parameters are comparable.
- The Assessor calculated S_{WT} and S_{WR} are the same as those calculated by the applicant.
- The 95% upper confidence bound calculated by the Assessor and the applicant are same.

4.1.1.4.4 Additional Information for the Study

Root Mean Square Error	**SWT values** AUC72: 0.29 Cmax: 0.26	**SWR values** AUC72: 0.176 Cmax: 0.176
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 Median Tmax T/R ratio: 0.83 The Tmax range for T and R is comparable (please see the Tmax evaluation below).	
Were the subjects dosed in groups? **If yes, was the statistical analysis proper? Is reanalysis by Assessor necessary?**	☐ Yes ☒ No	
Are there measurable drug concentrations at 0 hr? **If yes, please comment (and take necessary action, if needed).**	☒ Yes ☐ No See details in Section 4.1.1.3.3 Reanalysis of Study Samples.	
Are there first measurable drug concentration 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	

Comments on PK results: Adequate

- Per the PSG for Warfarin Sodium Tablets,[4] for an NTI test product to be considered bioequivalent to the RLD, the test product must pass the following three (3) criteria when conducting statistical analysis using the reference-scaled average bioequivalence approach for NTI drugs:

  1. The 90% CIs of test/reference geometric mean ratio must fall within the limits of 80-125% using average BE approach.
  2. A 95% upper confidence bound must be less than or equal to 0 using reference-scaled average BE approach.
  3. The upper limits of 90% CIs of S_{WT}/S_{WR} are less than a standard value of 2.5.

  The test product met all three criteria for the fasting BE study.

Tmax evaluation:

- The assessor verified and found that the median Tmax for the test product is comparable to the previously approved ANDAs for this drug product (see the details below).
- For the current test product: the median Tmax is 20.00 hrs (range 9.00 - 36.00 hrs) for the Test product and 24 hrs (range 4.5 - 28.00 hrs) for the Reference product with T/R ratio of 0.83. The assessor provides the following justification to address the observed Tmax difference based on the previously approved ANDAs for this drug product.
- For example: In the approved ANDA # 212948[21]: The median Tmax was 20.00 hrs (range 6.00 - 28.00 hrs) for the Test product and 16.00 hrs (range 6.00 - 28.00 hrs) for the Reference product with T/R ratio of 1.25. Per RLD Label, following chronic oral administration of Tegretol-XR tablets, plasma levels peak at approximately 3 to 12 hours, which shows wide variation. The assessor of A212948 provided the following justification to address the observed Tmax difference.
- *The assessor firstly evaluated the distribution of Tmax values by generating a stick plot using the individual Tmax values for both Test and Reference products. The percentage of T/R ratios <0.8, within 0.8-1.2 and >1.2 are 23.08%, 42.31% and 34.62%, respectively, which shows the majority of T/R ratios are within 0.8-1.2. The stick plots showed that the Tmax values for test and reference products are similarly distributed in the fasting study*.

- *RLD Label states "Because Tegretol induces its own metabolism, the half-life is also variable. Autoinduction is completed after 3 to 5 weeks of a fixed dosing regimen. Initial half-life values range from 25 to 65 hours, decreasing to 12 to 17*

[21] GDRP; A212948; link: https://panorama.fda.gov/task/view?ID=5d2353a800051d67ce0545990d68d725
Document name: A212948N000DB-Review01-07082019

hours on repeated doses". For most of the indications, this drug product is indicated for chronic use, administered twice daily. Carbamazepine induces its own metabolism (autoinduction) on chronic use. For this reason, the assessor did not use non-parametric superposition approach to evaluate the effects of multiple doses on the Tmax difference between the test and RLD products, as the result generated from fixed elimination half-life will not reflect actual concentration levels at steady state.

- *Previously the DB consulted the OGD clinical group regarding the Tmax differences between test and reference products for Carbamazepine Extended Release Tablet for* (b) (4) *As stated in the consult, there is uncertainty of the significance of the shape of the time/concentration curve, on the therapeutic effect and potential adverse events, as there is no PK/PD relationship available. Since the ER product was approved based on comparison to the IR product, the Tmax difference between test and reference might not be a concern.*
- Furthermore, the current assessor searched for some in-house approved/pending ANDAs for this drug product (Carbamazepine ER tablets, 400 mg) for the fasting BE studies and summarized the median Tmax data in the following table.

Application No.	Median Tmax (Min-Max) (hrs)		T/R	PK Evaluation	Approval Status
	Test	Reference			
ANDA 212948	20 (b) (4)	16.0 (b) (4)	1.25	Adequate	Approved
(b) (4)					
ANDA 213311	24 (b) (4)	24 (b) (4)	1.0	Adequate	Approved
ANDA 213159	24	24	1.0	Adequate	Pending
(b) (4)					
ANDA 078115	27 (b) (4)	27 (b) (4)	1.0	Adequate	Approved
ANDA 205571	21	16	1.31	Adequate	Approved
ANDA 212948	20	16	1.25	Adequate	Approved
ANDA 216235*	20	24	0.833	Adequate based on above listed approved ANDAs	Pending

*Current application

(b) (4)

PK data from withdrawn ANDAs:

ANDA	Test T_{max} Median	Test T_{max} Mean	Referance T_{max} Median	Referance T_{max} Mean	T/R ratio Median T_{max}	T/R ratio Mean T_{max}
(b) (4)						

- As shown in the tables above, the other in-house applications did not show significant difference in median Tmax between test and reference products. The median Tmax of current test product falls within that in in house ANDAs. The Tmax range from the current application (9.0 to 36.0 hrs for the test product) is comparable to the applications listed in the above table.
- In conclusion, based on above justifications, the Tmax difference between test and reference product in the fasting study is acceptable.

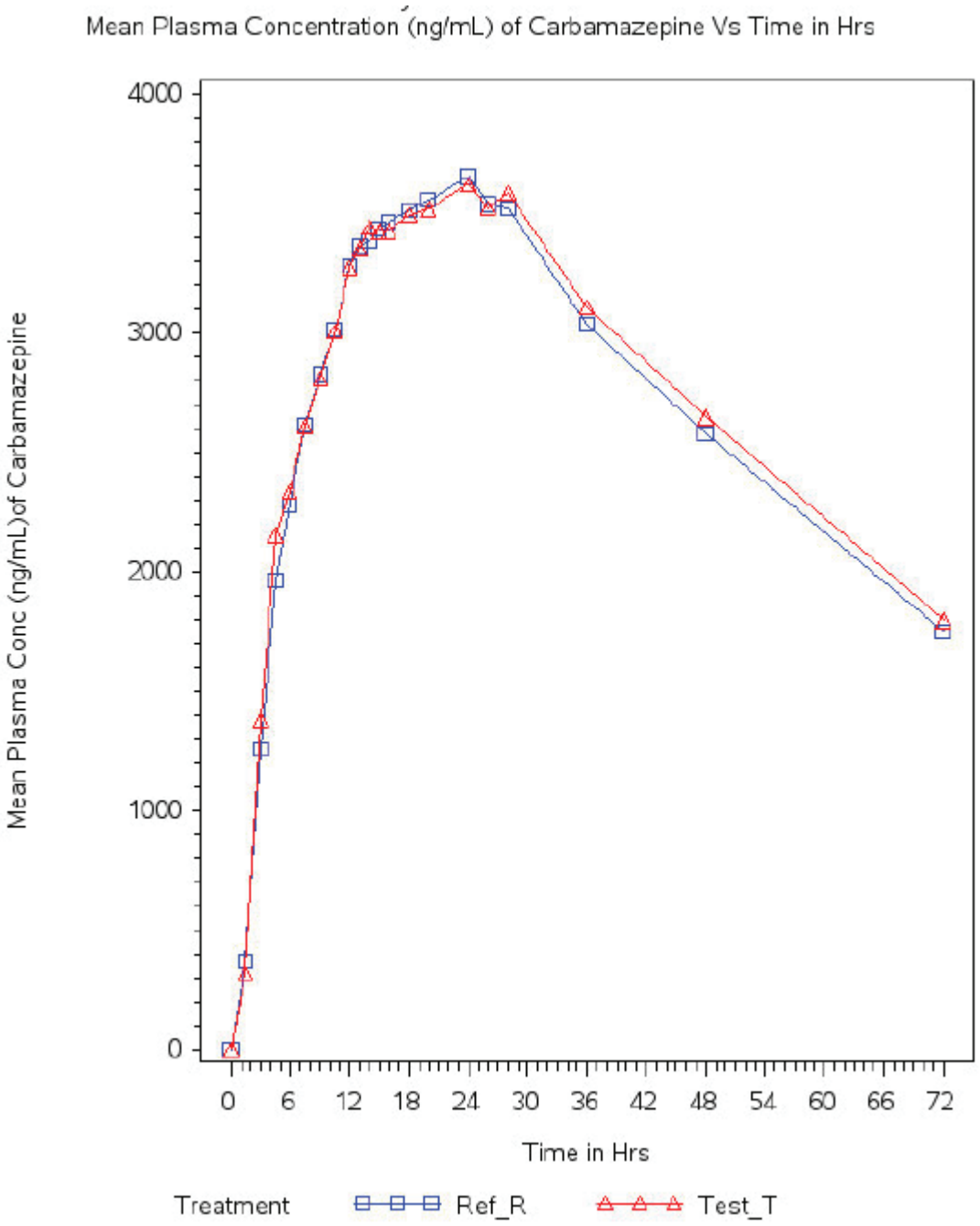
4.1.1.5 Overall Comment

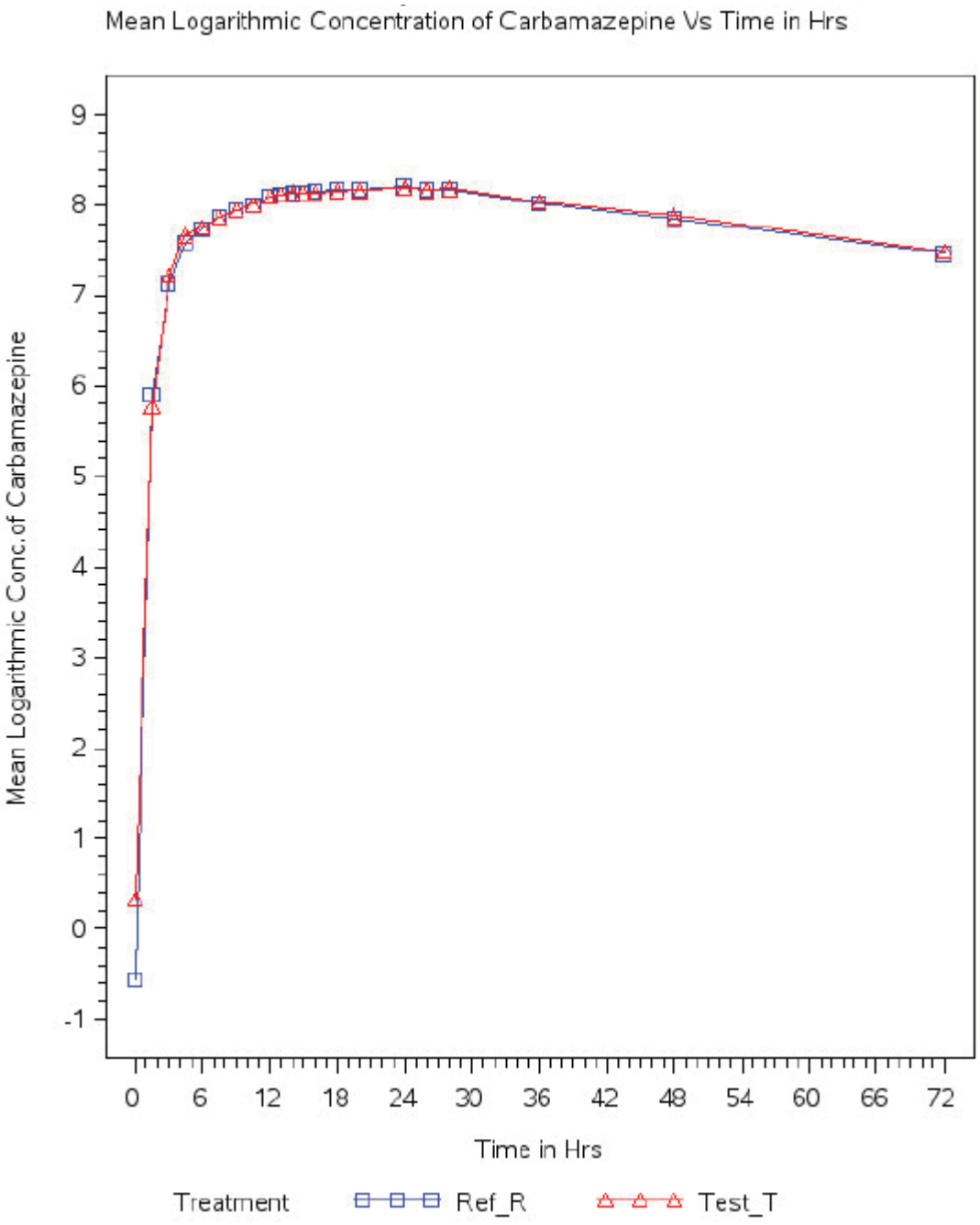
Was the fasting Bioequivalence study acceptable? Acceptable.

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Time (hr)	Test (n=105)		Reference (n=106)		Ratio
	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	
0	1.39	721.71	0.57	1029.56	2.43
1.5	322.08	64.97	368.16	57.65	0.87
3	1377.32	27.53	1254.47	30.99	1.10
4.5	2153.21	21.13	1963.67	26.81	1.10
6	2335.91	20.24	2279.95	22.97	1.02
7.5	2609.00	19.49	2613.66	21.25	1.00
9	2809.17	20.93	2824.04	20.50	0.99
10.5	3009.27	22.21	3015.18	20.18	1.00
12	3269.37	22.59	3274.98	20.37	1.00
13	3352.68	23.24	3360.01	20.77	1.00
14	3444.63	23.70	3384.21	20.37	1.02
15	3424.14	23.24	3432.60	20.75	1.00
16	3424.30	23.98	3462.87	20.97	0.99
18	3494.20	23.99	3515.44	21.01	0.99
20	3517.63	25.37	3556.45	22.33	0.99
24	3623.24	26.98	3653.49	23.28	0.99
26	3520.04	27.17	3538.33	23.77	0.99
28	3585.04	28.26	3522.20	23.82	1.02
36	3104.37	30.34	3032.52	24.79	1.02
48	2645.59	32.33	2578.70	25.32	1.03
72	1795.41	33.74	1749.44	28.21	1.03

Mean Plasma Time curve, Single-Dose Fasting Bioequivalence Study




Mean Logarithmic Concentration of Carbamazepine Vs Time in Hrs
Mean Logarithmic Conc. of Carbamazepine
9
8
7
6
5
4
3
2
1
0
-1
0
6
12
18
24
30
36
42
48
54
60
66
72
Time in Hrs
Treatment
Ref_R
Test_T

4.1.2 Single-Dose Fed Bioequivalence Study

4.1.2.1 Study Design

4.1.2.1.1 Study Information

Study Number	ARL/17/125
Study Title	A Randomized, Balanced, Open Label, Two Treatment, Two Sequence, Four Period, Single Dose, Fully Replicated, Crossover, Bioequivalence Study of Test Product Carbamazepine Extended-Release Tablets, 400 mg of Sciecure Pharma Inc, with Reference Product Tegretol®-XR (carbamazepine extended-release tablets) 400 mg of Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936., in Normal, Healthy, Adult, Male and/ or Female Human Subjects under Fed Conditions.
Study Type	☑ In Vivo BE ☐ In Vitro BE ☐ Permeability ☐ Other
Submission Location:	
Study Report	5.3.1.2
Validation Report	5.3.1.4
Bioanalytical Report	5.3.1.4
Clinical Site (Name, Address, Phone #, Fax #)	Accutest Research Laboratories (I) Pvt. Ltd. 1st & 2nd Floor, Synergy Square Complex, Krishna Industrial Estate, BIDC, Gorwa, Vadodara – 390016, India. Tel.: +91 265-2280161,62,63 Fax: +91 265-2280164
Principal Clinical Investigator (Name, Email)	Dr. Tushar Shah, M.B.B.S. tushar.shah@accutestglobal.com
Analytical Site (Name, Address, Phone #, Fax #)	(b) (4)
Principal Analytical Investigator (Name, Email)	
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) 123 Days (b) -70ºC ±10ºC
Long-Term Storage Stability Coverage (no. days @ temp ºC)	178 days @ -20ºC ±5ºC and @ -70ºC ±10ºC
LTSS Data Location	In module 5.3.1.4, (5314-bioanal-report) refer annex 16.16 of Bio-analytical report of Clinical study report (Addendum to MV report no:

	ARL/REP/MI/166CBZ/00/ADD08, Section No. 13.1, Page No. 29 to 37 of 39)

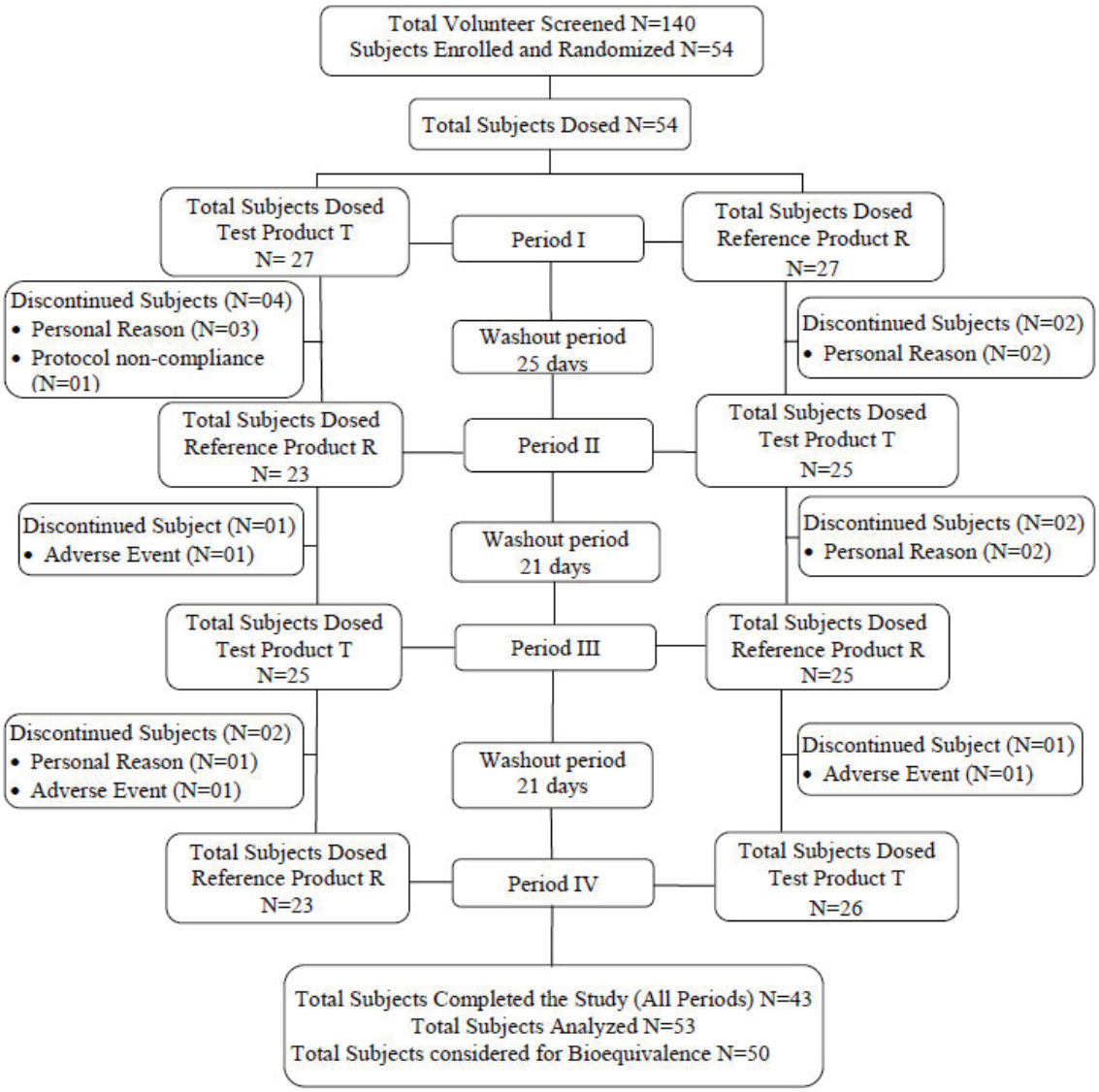
4.1.2.1.2 Product Information

Same as the fasting study.

4.1.2.1.3 Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	Enrolled: 54 Dosed: Period I: 54 Period II: 48 Period III: 50 Period IV: 49 Completed all 4 periods: 43 Samples Analyzed: 53 Subjects considered for BE: 51 Please see the details below.*
No. of Sequences	2
No. of Periods	4
No. of Treatments	2
No. of Groups	1
Washout Period	21 days
Randomization	☒ Yes ☐ No
Blood Sampling Times	0.00 (pre-dose) and 1.50, 3.00, 4.50, 6.00, 7.50, 9.00, 10.50, 12.00, 13.00, 14.00, 15.00, 16.00, 18.00, 20.00, 24.00, 26.00, 28.00, 36.00, 48.00 and 72.00hours post-dose in each study period.
IRB Approval	☒ Yes ☐ No Final version: approved 13 May 2017 Amendment: approved 12 August 2017
Informed Consent	☒ Yes ☐ No Final version: approved 13 May 2017 Amendment: approved 12 August 2017
Length of Fasting	At least 10.00 hours fasting, then received the high-fat and high-calorie non-vegetarian breakfast, which was started by subject exactly 30 minutes prior to drug administration.
Length of Confinement	Subjects were confined within the facility for at least 10.50 hours prior to dosing until 72.00 hours post dose 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

Standard FDA Meal* Used?	☐ **Yes**	☑ **No**			
If No, then meal components and composition is listed in the tables below					
Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study					
Ingredients	**Amount (g)**	**Energy (kcal)**	**Protein (kcal)**	**Fat (kcal)**	**Carbohydrate (kcal)**
Whole Milk	240 mL	157	31.6	80.1	45.2
Aloo Tiki	2 no (~70 g)	220	10.8	101.7	107.6
Chicken fry	50 g	116	58.28	52.74	5.16
Bread Butter (2 slices of Bread with butter)	45g	123	15.6	3.6	104.0
	20 g	146	0.0	145.8	0.0
Egg Fry (2 eggs fried in butter)	~90 g	210	53.2	156.6	0.0
TOTAL	-	972	169	541	262
PERCENTAGE	-	100	17.44	55.61	26.95



Notes: 1) Subject No. (b) (6) were discontinued from study period-II only.
2) Subjec (b) (6) were discontinued from study period-III only.
3) Subject (b) (6) was discontinued from study period-II and period-IV only.

Comments on Study Design: Adequate

- The applicant conducted an open-label, single-dose, randomized, two-treatment, four-period, two-sequence, fully-replicate, crossover design study as recommended by the PSG for Carbamazepine ER Tablets.

- The washout periods (21 days) are adequate considering that the half-life for Carbamazepine ER Tablets ranges from 25 to 65 hours.

- Per fed study protocol #ARL/17/125, the AUC was truncated at 72 hours. The current PSG for this drug product does not mention truncation of AUC at 72 hours.

Nevertheless, the truncation of AUC at 72 hours is acceptable, as (i) based on reported carbamazepine half-life of 25–65 hours after initial dose (RLD label), carbamazepine is a long half-life drug, and (ii) the DBs has precedence of accepting the truncation of AUC at 72 hours for the same drug product (b) (4) 213311 Carbamazepine ER Tablets).[3]

- Per the applicant's fed study protocol #ARL/17/125, inclusion of subjects for pharmacokinetic and statistical analysis will be done as per the following table:

Category	Study Period completion status	S_{WR} calculations	S_{WT} calculations	Scaled Average BE (if $S_{WR} \geq 0.294$)	Average BE (if $S_{WR} < 0.294$)	90% CI for σ_{WT}/σ_{WR}
A	All 4 study periods	Yes	Yes	Yes	Yes	Yes
B	3 study periods with Reference twice and Test once	Yes	No	No	Yes	No
C	3 study periods with Reference once and Test twice	No	Yes	No	Yes	No
D	2 study periods with Reference once and Test once	No	No	No	Yes	No
E	2 study periods with Test twice	No	Yes	No	No	No
F	2 study periods with Reference twice	Yes	No	No	No	No
G	1 study period (with any one treatment)	No	No	No	No	No

Details:

- A total of 54 subjects were planned and enrolled in this study. A total of 54 subjects were dosed in period-I.

- Subject no. (b) (6) were dropped out from the study due to personal reason in period-II only.

- Subject (b) (6) was withdrawn from the study in check in of study period-II due to protocol non-compliance (Positive Breath Alcohol test).

- A total of 48 subjects were dosed in period-II.

- Subject (b) (6) were dropped out from the study due to personal reason in period-III only.

- Subject (b) (6) was withdrawn from the study on check-in of study period-III due to adverse event.

- A total of 50 subjects were dosed in period-III.

- Subject no. (b) (6) were withdrawn from the study after dosing in Period-III due to adverse event. Per the DB summary table for dropout information, Subject no. (b) (6) completed PII only and finally withdrawn from the study in P-III.

- Subject (b) (6) was dropped out from the study due to personal reason in period-IV only.

- A total of 49 subjects were dosed in period-IV.

- A total of 43 subjects were completed the clinical phase (all the periods) of study
- successfully. A total of plasma samples for 53 subjects were analyzed.

- The data of 51 subjects (excluding subject no. (b) (6)) were considered to perform pharmacokinetic analysis. The data of 45 subjects (excluding subject no. (b) (6)) were considered for calculation within subject SD for reference products (i.e R vs. R variability). The data of 48 subjects (excluding subject no. (b) (6)) were considered for calculation within subject SD for test and test products (i.e T vs T variability).

4.1.2.2 Clinical Results

4.1.2.2.1 Demographic Profile of Subjects

Study No. ARL/17/125			
		Treatment Groups	
		Test Product (T) N=50*	Reference Product (R) N=50*
Age (years)	Mean ± SD	30.86 ± 05.91	30.86 ± 05.91
	Range	19 - 44	19 - 44
Age Groups	< 18	Nil	Nil
	18 – 40	46 (92.00 %)	46 (92.00 %)
	41 – 64	04 (08.00 %)	04 (08.00 %)
	65 – 75	Nil	Nil
	> 75	Nil	Nil
Sex	Male	50 (100.00 %)	50 (100.00 %)
	Female	00 (00.00 %)	00 (00.00 %)
Race	Asian	50 (100.00 %)	50 (100.00 %)
	Black	Nil	Nil
	Caucasian	Nil	Nil
	Hispanic	Nil	Nil
	Other	Nil	Nil
BMI (kg/m^2)	Mean ± SD	21.73 ± 02.05	21.73 ± 02.05
	Range	18.60 – 24.73	18.60 – 24.73
Other Factors		-	-

*Assessor's note, the applicant's table above for "Demographic Profile of Subjects" only listed total subject number as "50". The data of 50 subjects (excluding subject no. (b) (6) were included to perform pharmacokinetic analysis by the applicant (see section 4.1.2.4.2 for the table of "Geometric Means and 90% Confidence Intervals - Applicant Calculated": *"(No of subjects completed= 50)"*. However, the data of 51 subjects (excluding subject no. (b) (6)) were considered to perform pharmacokinetic analysis by assessor (see 4.4.2 SAS Output for fed_STAT, table "Class Level Information") and below:

Class Level Information		
Class	**Levels**	**Values**
SEQ	2	1 2
SUBJ	51	(b) (6)
PER	4	1 2 3 4
TRT	2	A B

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No

4.1.2.2.2 Dropout Information

Study No. ARL/17/125				
Subject No	**Reason for dropout/replacement***	**Period**	**Replaced?**	**Replaced with**
(b) (6)	Subject was withdrawn from the study at 11:18 on 19 September 2017 due to adverse event. Treatment given was Test product T in Period-I.	I and III	No	NA
	Subject was dropped out from the study due to personal reason.	III	No	NA
	Subject was dropped out from the study due to personal reason.	II	No	NA
	Subject was withdrawn from the study at 16:53 on 03 November 2017 due to adverse event. Treatment given was Reference product R in Period-II.	III	No	NA
	Subject was dropped out from the study due to personal reason	IV	No	NA
	Subject was dropped out from the study due to personal reason	III	No	NA
	Subject was dropped out from the study due to personal reason	II	No	NA
	Subject was dropped out from the study due to personal reason	II	No	NA
	Subject was dropped out from the study due to personal reason	II	No	NA
	Subject was withdrawn from the study at 17:20 on 13 October 2017 due to protocol non-compliance. Treatment given was Test product T in Period-I.	II	No	NA
	Subject was withdrawn from the study at 10:58 on 19 September 2017 due to adverse event. Treatment given was Reference product R in Period-I.	I and III	No	NA

Notes: 1) "*" Initially subject was discontinued from study period-I only then he was continued in period-II. After that he was again discontinued from the study in period-III.
2) "$" subject was discontinued from study period-III only.

3) "@" subject was discontinued from study period-II only.
4) "#" Initially subject was discontinued from study period-II only then he was continued in period-III. After that he was again discontinued from the study in period-IV.

NA= Not Applicable

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No ☐ N/A

4.1.2.2.3 Study Adverse Events

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study No. ARL/17/125	
	Test Product T (N=103)	Reference Product R (N=98)
Hemopoietic System		
Low Hemoglobin	00 (00.00 %)	01 (01.02 %)
Gastrointestinal System		
Vomiting	02 (01.94 %)	02 (02.04 %)
Total	02 (01.94 %)	03 (03.06 %)

Subjects Experiencing Emesis

Subject Number	Test/ Reference	Period	Time and Date of dosing	Time and Date of emesis	Duration Between Dosing and Start of Emesis (hours)
(b) (6)	T	I	19 September 2017, 09:02	19 September 2017, 11:10	2 hrs 8 min
	T	III	04 November 2017, 9:02	04 November 2017, 9:38	36 min
	R	I	19 September 2017, 09:34	19 September 2017, 10:49	1 hrs and 15 min
	R	III	04 November 2017, 9:34	04 November 2017, 9:40 AM	6 min

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

4.1.2.2.4 Protocol Deviations

Study No. ARL/17/125		
Type	**Subject #s (Test)**	**Subject #s (Reference)**
Blood Sample Time Point Deviation	23 Subjects (b) (6)	18 Subjects
Blood and Urine Laboratory Test Deviation (For Subject no. 05 on Check-in of period-IV)	-	-
High Fat High Calorie Non vegetarian Breakfast Deviation	01 Subject (b) (6)	02 Subjects (b) (6)
Statistical Analysis Plan Deviation	-	-

Refer Appendix 16.2.2 of Clinical Study Report.
Assessor note: The assessor verified the fed clinical study report, which mentions that Subjects (b) (6) were not able to consume high-fat and high-calorie non-vegetarian breakfast completely. There was no impact of deviation on data/subject safety as subject no. 47 had consumed 810 Kcal in Period-I and subject (b) (6) had consumed 811 and 848 Kcal respectively in Period-III and Period-IV which was within the range of calorie requirement of 800 to 1000 calories as per FDA regulatory guidance[23]. The assessor upon verification of the report considers the protocol deviation should not have impact.

Note: The Assessor agrees with the applicant that the above deviations did not impact the study outcome.

If the applicant used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is 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 ☐ N/A

[23] Guidance for Industry - Food-Effect Bioavailability and Fed Bioequivalence Studies; Link: https://www.fda.gov/media/70945/download

Comments on Clinical Results: Adequate

1. Total of five (05) adverse events were observed during entire course of the study. Out of which two (02) AEs [02 (01.94 %)] were reported in Test Product T treated subject and other three (03) AE [03 (03.06 %)] were reported in Reference Product R treated subject. Reported AEs were mild in severity, possibly or probably related to study medication and followed up till resolution.

2. No serious or significant adverse event was observed during the entire course of the study. No death, other serious adverse event and other significant adverse event reported during the entire course of the study.

3. No concomitant medications were used during the study. However, Subject (b) (6) who experienced AE (low hemoglobin) was given Tablet Livogen (Ferrous Fumarate-152 mg, Folic Acid-1500 mcg), once daily from 03 November 2017 to 17 November 2017 as a treatment of adverse event. There is no impact on the outcome of the fed BE study.

4.1.2.3 Bioanalytical Results

4.1.2.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

Same as the fasting study.

4.1.2.3.2 Sample Analysis Calibration and Quality Control

Bioequivalence Study No. ARL/17/125 Carbamazepine									
Parameter	**Standard Curve Samples**								
	CS-01	**CS-02**	**CS-03**	**CS-04**	**CS-05**	**CS-06**	**CS-07**	**CS-08**	**CS-09**
Concentration (ng/mL)	50.047	100.095	300.285	600.569	1201.138	2402.276	3603.414	5104.837	5995.681
Inter day Precision (% CV)	0.78	1.73	1.69	1.45	1.56	1.50	1.40	1.61	1.75
Inter day Accuracy (% Actual)	99.39	101.44	101.87	94.59	98.59	103.02	102.30	100.80	98.00
Linearity (Range of r^2)	0.9978 to 0.9996								
Linearity Range (ng/mL)	50.047 to 5995.681								
Sensitivity/LOQ (ng/mL)	50.047								

Bioequivalence Study No. ARL/17/125 Carbamazepine				
Parameter	**Quality Control Samples**			
	LQC	**M1QC**	**MQC**	**HQC**
Concentration (ng/mL)	149.643	800.764	2102.006	4804.584
Inter day Precision (% CV)	2.68	2.82	2.55	2.58
Inter day Accuracy (% Actual)	97.25	100.38	100.16	100.60

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 Assessor for additional actions.	☐ Yes ☒ No See comments below.
Were 20% of chromatograms included?	☒ Yes ☐ No Subjects # 22-32
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

Rejected Batches:

- Analytical run # ARL_17_125(b) (6) - % CV of LQC out of acceptance criteria. Batch was repeated as ARL_17_125_(b) (6)_A
- Analytical run # ARL_17_125_SUB_20 - The batch was stopped after acquiring sample 20/W/T10 due to power failure. Batch was repeated as RL_17_125_(b) (6)_A
- For analytical run # ARL_17_125_(b) (6) %CV of M1QC not within acceptance criteria. Batch was repeated as ARL_17_125_(b) (6)_A
- Analytical run # ARL_17_125(b) (6): The system was stopped after sample: 52/Y/T18 due to power failure. Batch was repeated as ARL_17_125_(b) (6)_A
- Analytical run # RL_17_125_(b) (6) was processed on 11/01/18 but could not acquire due to power failure. Batch was repeated as ARL_17_125_(b) (6).

Reinjections and Reintegrations:

None.

Assessor note: The assessor verified and confirms that the above rejected runs were conducted as per the effective SOP's listed above. The data is adequate.

4.1.2.3.3 Reanalysis of Study Samples

Study No. ARL/17/125 In Module 5.3.1.4 (5314-bio-ana-rep), page no. 27 to 48 of 53 Carbamazepine								
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[8]	00	00	0.00	0.00	00	00	0.00	0.00
Power failure (Code C1)	105	86	2.55	2.09	105	86	2.55	2.09
Inconsistent internal standard area response (code B)	02	00	0.05	0.00	02	00	0.05	0.00
Batch Repeat (Code E)	84	84	2.04	2.04	84	84	2.04	2.04
Positive Pre-dose (code F)	03	02	0.07	0.05	00	00	0.00	0.00
Total	194	172	4.71	4.17	191	170	4.63	4.13

Listing of repeat sample analysis for Carbamazepine, Positive pre-dose (code F)

Sr. no.	Sample ID	Initial run ID	Initial conc. (ng/mL)	Repeat run ID	Repeat conc. (ng/mL)	Final reported value (ng/mL)	Instrument ID
01	35/Y/T02	ARL_17_125_(b) (6)	124.652	ARL_17_125_SUB_Repetition	131.29	131.290	MI/01/020/0020
02	48/X/T08	ARL_17_125_	2613.971	ARL_17_125_SUB_Repetition	2775.109	2775.109	MI/01/020/0020

Listing of repeat sample analysis for Carbamazepine, Inconsistent internal standard area response (code B)

Instrument ID – MI/01/020/0020											
Sr. No.	Sample Code	Initial Conc. (A) (ng/mL)	Initial run ID	Repeat-1 Conc. (B) (ng/mL)	Repeat-2 Conc. (C) (ng/mL)	Repeat run ID	Mean of repeats (D) (ng/mL)	SD of repeats	% CV of repeat analysis	% Difference (D/A-1)*100	Final Reported Conc. (ng/mL)
1	33/Z/T01	96.037	ARL_17_125_ (b) (6)	102.587	102.744	ARL_17_125_SUB_Repetition	102.666	0.111	0.11	6.90	96.037
2	33/W/T01	100.565	ARL_17_125_	101.325	103.134	ARL_17_125_SUB_Repetition	102.230	1.279	1.25	1.66	100.565
3	35/W/T01	57.963	ARL_17_125_	60.323	61.292	ARL_17_125_SUB_Repetition	60.808	0.685	1.13	4.91	57.963
4	41/Z/T01	68.738	ARL_17_125_	68.383	69.182	ARL_17_125_SUB_Repetition	68.783	0.565	0.82	0.07	68.738
5	41/W/T01	63.846	ARL_17_125_	65.244	65.951	ARL_17_125_SUB_Repetition	65.598	0.500	0.76	2.74	63.846

All the other repeated samples(Code C1, Code E) shown in the applicant's bioanalytical report[24] are in accordance with SOP (b) (4), "*Repeat Sample Analysis*." (criteria described below):

- **Code B**: For analyte carbamazepine, as per the SOP, two (2) samples were reanalyzed due to the following reason. The Assessor spot checked the raw data[25] for the reanalyzed sample due to this reason. The IS peak area of the above-mentioned sample is out of the +/- 50% of the batch average internal standard response (CCs and QCs only). The IS response for the QC's and CCs was approximately 3000K, whereas the IS response for the sample ID: 35/Y/T02 was 4876125. The applicant conducted reanalysis per their pre-established SOP and reported in repeat value in singlet. (as shown below).

[24] \\CDSESUB1\evsprod\anda216235\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\arl-17-125\5314-bioanal-report.pdf

[25] \\CDSESUB1\evsprod\anda216235\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\arl-17-125\result-tables-remaining-sub.pdf; page # 65 of 133

INCONSISTENT INTERNAL STANDARD AREA RESPONSE: CODE B

Analyst/ group leader will calculate the mean internal standard response in the batch by considering all samples of the batch including calibration curve and quality control samples (excluding system suitability and blank samples). Analyst/ group leader will calculate the percent difference of internal standard response of individual sample in the batch with respect to the mean internal standard response in the batch.

Note: *In cases where labeled internal standards are used, if for more than 20 % but less than 50 % of samples inclusive of Calibration Curve standards and Quality Control samples, internal standard deviation is observed to be significant i.e. greater than ± 50 % of the mean response of internal standard response in batch but accuracy of calibration curve standards and quality control samples is still within acceptance as per SOP for "BATCH ACCEPTANCE OF SUBJECT SAMPLE ANALYSIS", then batch can be accepted without repetition. However individual repeats for internal standard variation from such a batch, if any, will be identified for repetition under Code B.*

INCOMPLETE ANALYSIS: CODE C

Typical reasons of incomplete analysis are as follows but not limited to:

Power failure, software error or equipment failure.

Sample loss due to vial breaking or spillage.

Power failure, software error or equipment failure: Code C1

If a batch is interrupted due to power failure, software error or equipment failure (such as auto sampler/ pump malfunctioning or drift in response), analyst/ group leader will rectify the problem by addressing the interruption to engineer(s).

Analyst/ group leader will ensure that unanalyzed samples of interrupted batch are within validated period of auto sampler stability and that reinjection reproducibility has been established during method validation. Based on stability

data available, sample analysis will be carried out in following way:

Analyst/ group leader will reanalyze entire interrupted batches which are not within validated period of auto sampler stability under Code C1.

Analyst/ group leader will re-inject entire interrupted batches by giving extension 'R' to the acquisition batch, which are within validated period of auto sampler stability and if reinjection reproducibility has been established during method validation.

Also, if in case, some unknown sample(s) from an acquisition batch are not acquired/skipped, they will be repeated under Code C1. In such an event, if calibration curve standards or quality control samples are not acquired/ skipped, but the batch meets the acceptance criteria in terms of all predefined criteria excluding these samples, the batch will be accepted, without repeating or re-injecting them.

Sample loss due to vial breaking, extraction cartridge related issues or accidental spillage of sample: Code C2

Analyst will repeat such sample(s) in singlet, which are thus lost during analysis.

- **Code: F**: The applicant repeated 5 pre-dose (0.0hr) samples in duplicate due to positive pre-dose (code F) as per BAL/003/00/N, "Repeat Sample Analysis," Section 10.1.3.6 POSITIVE PRE-DOSE: CODE F. *Pre-dose subject samples in any period, with concentration greater than or equal to concentration of LLOQ of the analyte, will be repeated under this code; in duplicate.* For all the pre-dose samples, the % difference between the mean of repeat values and initial value were within ± 15% of the initial value and CV (%) of the repeat values were within 20% variation. Hence, the initial values were reported for all the samples repeated under per code F. For subjects (b) (6), in Period II, III, and IV, the assessor verified and confirms that the pre-dose concentrations were all less than 5% of the respective Cmax for that subject and that period. Therefore, those subjects were included in PK and statistical analysis.

BATCH REPEATS: CODE E

Batches which do not meet acceptance criteria as per SOP for 'BATCH ACCEPTANCE OF SUBJECT SAMPLE ANALYSIS' will be repeated under this code in singlet.

POSITIVE PRE-DOSE: CODE F

Pre-dose subject samples in any period, with concentration greater than or equal to concentration of LLOQ of the analyte, will be repeated under this code; in duplicate.

Note: Do not use the reanalysis results obtained simultaneously for other analyte, when the sample is repeated; refer specifically to cases of combination of drugs.

Does the Assessor agree with the reanalysis of study samples: analytical and/or PK repeat?	☒ Yes ☐ No
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

Incurred Sample Reanalysis (ISR):

To demonstrate reproducible quantitation of incurred subject samples, a total of 416 (10.09%) of the study samples for carbamazepine which were selected as per the SOP titled: Incurred Sample Reanalysis SOP, were reassayed. Samples around Cmax and later in the elimination phase were selected. The incurred sample reproducibility (ISR) values were used for comparison purposes and are included in the analytical report but not used in determining the final reported value. Incurred sample repeats were considered acceptable if the original and reassay values from two-thirds of the repeated samples had a relative percent difference of ≤ 20%. The results of the incurred sample repeats showed that 97.12% met the acceptance criteria(page # 55 of 190 in the bioanalytical report). The applicant's ISR analysis was consistent with the FDA's *Guidance for Industry: Bioanalytical Method Validation (September 2013)*.[26]

Comments on Bioanalytical Results: Adequate

[26] Guidance for Industry – Bioanalytical Method Validation. September 2013. https://www.fda.gov/downloads/Drugs/Guidances/ucm368107.pdf.

4.1.2.4 Pharmacokinetic Results

4.1.2.4.1 Arithmetic Mean Pharmacokinetic Parameters

ARITHMETIC MEANS AND RATIOS - REPLICATE 1 (PERIODS 1 AND 2)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	226907.8	12.77	163781.2	304943.6	234528.4	13.46	161755.3	300799.3	0.97
CMAX	ng/mL	4406.863	10.69	3254.13	5453.17	4573.303	12.60	3328.68	5864.40	0.96
TMAX	hr	24.000	.	9.00	28.00	22.000	.	7.50	48.00	1.09

* Tmax values are presented as median, range.

ARITHMETIC MEANS AND RATIOS - REPLICATE 2 (PERIODS 3 AND 4)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	218755.5	17.10	146009.0	315239.5	226761.1	14.03	164046.0	297192.5	0.96
CMAX	ng/mL	4296.783	14.53	3080.68	5648.78	4433.961	13.70	3291.61	5970.62	0.97
TMAX	hr	24.000	.	9.00	36.00	18.000	.	9.00	36.00	1.33

* Tmax values are presented as median, range.

ARITHMETIC MEANS AND RATIOS - ALL PERIODS (PERIODS 1, 2, 3, AND 4)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	222790.5	15.07	146009.0	315239.5	230685.6	13.77	161755.3	300799.3	0.97
CMAX	ng/mL	4351.267	12.72	3080.68	5648.78	4504.365	13.16	3291.61	5970.62	0.97
TMAX	hr	24.000	.	9.00	36.00	20.000	.	7.50	48.00	1.20

* Tmax values are presented as median, range.

4.1.2.4.2 Geometric Means and 90% Confidence Intervals - Applicant Calculated

Reference Scaled Average Bioequivalence Approach Used	**√ Yes** **☐ No**
If No, then complete Table 3A only If Yes, then complete Tables 3A and 3B	
Carbamazepine Extended Release Tablets 400 mg (No of subjects completed= 50) Single oral dose (1 x 400 mg Tablets) Least Squares Geometric Means, Ratio of Means and 90% Confidence Interval	
Fed Bioequivalence Study (Study Code: ARL/17/125)	

Parameter	Test	N*	RLD	N*	Ratio	90% C.I.
AUC_{0-72} (ng*hr/mL)	219666.8155	99	228023.5169	95	96.3352	94.3314 - 98.3815
C_{max} (ng/mL)	4301.6565	99	4455.6433	95	96.5440	94.6269 - 98.4999

*Note: * No. of observation used for test and reference product*

Parameter	**T/R Ratio**	**Lower 90% CI**	**Upper 90% CI**	**S^2_{WR}**	**sWR**	**S^2_{WT}**	**sWT**
LAUC72 (ng*hr/mL)	95.8443	94.3314	98.3815	0.008659	0.0931	0.007570	0.0870
LCMAX (ng/mL)	96.6111	94.6269	98.4999	0.008528	0.0923	0.005825	0.0763

Parameter	**sWT / sWR Ratio**	**90% Upper Confidence Bound of sWT / sWR Ratio**	**Criteria Bound**	**Method Used**	**Outcome**
LAUC72 (ng*hr/mL)	0.935026	1.204966	-0.0047	ABE and SABE	Bioequivalent
LCMAX (ng/mL)	0.826437	1.065029	-0.0053	ABE and SABE	Bioequivalent

Note:
SABE= Scaled Average Bioequivalence
ABE=Average Bioequivalence

4.1.2.4.3 Geometric Means and 90% Confidence Intervals - Assessor Calculated

Carbamazepine Extended-Release Tablets USP 1 × 400 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study No. ARL/17/125							
Parameter	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
AUC_{0-72} (ng*hr/mL)	220811.6	99	228838.0	95	0.96	94.48	98.55
C_{max} (ng/mL)	4319.80	99	4469.38	95	0.97	94.72	98.62

Parameter	**Unscaled Lower 90% CI**	**Unscaled Upper 90% CI**	**Point Estimate**	**sWT**	**sWR**	**sWT sWR ratio**	**sWT/ sWR Lower 90% CI**	**sWT/ sWR Upper 90% CI (≤ 2.5)**
LAUCT (ng*hr/mL)	94.48	98.55	0.96	0.0870073	0.0930533	0.9350258	0.73	1.20
LCMAX (ng/mL)	94.72	98.62	0.97	0.0763201	0.0923483	0.8264374	0.64	1.06

Unscaled	sWT sWR ratio	95% Upper Confidence Bound	OUTCOME
PASS	PASS	-0.004426	PASS
PASS	PASS	-0.005095	PASS

Assessor's Note:

- The Assessor-calculated PK parameters (arithmetic mean and geometric least squares mean) are the same as those calculated by the applicant (Test: n=99, Ref.: n=95).
- The Assessor calculated S_{WT} and S_{WR} are the same as those calculated by the applicant.**Error! Bookmark not defined.**
- The 95% upper confidence bound calculated by the Assessor and the applicant are comparable.

Overall, the Assessor and applicant calculated results are comparable.

4.1.2.4.4 Additional Information for the Study

Root Mean Square Error	**SWT values** AUC72: 0.087 Cmax: 0.0763	**SWR values** AUC72: 0.093 Cmax: 0.0923
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 The median Tmax T/R ratio is 1.2. The Tmax range for T and R is comparable and similar to the other approved products for this ANDA (please see the Tmax evaluation below).	
Were the subjects dosed in groups? **If yes, was the statistical analysis proper? Is reanalysis by Assessor necessary?**	☐ Yes ☒ No	
Are there measurable drug concentrations at 0 hr? **If yes, please comment (and take necessary action, if needed).**	☒ Yes ☐ No See details in Section 4.1.2.3.3 Reanalysis of Study Samples.	
Are there first measurable drug concentration 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	

Comments on PK results: Adequate

- Per the PSG for Warfarin Sodium Tablets,[4] for an NTI test product to be considered bioequivalent to the RLD, the test product must pass the following three (3) criteria when conducting statistical analysis using the reference-scaled average bioequivalence approach for NTI drugs:

1. The 90% CIs of test/reference geometric mean ratio must fall within the limits of 80-125% using average BE approach.
2. A 95% upper confidence bound must be less than or equal to 0 using reference-scaled average BE approach.
3. The upper limits of 90% CIs of S_{WT}/S_{WR} are less than a standard value of 2.5.

The test product met all three criteria for the fed BE study.

Tmax evaluation:

- The assessor verified and found that the median Tmax for the test product is comparable to the previously approved ANDAs for this drug product (see the details below).
- For the current test product: the median Tmax is 24.00 hrs (range 9.00 - 36.00 hrs) for the Test product and 20 hrs (range 7 - 48.00 hrs) for the Reference product with T/R ratio of 1.2. The assessor provides the following justification to address the observed Tmax difference based on the previously approved ANDAs for this drug product.
- For example: In the fed study for approved ANDA # 212948[27]: The median Tmax was 19.00 hrs (range 8.00 - 32.00 hrs) for the Test product and 24.00 hrs (range 6.00 - 36.00 hrs) for the Reference product with T/R ratio of 0.79, which is close to 0.8. Per RLD Label, following chronic oral administration of Tegretol-XR tablets, plasma levels peak at approximately 3 to 12 hours, which shows wide variation. The assessor of A212948 provided the following justification to address the observed Tmax difference.
- *The assessor firstly evaluated the distribution of Tmax values by generating a stick plot using the individual Tmax values for both Test and Reference products. The percentage of T/R ratios <0.8, within 0.8-1.2 and >1.2 are 36.26%, 40.66% and 23.08%, respectively, which shows the majority of T/R ratios are within 0.8-1.2. The stick plots showed that the Tmax values for test and reference products are similarly distributed in the fed study*.

- *RLD Label states "Because Tegretol induces its own metabolism, the half-life is also variable. Autoinduction is completed after 3 to 5 weeks of a fixed dosing regimen. Initial half-life values range from 25 to 65 hours, decreasing to 12 to 17 hours on repeated doses". For most of the indications, this drug product is indicated for chronic use, administered twice daily. Carbamazepine induces its own metabolism (autoinduction) on chronic use. For this reason, the assessor did not use non-parametric superposition approach to evaluate the effects of multiple doses on the Tmax difference between the test and RLD products, as the result generated from fixed elimination half-life will not reflect actual concentration levels at steady state.*

[27] GDRP; A212948; link: https://panorama.fda.gov/task/view?ID=5d2353a800051d67ce0545990d68d725
Document name: A212948N000DB-Review01-07082019

- *Previously the DB consulted the OGD clinical group regarding the Tmax differences between test and reference products for Carbamazepine Extended Release Tablet for* (b) (4) *As stated in the consult, there is uncertainty of the significance of the shape of the time/concentration curve, on the therapeutic effect and potential adverse events, as there is no PK/PD relationship available. Since the ER product was approved based on comparison to the IR product, the Tmax difference between test and reference might not be a concern.*
- Furthermore, the current assessor searched for some in-house approved/pending ANDAs for this drug product (Carbamazepine ER tablets, 400 mg) for the fed BE studies and summarized the median Tmax data in the following table.

Application No.	Median Tmax (Min-Max) (hrs)		T/R	PK Evaluation	Approval Status
	Test	Reference			
ANDA 212948	19.0 (b) (4)	24.0 (b) (4)	0.79	Adequate	Approved
(b) (4)					
ANDA 213311	22 (b) (4)	20 (b) (4)	1.10	Adequate	Approved
ANDA 213159	28	24	1.17	Adequate	Pending
(b) (4)					
ANDA 078115	20.0 (b) (4)	18.0 (b) (4)	1.11	Adequate	Approved
ANDA 205571	22 (b) (4)	18 ((b) (4)	1.31	Adequate	Approved
(b) (4)					
ANDA 216235*	24 (b) (4)	20 (b) (4)	1.2	Adequate based on above listed approved ANDAs	Pending

*Current application

(b) (4)

PK data from withdrawn ANDAs:

ANDA	Test T_{max} Median	Test T_{max} Mean	Referance T_{max} Median	Referance T_{max} Mean	T/R ratio Median T	T/R ratio Mean T
[redacted]						(b) (4)

- [redacted] (b) (4)
- In conclusion, based on above justifications, the Tmax difference between test and reference product in the fed study is acceptable.

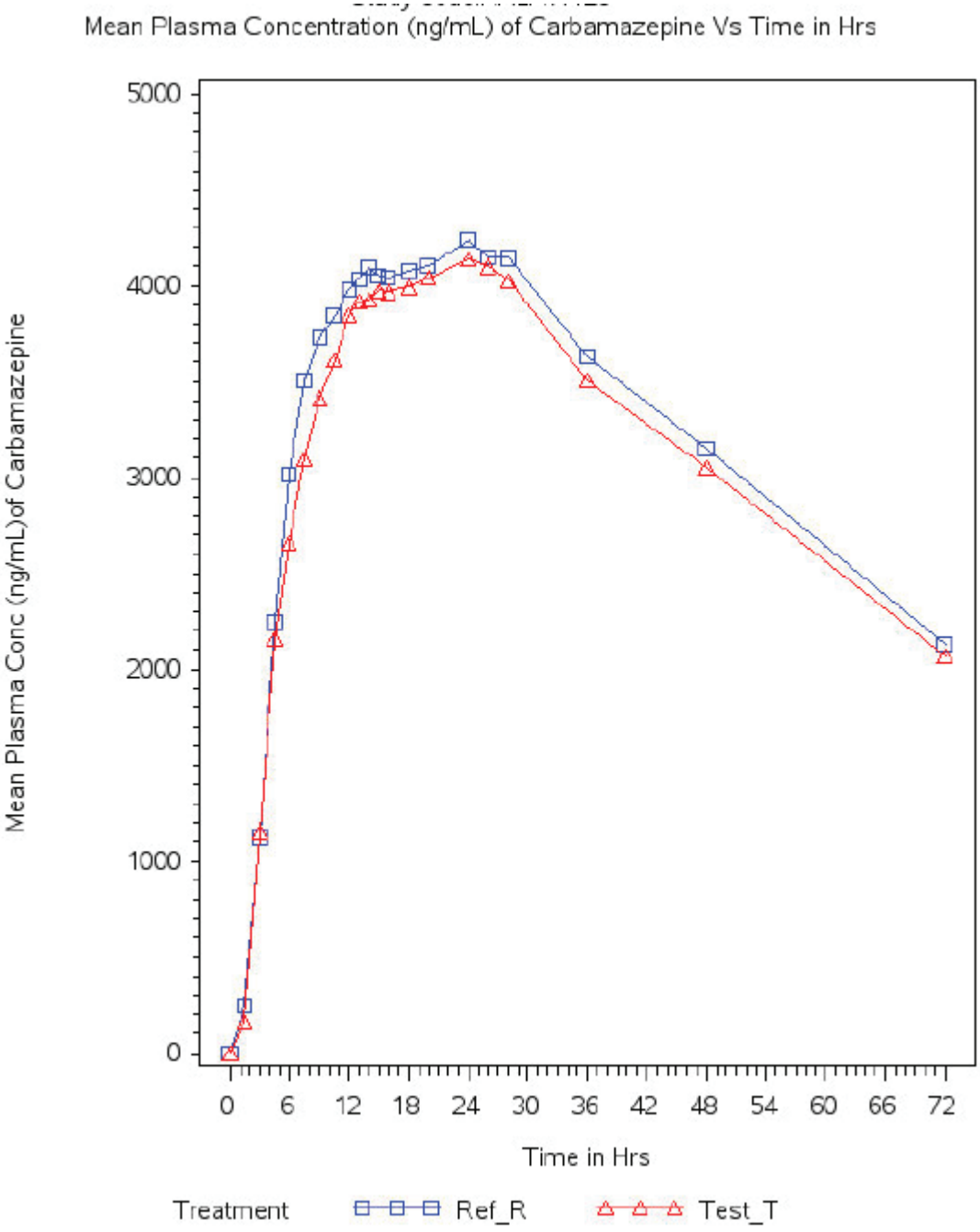
4.1.2.5 Overall Comment

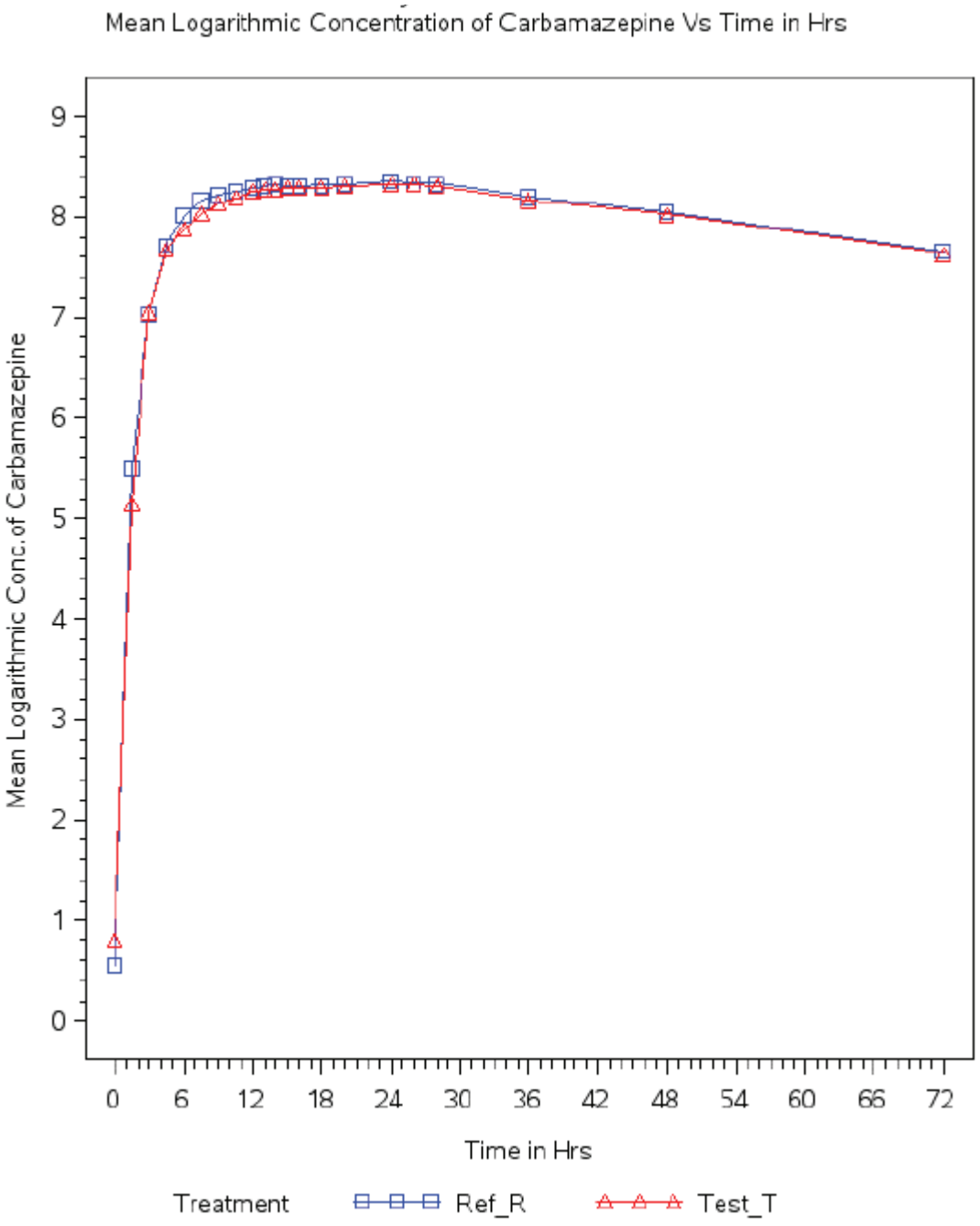
Was the Fed Bioequivalence study acceptable? Acceptable

Mean Plasma Concentrations Time Curve, Single-Dose Fed Bioequivalence Study

Time (hr)	Test (n=99)		Reference (n=95)		T/R Ratio
	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	
0.00	2.25	587.22	1.73	695.07	1.30
1.50	170.58	119.35	245.86	115.89	0.69
3.00	1148.28	48.06	1129.04	55.34	1.02
4.50	2159.95	22.78	2247.20	22.93	0.96
6.00	2657.35	13.65	3018.25	18.42	0.88
7.50	3100.60	12.91	3504.98	13.98	0.88
9.00	3414.90	12.48	3732.51	12.65	0.91
10.50	3614.02	12.57	3846.18	10.77	0.94
12.00	3848.95	13.11	3980.29	12.38	0.97
13.00	3920.91	12.38	4037.44	11.79	0.97
14.00	3929.66	12.00	4099.59	12.58	0.96
15.00	3976.05	12.57	4052.90	12.40	0.98
16.00	3968.84	12.49	4041.60	12.46	0.98
18.00	3994.50	13.36	4079.52	12.85	0.98
20.00	4046.20	13.82	4107.84	14.91	0.98
24.00	4139.32	14.13	4237.97	14.90	0.98
26.00	4101.50	14.70	4152.31	14.93	0.99
28.00	4028.99	14.93	4147.57	15.81	0.97
36.00	3509.29	17.51	3633.34	16.10	0.97
48.00	3055.02	20.03	3149.49	18.09	0.97
72.00	2068.41	24.55	2133.73	22.75	0.97

Mean Plasma Time curve, Single-Dose Fed Bioequivalence Study




Mean Logarithmic Concentration of Carbamazepine Vs Time in Hrs
Mean Logarithmic Conc.of Carbamazepine
0
1
2
3
4
5
6
7
8
9
0
6
12
18
24
30
36
42
48
54
60
66
72
Time in Hrs
Treatment
Ref_R
Test_T

4.2 Formulation Data

4.2.1 Test Formulation

Ingredient	Amount (mg) / tablet			Amount (%) / tablet		
	400mg	200mg	100mg	400mg	200mg	100mg
(b) (4)						
Carbamazepine, USP	400.00	200.00	100.00			
Hypromellose (b) (4) USP						
Hydroxyethyl Cellulose (b) (4) NF						
(b) (4)						
Mannitol, USP						
Dextrates, Hydrated, NF						
Sodium Lauryl Sulfate, USP/NF						
(b) (4)						
Magnesium Stearate, USP						
Cellulose Acetate (b) (4)						
(b) (4)						
Polyethylene Glycol 3350, NF						
(b) (4)						
Opacode Monogramming Ink S-1-17823 Black [A]						
Total Weight				100.00%	100.00%	100.00%

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Quantitative formula for Opacode Monogramming Ink S-1-17823 Black, NF

Ingredients/Compendial Reference	%w/w
(b) (4)	(b) (4)
ISOPROPYL ALCOHOL (USP, PhEur, JP)	
FERROSOFERRIC OXIDE (NF)/BLACK IRON OXIDE (JPE, JECFA, ChP)	
N-BUTYL ALCOHOL NF	
PROPYLENE GLYCOL (USP, FCC, PhEur, JP, JSFA, ChP)	
AMMONIUM HYDROXIDE (b) (4) (NF, PhEur, FCC)	

(b) (4)

[29] DARRTS, NDA 020234, New/Annual Report, Annual Report-15, dated 05/20/2011. EDR, Sequ 0025 (149), Module 3.2.P.3.3. manuf-process-and-controls.pdf and Module 3.2.P.5.1-Specifications\testing-monograph-400mg.pdf.

(b) (4)

The formulation design of the test product is similar to that of the RLD product. Any differences in amount and type of excipients are not expected to contribute to any significant changes in PK or safety profiles of the test as compared to the RLD.

[30] DARRTS, NDA 020234, Rev-Quality-03(General Review), Supplement-21 (Manufacturing (CMC)), 03/25/2002.

4.2.2 Inactive Ingredients (IIG Table)

Ingredient	Amount (mg) / tablet			Maximum amount (mg)/MDD (1600 mg)	IIG limit for Oral (mg)
	400mg	200mg	100mg		
Intra Granular					
Hypromellose (b) (4) USP	(b) (4)				
Hydroxyethyl Cellulose (b) (4) NF					
(b) (4)					
Mannitol, USP					
Dextrates, Hydrated, NF					
Sodium Lauryl Sulfate, USP/NF					
(b) (4)					
Magnesium Stearate, USP					
Cellulose Acetate (b) (4)					
(b) (4)					
Polyethylene Glycol 3350, NF					

Opacode Ink S-1-17823	400mg	200mg	100mg	Maximum amount (mg)/MDD (1600 mg)	IIG limit for Oral (mg)
Shellac	(b) (4)				
Isopropyl Alcohol					
Ferrosoferric Oxide					
N-Butyl Alcohol					
Propylene Glycol					
Ammonium Hydroxide (b) (4)					

Per the FDA's Substance Registration System (https://fdasis.nlm.nih.gov/srs/srs.jsp),

(b) (4)

- (b) (4)

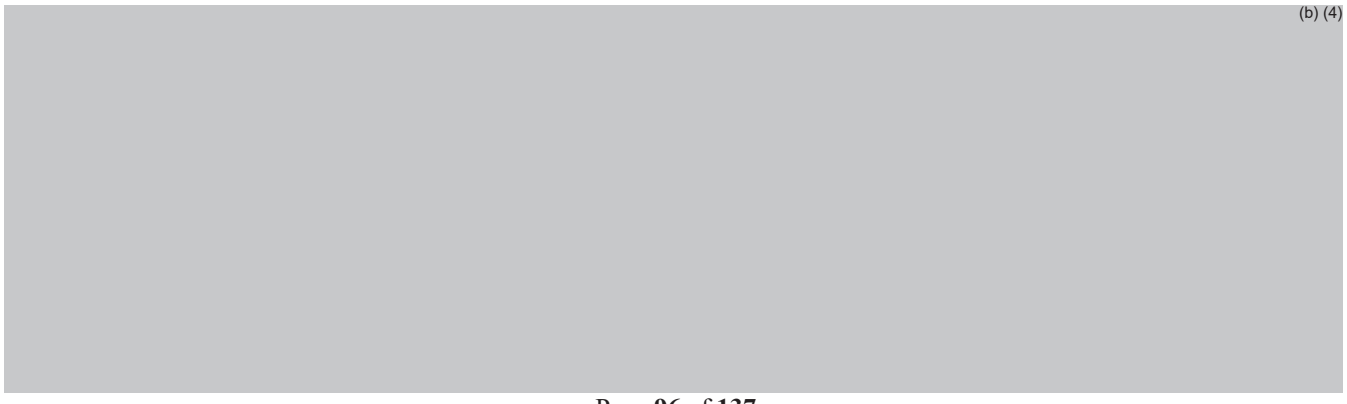
Quantitative formula for Opacode Monogramming Ink S-1-17823 Black, NF

Ingredients/Compendial Reference	%w/w
(b) (4)	(b) (4)
ISOPROPYL ALCOHOL (USP, PhEur, JP)	
FERROSOFERRIC OXIDE (NF)/BLACK IRON OXIDE (JPE, JECFA, ChP)	
N-BUTYL ALCOHOL NF	
PROPYLENE GLYCOL (USP, FCC, PhEur, JP, JSFA, ChP)	
AMMONIUM HYDROXIDE (b) (4) (NF, PhEur, FCC)	

(b) (4)

(b) (4)


(b) (4)


(b) (4)

Applicant's Calculation of total Iron content per day

Table 5. Elemental Iron Content

Ingredient	100 mg strength	200 mg strength	400 mg strength
Ferrosoferric Oxide Black in Opacode Monogramming Ink S-1-17823 Black, NF per tablet	(b) (4)		
Ferrosoferric Oxide Black per day			
Total Elemental Iron per day (mg)			

The maximum daily dosage (MDD) is 1600 mg per day and the maximum possible dose of Carbamazepine Extended-Release Tablet is 4 tablets a day for every strength. The only component with elemental iron is Opacode Monogramming Ink S-1-17823 Black that contains maximum of 3 (b) (4) Therefore, the maximum total elemental iron per day (mg) is (b) (4)

The total elemental iron contained in Carbamazepine ER Tablets 100 mg, 200 mg and 400 mg is within the 5 mg per day limit in accordance with 21 CFR 73.1200.

Assessor note: The assessor agrees with the above calculations.

(b) (4)

- Similar to the RLD formulation, all the strengths of the test product (100 mg, 200 mg and 400 mg), Carbamazepine ER Tablets are compositionally proportional.

- The formulation proportionality between the bio-strength (400 mg) and 200 mg and 100 mg strengths were analyzed by separating the release-control excipients from non-release control excipients, as follows:

(b) (4)

(b) (4)

Therefore, the formulations of 100 mg and 200 mg strengths are proportionally similar to that of the bio strength (400 mg).

Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	☒ Yes ☐ No ☐ N/A Please see above calculations

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: Adequate

1. Per the PSG, in vivo BE studies for the 100 mg and 200 mg strengths may not be needed based on (i) acceptable BE studies for the 400 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.
2. All inactive ingredients utilized in the formulation (for all strengths) are below the listed IIG levels for orally administered drug products. The formulation of lower strengths – 100 mg and 200 mg are deemed compositionally proportional to that of the bio strength, 400 mg of the test product as per the SUPAC-MR guidance.
3. The RLD formulation is an osmotic-controlled release oral delivery system (OROS) based ER tablet that comprises a semi-permeable coating having release portal on one side.[43] The release portal provides the drug release in controlled manner over a period. (b) (4) The excipients in the test formulation are same or lower than the amounts in the RLD and other previously approved (A213311, A211623 and A205571) or BE adequate products (same as the current test product).
4. The composition of all the lower strengths of the test product is proportionally similar to the bio-strength 400 mg of test product (as shown above).
5. The formulations of the test product re acceptable.

[43] DARRTS, NDA 020234, New/Annual Report, Annual Report-15, dated 05/20/2011. EDR, Sequ 0025 (149), Module 3.2.P.3.3. manuf-process-and-controls.pdf and Module 3.2.P.5.1-Specifications\testing-monograph-400mg.pdf.

4.3 Dissolution Testing

4.3.1 Dissolution Data

4.3.1.1 QC Method – Water

Dissolution Conditions	**Apparatus:**	USP Apparatus I (10 mesh Basket)
	Speed of Rotation:	100 rpm
	Medium:	Water
	Volume:	900 mL
	Temperature:	37°C
Firm's Proposed Specifications	1h: Report Results 3h: (b) (4)% 6h: % 9h Report Results	12h: (b) (4)% 18h: Repo Results 24h NLT (b) (4)%
Dissolution Testing Site (Name, Address)	Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301	

Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)**							**Study Report Location**
						1	**3**	**6**	**9**	**12**	**18**	**24**	
AMVP-03-QCII-2018-110; QS-FP-028-01	03/14/2019	Lot# 201803092 Mfr.: Beijing Sciecure Mfr date: 03/20/2018	100 mg carbamazepine per tablet, extended-release tablet	12	**Mean (%)**	1	28	58	72	79	86	86	AMVR-03-QCII-2018-110
					Range (%)	(b) (4)							
					%CV	n/a	9	4	3	5	2	7	
	11/27/2018	Lot# 17030042 Mfr.: Beijing Sciecure Mfr date: 03/21/2017		12	**Mean (%)**	1	21	48	61	73	83	90	
					Range (%)	(b) (4)							
					%CV	n/a	9	5	6	2	4	3	
	11/27/2018	Lot# 17030032 Mfr.: Beijing Sciecure Mfr date: 03/04/2017		12	**Mean (%)**	1	23	51	67	77	84	89	
					Range (%)	(b) (4)							
					%CV	n/a	9	6	5	2	5	3	
	01/03/2019	(Reference Product) Lot# F0226 Mfr: Novartis Inc. Exp. Date: 03/2019	100 mg carbamazepine per tablet, extended-release tablet	12	**Mean (%)**	0	21	54	69	77	84	86	
					Range (%)	(b) (4)							
					%CV	n/a	18	6	4	2	1	1	

Dissolution Conditions	**Apparatus:**	USP Apparatus I (10 mesh Basket)
	Speed of Rotation:	100 rpm
	Medium:	Water
	Volume:	900 mL
	Temperature:	37°C
Firm's Proposed Specifications	1h: Report Results 3h: (b) (4)% 6h: % 9h Report Results	12h: (b) (4)% 18h: Report Results 24h NLT (b) (4)%
Dissolution Testing Site (Name, Address)	Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301	

Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)**							**Study Report Location**
						1	**3**	**6**	**9**	**12**	**18**	**24**	
AMVP-03-QCII-2018-110; QS-FP-029-01	05/20/2019	Lot# 201806022 Mfr.: Beijing Sciecure Mfr date: 06/05/2018	200 mg carbamazepine per tablet, extended-release tablet	12	**Mean (%)**	2	27	55	69	77	83	83	AMVR-03-QCII-2018-110
					Range (%)							(b) (4)	
					%CV	n/a	8	4	3	3	2	2	
	11/29/2018	Lot# 201806031 Mfr.: Beijing Sciecure Mfr date: 06/08/2018		12	**Mean (%)**	1	27	56	72	81	88	90	
					Range (%)							(b) (4)	
					%CV	n/a	6	5	3	2	2	2	
	11/24/2018	Lot# 201806021 Mfr.: Beijing Sciecure Mfr date: 06/05/2018		12	**Mean (%)**	1	25	57	71	79	86	88	
					Range (%)							(b) (4)	
					%CV	n/a	3	4	2	1	1	1	
	03/12/2019	(Reference Product) Lot# F0316 Mfr: Novartis Inc. Exp. Date: 05/2019	200 mg carbamazepine per tablet, extended-release tablet	12	**Mean (%)**	1	24	57	73	80	86	88	
					Range (%)							(b) (4)	
					%CV	n/a	16	6	4	3	2	2	

Dissolution Conditions	**Apparatus:**	USP Apparatus I (10 mesh Basket)
	Speed of Rotation:	100 rpm
	Medium:	Water
	Volume:	1800 mL
	Temperature:	37°C
Firm's Proposed Specifications	1h: Report Results 3h: (b) (4)% 6h: % 9h Report Results	12h: (b) (4)% 18h: Report Results 24h NLT (b) (4)%
Dissolution Testing Site (Name, Address)	Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301	

Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)**							**Study Report Location**
						1	**3**	**6**	**9**	**12**	**18**	**24**	
AMVP-03-QCII-2018-110; QS-FP-030-01	05/20/2019	Lot# 201803091 Mfr.: Beijing Sciecure Mfr date: 03/20/2018	400 mg carbamazepine per tablet, extended-release tablet	12	**Mean (%)**	3	29	55	72	80	90	90	AMVR-03-QCII-2018-110
					Range (%)							(b) (4)	
					%CV	n/a	9	6	3	3	6	6	
	11/24/2018	Lot# 17030041 Mfr.: Beijing Sciecure Mfr date: 03/21/2017		12	**Mean (%)**	1	26	51	67	77	82	84	
					Range (%)							(b) (4)	
					%CV	n/a	4	2	3	2	1	1	
	04/27/2017	Lot#17030031 Mfr.: Beijing Sciecure Mfr date: 03/04/2017		12	**Mean (%)**	3	28	56	72	80	87	87	
					Range (%)							(b) (4)	
					%CV	n/a	8	5	4	6	3	3	
	01/03/2019	(Reference Product) Lot# F1156 Mfr: Novartis Inc. Exp. Date: 03/2019	400 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	5	30	61	75	80	82	83	
					Range (%)							(b) (4)	
					%CV	n/a	11	7	5	3	3	2	

4.3.1.2 pH 1.2 Hydrochloric Acid Buffer

Dissolution Conditions			Apparatus:	USP Apparatus I (10 mesh Basket)							
			Speed of Rotation:	100 rpm							
			Medium:	pH 1.2							
			Volume:	900 mL							
			Temperature:	37°C							
Firm's Proposed Specifications			n/a								
Dissolution Testing Site (Name, Address)			Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301								
Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)							Study Report Location
						1	3	6	9	12	18	24	
AMVP-03-QCII-2018-110	05/24/2019	Lot# 201803092 Mfr.: Beijing Sciecure Mfr date: 03/20/2018	100 mg carbamazepine per tablet, extended-release tablet	12	Mean (%)	0	20	49	63	71	76	80	AMVR-03-QCII-2018-110
					Range (%)	(b) (4)							
					%CV	n/a	18	4	4	3	4	2	
	01/04/2019	(Reference Product) Lot# F0226 Mfr: Novartis Inc. Exp. Date: 03/2019	100 mg carbamazepine per tablet, extended-release tablet	12	Mean (%)	0	17	50	67	76	84	85	
					Range (%)	(b) (4)							
					%CV	n/a	18	5	2	3	4	5	

Dissolution Conditions			Apparatus:	USP Apparatus I (10 mesh Basket)							
			Speed of Rotation:	100 rpm							
			Medium:	pH 1.2							
			Volume:	900 mL							
			Temperature:	37°C							
Firm's Proposed Specifications			n/a								
Dissolution Testing Site (Name, Address)			Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301								
Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)							Study Report Location
						1	3	6	9	12	18	24	

AMVP-03-QCII-2018-110	05/23/2019	Lot# 201806022 Mfr.: Beijing Sciecure Mfr date: 06/05/2018	200 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	1	21	47	62	69	77	78	AMVR-03-QCII-2018-110
					Range (%)	(b) (4)							
					%CV	n/a	9	3	2	3	3	3	
	03/19/2019	(Reference Product) Lot# F0316 Mfr: Novartis Inc. Exp. Date: 05/2019	200 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	1	20	51	69	78	85	87	
					Range (%)	(b) (4)							
					%CV	n/a	19	7	3	2	2	2	

Dissolution Conditions			**Apparatus:**	USP Apparatus I (10 mesh Basket)							
			Speed of Rotation:	100 rpm							
			Medium:	pH 1.2							
			Volume:	1800 mL							
			Temperature:	37°C							
Firm's Proposed Specifications			n/a								
Dissolution Testing Site (Name, Address)			Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301								
Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)**							**Study Report Location**
						1	**3**	**6**	**9**	**12**	**18**	**24**	
AMVP-03-QCII-2018-110	05/29/2019	Lot# 201803091 Mfr.: Beijing Sciecure Mfr date: 03/20/2018	400 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	2	25	49	65	74	82	84	AMVR-03-QCII-2018-110
					Range (%)	(b) (4)							
					%CV	n/a	8	5	3	3	3	3	
	01/05/2019	(Reference Product) Lot# F1156 Mfr: Novartis Inc. Exp. Date: 03/2019	400 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	3	23	53	70	78	82	85	
					Range (%)	(b) (4)							
					%CV	n/a	13	4	2	1	0	1	

4.3.1.3 pH 4.5 Acetate Buffer

Dissolution Conditions			Apparatus:	USP Apparatus I (10 mesh Basket)							
			Speed of Rotation:	100 rpm							
			Medium:	pH 4.5							
			Volume:	900 mL							
			Temperature:	37°C							
Firm's Proposed Specifications			n/a								
Dissolution Testing Site (Name, Address)			Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301								
Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)							Study Report Location
						1	3	6	9	12	18	24	
AMVP-03-QCII-2018-110	05/27/2019	Lot# 201803092 Mfr.: Beijing Sciecure Mfr date: 03/20/2018	100 mg carbamazepine per tablet, extended-release tablet	12	Mean (%)	0	23	53	67	75	82	83	AMVR-03-QCII-2018-110
					Range (%)	(b) (4)							
					%CV	n/a	1	3	2	2	2	2	
	01/05/2019	(Reference Product) Lot# F0226 Mfr: Novartis Inc. Exp. Date: 03/2019	100 mg carbamazepine per tablet, extended-release tablet	12	Mean (%)	1	20	54	71	78	86	88	
					Range (%)	(b) (4)							
					%CV	n/a	18	8	3	2	2	2	

Dissolution Conditions			Apparatus:	USP Apparatus I (10 mesh Basket)							
			Speed of Rotation:	100 rpm							
			Medium:	pH 4.5							
			Volume:	900 mL							
			Temperature:	37°C							
Firm's Proposed Specifications			n/a								
Dissolution Testing Site (Name, Address)			Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301								
Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)							Study Report Location
						1	3	6	9	12	18	24	

AMVP-03-QCII-2018-110	05/25/2019	Lot# 201806022 Mfr.: Beijing Sciecure Mfr date: 06/05/2018	200 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	1	22	50	64	73	82	84	AMVR-03-QCII-2018-110
					Range (%)	(b) (4)							
					%CV	n/a	18	5	3	3	2	2	
	03/21/2019	(Reference Product) Lot# F0316 Mfr: Novartis Inc. Exp. Date: 05/2019	200 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	2	23	56	72	79	85	87	
					Range (%)	(b) (4)							
					%CV	n/a	15	6	3	3	2	1	

Dissolution Conditions			**Apparatus:**	USP Apparatus I (10 mesh Basket)							
			Speed of Rotation:	100 rpm							
			Medium:	pH 4.5							
			Volume:	1800 mL							
			Temperature:	37°C							
Firm's Proposed Specifications			n/a								
Dissolution Testing Site (Name, Address)			Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301								
Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)**							**Study Report Location**
						1	**3**	**6**	**9**	**12**	**18**	**24**	
AMVP-03-QCII-2018-110	06/03/2019	Lot# 201803091 Mfr.: Beijing Sciecure Mfr date: 03/20/2018	400 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	3	26	51	67	75	84	88	AMVR-03-QCII-2018-110
					Range (%)	(b) (4)							
					%CV	n/a	6	4	4	3	2	3	
	01/08/2019	(Reference Product) Lot# F1156 Mfr: Novartis Inc. Exp. Date: 03/2019	400 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	4	27	59	75	80	81	82	
					Range (%)	(b) (4)							
					%CV	n/a	9	4	2	3	3	3	

4.3.1.4 pH 6.8 Phosphate Buffer

Dissolution Conditions			Apparatus:	USP Apparatus I (10 mesh Basket)							
			Speed of Rotation:	100 rpm							
			Medium:	pH 6.8							
			Volume:	900 mL							
			Temperature:	37°C							
Firm's Proposed Specifications			n/a								
Dissolution Testing Site (Name, Address)			Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301								
Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)							Study Report Location
						1	3	6	9	12	18	24	
AMVP-03-QCII-2018-110	05/29/2019	Lot# 201803092 Mfr.: Beijing Sciecure Mfr date: 03/20/2018	100 mg carbamazepine per tablet, extended release tablet	12	Mean (%)	-1	22	50	64	71	78	80	AMVR-03-QCII-2018-110
					Range (%)	(b) (4)							
					%CV	n/a	9	6	4	3	2	2	
	01/07/2019	(Reference Product) Lot# F0226 Mfr: Novartis Inc. Exp. Date: 03/2019	100 mg carbamazepine per tablet, extended release tablet	12	Mean (%)	0	18	50	64	71	78	79	
					Range (%)	(b) (4)							
					%CV	n/a	24	7	3	2	2	1	

Dissolution Conditions			Apparatus:	USP Apparatus I (10 mesh Basket)							
			Speed of Rotation:	100 rpm							
			Medium:	pH 6.8							
			Volume:	900 mL							
			Temperature:	37°C							
Firm's Proposed Specifications			n/a								
Dissolution Testing Site (Name, Address)			Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301								
Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)							Study Report Location
						1	3	6	9	12	18	24	

AMVP-03-QCII-2018-110	05/28/2019	Lot# 201806022 Mfr.: Beijing Sciecure Mfr date: 06/05/2018	200 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	1	21	49	64	71	78	81	AMVR-03-QCII-2018-110
					Range (%)	(b) (4)							
					%CV	n/a	12	3	2	2	1	1	
	03/26/2019	(Reference Product) Lot# F0316 Mfr: Novartis Inc. Exp. Date: 05/2019	200 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**								
					Range (%)	(b) (4)							
					%CV	n/a	21	8	3	2	2	2	

Dissolution Conditions			**Apparatus:**	USP Apparatus I (10 mesh Basket)									
			Speed of Rotation:	100 rpm									
			Medium:	pH 6.8									
			Volume:	1800 mL									
			Temperature:	37°C									
Firm's Proposed Specifications			n/a										
Dissolution Testing Site (Name, Address)			Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301										
Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)**							**Study Report Location**
						1	**3**	**6**	**9**	**12**	**18**	**24**	
AMVP-03-QCII-2018-110	06/10/2019	Lot# 201803091 Mfr.: Beijing Sciecure Mfr date: 03/20/2018	400 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	2	25	50	64	72	79	83	AMVR-03-QCII-2018-110
					Range (%)	(b) (4)							
					%CV	n/a	6	4	3	2	2	2	
	01/21/2019	(Reference Product) Lot# F1156 Mfr: Novartis Inc. Exp. Date: 03/2019	400 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	3	22	49	64	69	73	74	
					Range (%)	(b) (4)							
					%CV	n/a	23	9	5	4	3	2	

4.3.1.5 In vitro alcohol dose dumping

Alcohol Dose Dumping Testing (0.1 N HCl) – 0% Alcohol

Dissolution Conditions	**Apparatus:**	USP Apparatus I (10 mesh Basket)
	Speed of Rotation:	100 rpm
	Medium:	100% 0.1N HCl (as control condition)
	Volume:	900 mL
	Temperature:	37°C
Firm's Proposed Specifications	n/a	
Dissolution Testing Site (Name, Address)	Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301	

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours) 0.25	0.5	0.75	1	1.25	1.5	1.75	2	Study Report Location
AMVP-03-QCII-2018-110	05/30/2019	Lot# 201803092 Mfr.: Beijing Sciecure Mfr date: 03/20/2018	100 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**									AMVR-03-QCII-2018-110
					Range (%)	(b) (4)								
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	
	01/15/2019	(Reference Product) Lot# F0226 Mfr: Novartis Inc. Exp. Date: 03/2019	100 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	0	0	0	0	1	3	5	7	
					Range (%)								(b) (4)	
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	

Dissolution Conditions	**Apparatus:**	USP Apparatus I (10 mesh Basket)
	Speed of Rotation:	100 rpm
	Medium:	100% 0.1N HCl (as control condition)
	Volume:	900 mL
	Temperature:	37°C
Firm's Proposed Specifications	n/a	
Dissolution Testing Site (Name, Address)	Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301	

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)								Study Report Location
						0.25	0.5	0.75	1	1.25	1.5	1.75	2	
AMVP-03-QCII-2018-110	05/31/2019	Lot# 201806022 Mfr.: Beijing Sciecure Mfr date: 06/05/2018	200 mg carbamazepine per tablet, extended release tablet	12	Mean (%)	0	0	1	2	3	5	8	10	AMVR-03-QCII-2018-110
					Range (%)	(b) (4)								
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	
	04/02/2019	(Reference Product) Lot# F0316 Mfr: Novartis Inc. Exp. Date: 05/2019	200 mg carbamazepine per tablet, extended release tablet	12	Mean (%)	0	0	0	1	3	5	7	9	
					Range (%)	(b) (4)								
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	

400 mg (0% Alcohol)

Dissolution Conditions	**Apparatus:**	USP Apparatus I (10 mesh Basket)
	Speed of Rotation:	100 rpm
	Medium:	100% 0.1N HCl (as control condition)
	Volume:	1800 mL
	Temperature:	37°C
Firm's Proposed Specifications	n/a	
Dissolution Testing Site (Name, Address)	Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301	

Study Ref. No.	Testing Date	Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)								Study Report Location
						0.25	0.5	0.75	1	1.25	1.5	1.75	2	
AMVP-03-QCII-2018-110	06/13/2019	Lot# 201803091 Mfr.: Beijing Sciecure Mfr date: 03/20/2018	400 mg carbamazepine per tablet, extended release tablet	12	Mean (%)	0	0	0	2	5	8	11	15	AMVR-03-QCII-2018-110
					Range (%)	(b) (4)								
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	
	02/18/2019	(Reference Product) Lot# F1156 Mfr: Novartis Inc. Exp. Date: 03/2019	400 mg carbamazepine per tablet, extended release tablet	12	Mean (%)	0	0	1	3	6	9	12	14	
					Range (%)	(b) (4)								
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	

(5% Alcohol)

100 mg

Dissolution Conditions														
			Apparatus:	USP Apparatus I (10 mesh Basket)										
			Speed of Rotation:	100 rpm										
			Medium:	5% Alcohol + 95% 0.1N HCl										
			Volume:	900 mL										
			Temperature:	37°C										
Firm's Proposed Specifications			n/a											
Dissolution Testing Site (Name, Address)			Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301											
Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)**								**Study Report Location**
						0.25	**0.5**	**0.75**	**1**	**1.25**	**1.5**	**1.75**	**2**	
AMVP-03-QCII-2018-110	06/10/2019	Lot# 201803092 Mfr.: Beijing Sciecure Mfr date: 03/20/2018	100 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	0	0	0	0	1	2	4	7	AMVR-03-QCII-2018-110
					Range (%)								(b) (4)	
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	
	01/16/2019	(Reference Product) Lot# F0226 Mfr: Novartis Inc. Exp. Date: 03/2019	100 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	0	0	0	1	1	2	3	5	
					Range (%)								(b) (4)	
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	

200 mg (5% Alcohol)

Dissolution Conditions		
	Apparatus:	USP Apparatus I (10 mesh Basket)
	Speed of Rotation:	100 rpm
	Medium:	5% Alcohol + 95% 0.1N HCl
	Volume:	900 mL
	Temperature:	37°C
Firm's Proposed Specifications	n/a	

Dissolution Testing Site (Name, Address)			Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301											
Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)**								**Study Report Location**
						0.25	**0.5**	**0.75**	**1**	**1.25**	**1.5**	**1.75**	**2**	
AMVP-03-QCII-2018-110	06/03/2019	Lot# 201806022 Mfr.: Beijing Sciecure Mfr date: 06/05/2018	200 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	0	0	0	1	2	4	6	9	AMVR-03-QCII-2018-110
					Range (%)	(b) (4)								
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	
	04/03/2019	(Reference Product) Lot# F0316 Mfr: Novartis Inc. Exp. Date: 05/2019	200 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	0	0	0	1	3	5	7	10	
					Range (%)	(b) (4)								
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	

400 mg (5% Alcohol)

Dissolution Conditions	**Apparatus:**	USP Apparatus I (10 mesh Basket)
	Speed of Rotation:	100 rpm
	Medium:	5% Alcohol + 95% 0.1N HCl
	Volume:	1800 mL
	Temperature:	37°C
Firm's Proposed Specifications	n/a	
Dissolution Testing Site (Name, Address)	Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301	

Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)**								**Study Report Location**
						0.25	**0.5**	**0.75**	**1**	**1.25**	**1.5**	**1.75**	**2**	
AMVP-03-QCII-2018-110	06/14/2019	Lot# 201803091 Mfr.: Beijing Sciecure Mfr date: 03/20/2018	400 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	0	0	0	1	3	6	9	12	AMVR-03-QCII-2018-110
					Range (%)	(b) (4)								
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	
		(Reference Product)		12	**Mean (%)**	0	0	1	3	6	8	11	13	

	02/20/2019	Lot# F1156 Mfr: Novartis Inc. Exp. Date: 03/2019	400 mg carbamazepine per tablet, extended release tablet		**Range (%)**	(b) (4)								
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	

100 mg (20% Alcohol)

Dissolution Conditions			**Apparatus:**	USP Apparatus I (10 mesh Basket)									
			Speed of Rotation:	100 rpm									
			Medium:	20% Alcohol + 80% 0.1N HCl									
			Volume:	900 mL									
			Temperature:	37°C									
Firm's Proposed Specifications				n/a									
Dissolution Testing Site (Name, Address)				Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301									
Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)**								**Study Report Location**
						0.25	**0.5**	**0.75**	**1**	**1.25**	**1.5**	**1.75**	**2**	
AMVP-03-QCII-2018-110	06/11/2019	Lot# 201803092 Mfr.: Beijing Sciecure Mfr date: 03/20/2018	100 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	0	0	0	0	1	2	4	6	AMVR-03-QCII-2018-110
					Range (%)	(b) (4)								
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	
	01/16/2019	(Reference Product) Lot# F0226 Mfr: Novartis Inc. Exp. Date: 03/2019	100 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**									
					Range (%)	(b) (4)								
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	

200 mg (20% Alcohol)

Dissolution Conditions	**Apparatus:**	USP Apparatus I (10 mesh Basket)
	Speed of Rotation:	100 rpm
	Medium:	20% Alcohol + 80% 0.1N HCl
	Volume:	900 mL

			Temperature:	37°C											
Firm's Proposed Specifications			n/a												
Dissolution Testing Site (Name, Address)			Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301												
Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)**								**Study Report Location**
						0.25	**0.5**	**0.75**	**1**	**1.25**	**1.5**	**1.75**	**2**	
AMVP-03-QCII-2018-110	06/05/2019	Lot# 201806022 Mfr.: Beijing Sciecure Mfr date: 06/05/2018	200 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	0	0	0	0	1	1	3	4	AMVR-03-QCII-2018-110
					Range (%)	(b) (4)								
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	
	04/09/2019	(Reference Product) Lot# F0316 Mfr: Novartis Inc. Exp. Date: 05/2019	200 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	0	0	0	0	0	1	2	3	
					Range (%)	(b) (4)								
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	

400 mg (20% Alcohol)

Dissolution Conditions			**Apparatus:**	USP Apparatus I (10 mesh Basket)											
			Speed of Rotation:	100 rpm											
			Medium:	20% Alcohol + 80% 0.1N HCl											
			Volume:	1800 mL											
			Temperature:	37°C											
Firm's Proposed Specifications			n/a												
Dissolution Testing Site (Name, Address)			Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301												
Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)**								**Study Report Location**
						0.25	**0.5**	**0.75**	**1**	**1.25**	**1.5**	**1.75**	**2**	
AMVP-03-QCII-	06/17/2019	Lot# 201803091 Mfr.: Beijing Sciecure	400 mg carbamazepine per	12	**Mean (%)**	0	0	0	0	1	2	4	6	AMVR-03-QCII-
					Range (%)	(b) (4)								

2018-110		Mfr date: 03/20/2018	tablet, extended release tablet		**%CV**	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	2018-110
	02/26/2019	(Reference Product) Lot# F1156 Mfr: Novartis Inc. Exp. Date: 03/2019	400 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	0	0	0	1	2	3	5	8	
					Range (%)	(b) (4)								
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	

(40% Alcohol)

100 mg (40% Alcohol)

Dissolution Conditions			**Apparatus:**	USP Apparatus I (10 mesh Basket)										
			Speed of Rotation:	100 rpm										
			Medium:	40% Alcohol + 60% 0.1N HCl										
			Volume:	900 mL										
			Temperature:	37°C										
Firm's Proposed Specifications			n/a											
Dissolution Testing Site (Name, Address)			Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301											
Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)**								**Study Report Location**
						0.25	**0.5**	**0.75**	**1**	**1.25**	**1.5**	**1.75**	**2**	
AMVP-03-QCII-2018-110	06/12/2019	Lot# 201803092 Mfr.: Beijing Sciecure Mfr date: 03/20/2018	100 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	0	0	0	1	1	2	5	8	AMVR-03-QCII-2018-110
					Range (%)	(b) (4)								
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	
	02/14/2019	(Reference Product) Lot# F0226 Mfr: Novartis Inc. Exp. Date: 03/2019	100 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	0	0	1	1	2	2	3	3	
					Range (%)	(b) (4)								
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	

200 mg (40% Alcohol)

Dissolution Conditions	**Apparatus:**	USP Apparatus I (10 mesh Basket)

			Speed of Rotation:	100 rpm											
			Medium:	40% Alcohol + 60% 0.1N HCl											
			Volume:	900 mL											
			Temperature:	37°C											
Firm's Proposed Specifications			n/a												
Dissolution Testing Site (Name, Address)			Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301												
Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)**								**Study Report Location**	
						0.25	**0.5**	**0.75**	**1**	**1.25**	**1.5**	**1.75**	**2**		
AMVP-03-QCII-2018-110	06/13/2019	Lot# 201806022 Mfr.: Beijing Sciecure Mfr date: 06/05/2018	200 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	0	0	0	0	0	1	3	5	AMVR-03-QCII-2018-110	
					Range (%)	(b) (4)									
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a		
	04/11/2019	(Reference Product) Lot# F0316 Mfr: Novartis Inc. Exp. Date: 05/2019	200 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	0	0	1	1	2	3	3	4		
					Range (%)	(b) (4)									
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a		

400 mg (40% Alcohol)

Dissolution Conditions			**Apparatus:**	USP Apparatus I (10 mesh Basket)											
			Speed of Rotation:	100 rpm											
			Medium:	40% Alcohol + 60% 0.1N HCl											
			Volume:	1800 mL											
			Temperature:	37°C											
Firm's Proposed Specifications			n/a												
Dissolution Testing Site (Name, Address)			Beijing Sciecure Pharmaceutical Co., Ltd. Zhongbei Industrial Park, Beishicao Town, Shunyi District, Beijing 101301												
Study Ref. No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfr. Date) (Reference – Exp. Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (hours)**								**Study Report Location**	
						0.25	**0.5**	**0.75**	**1**	**1.25**	**1.5**	**1.75**	**2**		

AMVP-03-QCII-2018-110	06/18/2019	Lot# 201803091 Mfr.: Beijing Sciecure Mfr date: 03/20/2018	400 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	0	0	0	0	1	2	4	5	AMVR-03-QCII-2018-110
					Range (%)	(b) (4)									
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a		
	02/28/2019	(Reference Product) Lot# F1156 Mfr: Novartis Inc. Exp. Date: 03/2019	400 mg carbamazepine per tablet, extended release tablet	12	**Mean (%)**	0	1	1	2	3	4	4	5		
					Range (%)	(b) (4)									
					%CV	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a		

4.3.2 Dissolution Profiles

QC Method – Water

Figure 1 Dissolution Curve Comparison (Water) for RLD and Test Product of 100 mg

图 1 参比制剂与待测样品 100 mg 的溶出曲线比较图（水条件）

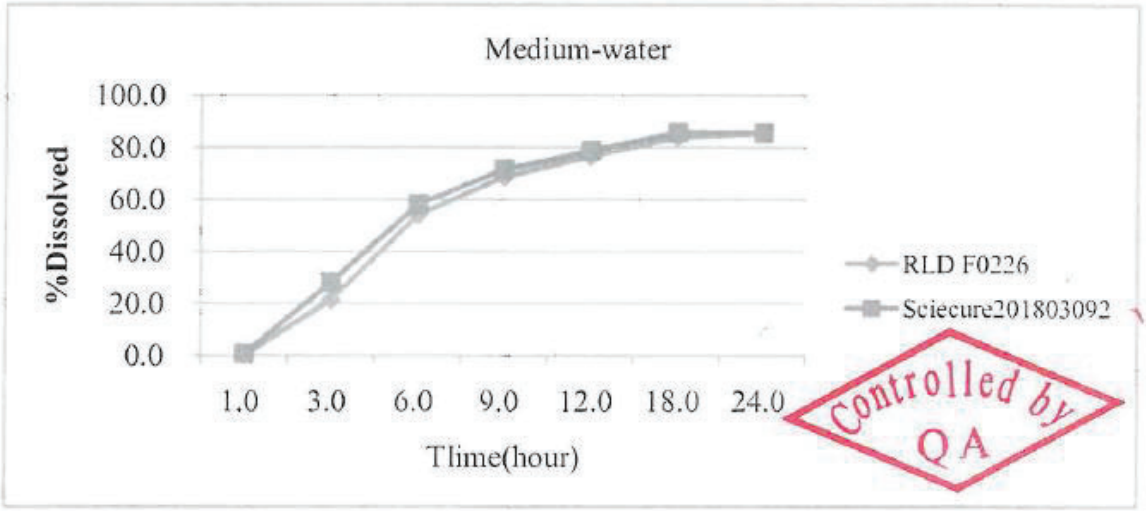
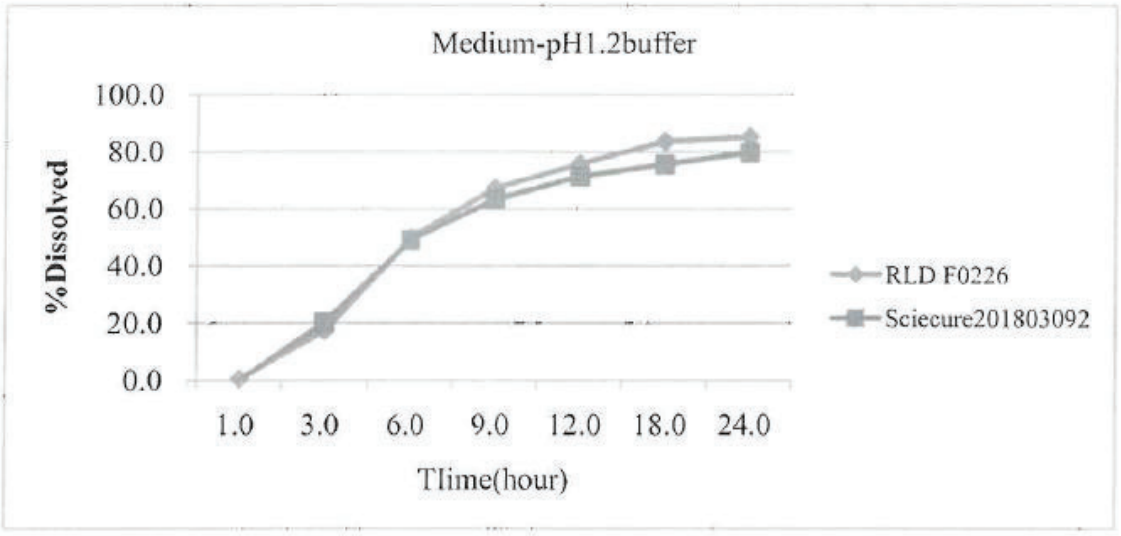


Figure 2 Dissolution Curve Comparison (pH 1.2) for RLD and Test Product of 100 mg

图 2 参比制剂与北京世桥生产的卡马西平缓释片 100 mg 溶出曲线比较图（pH 1.2）



igure 3 Dissolution Curve Comparison (pH 4.5) for RLD and Test Product of 100 mg

图 3 参比制剂与待测样品 100 mg 溶出曲线比较图（pH 4.5）

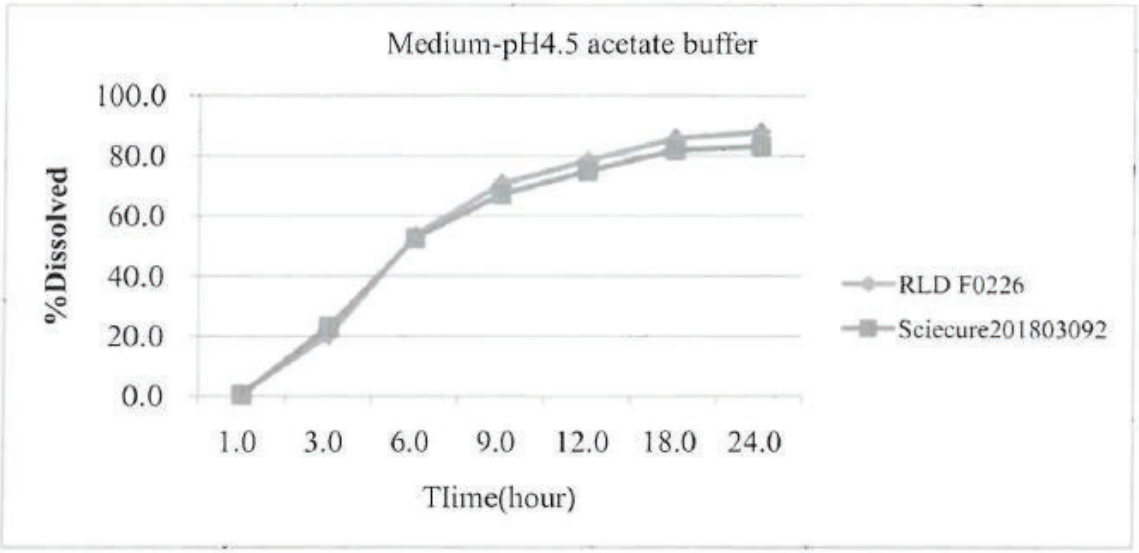
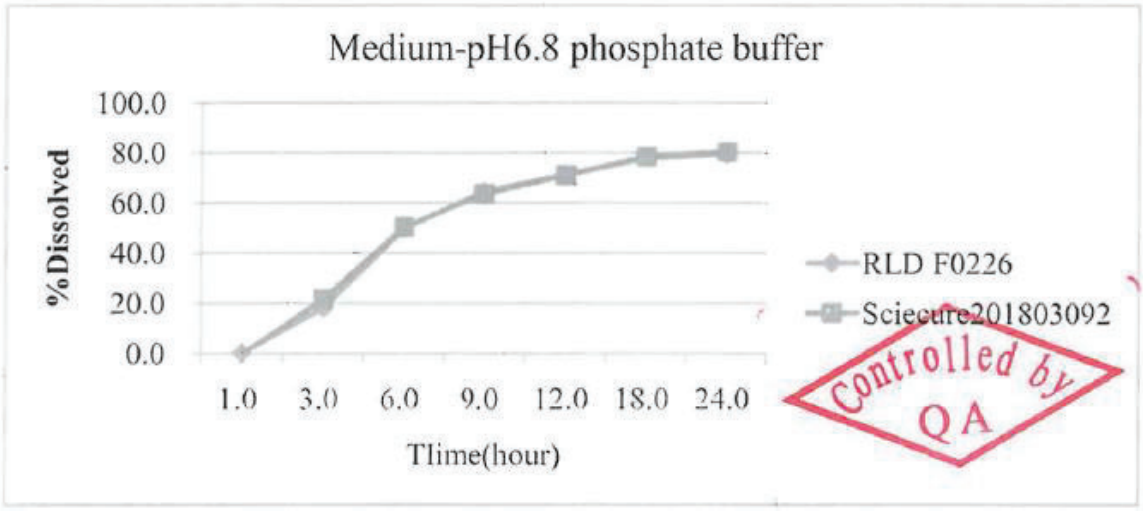


Figure 4 Dissolution Curve Comparison (pH 6.8) for RLD and Test Product of 100 mg

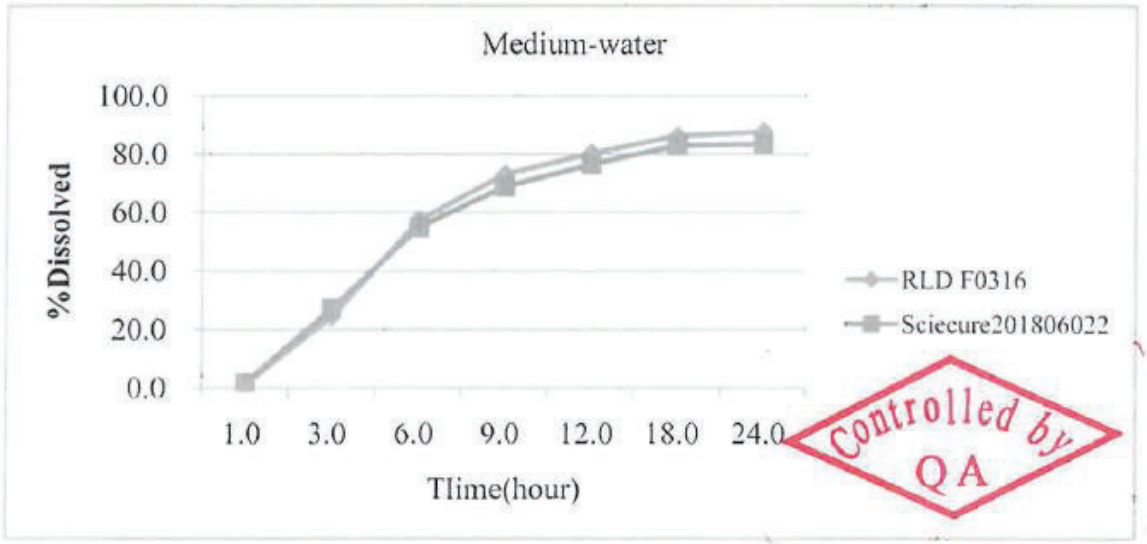
图 4 参比制剂与待测样品 100 mg 溶出曲线比较图（pH 6.8）



200 mg

Figure 5 Dissolution Curve Comparison (Water) for RLD and Test Product of 200 mg

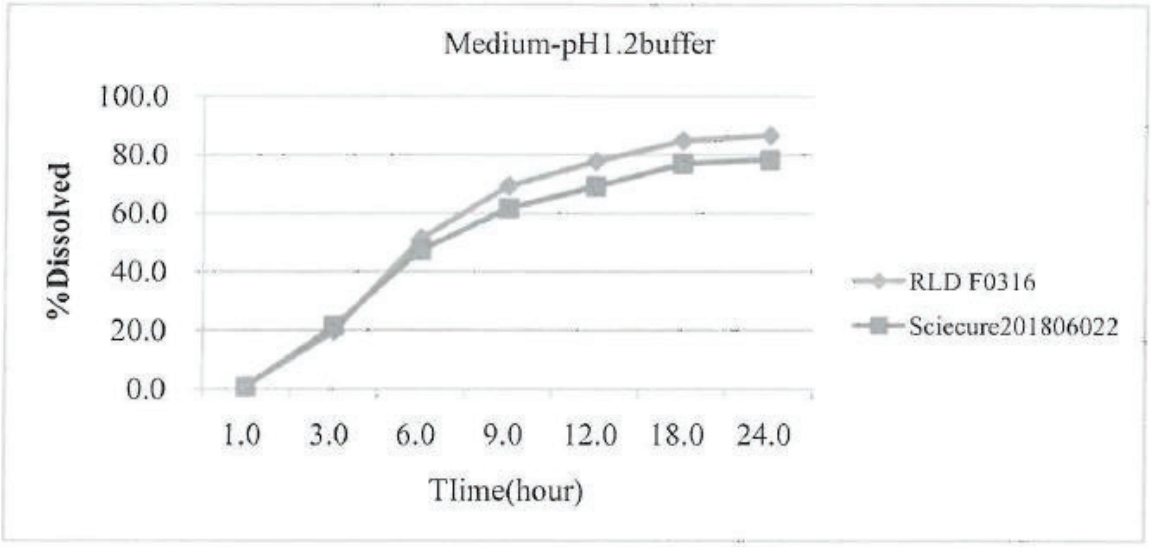
图 5 参比制剂与待测样品 200 mg 溶出曲线比较图（水）



pH 1.2 Hydrochloric Acid Buffer

Figure 6 Dissolution Curve Comparison (pH 1.2) for RLD and Test Product of 200 mg

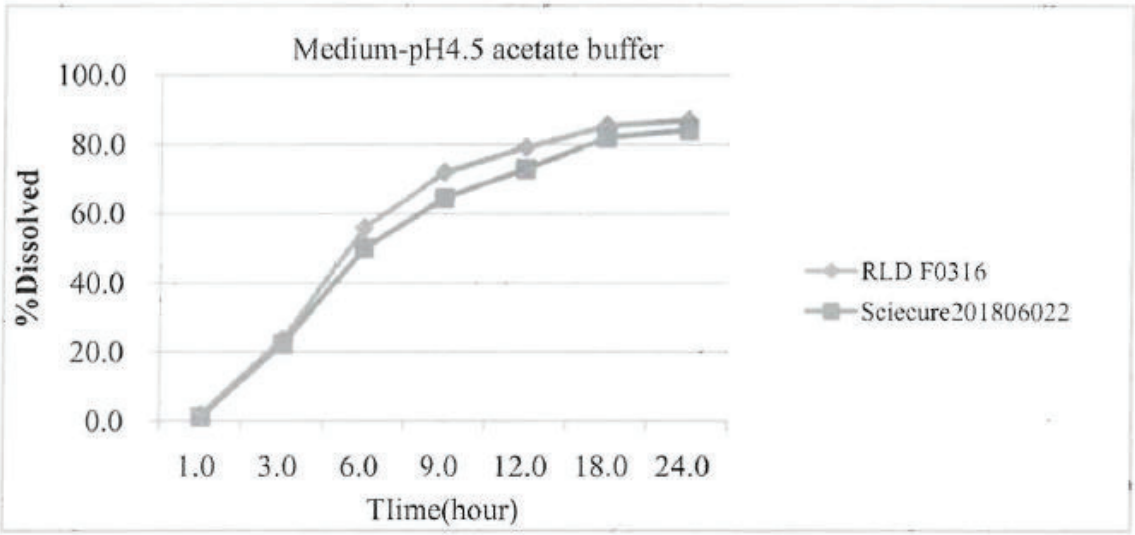
图 6 参比制剂与待测样品 200 mg 溶出曲线比较图（pH 1.2）



pH 4.5 Acetate Buffer

Figure 7 Dissolution Curve Comparison (pH 4.5) for RLD and Test Product of 200 mg

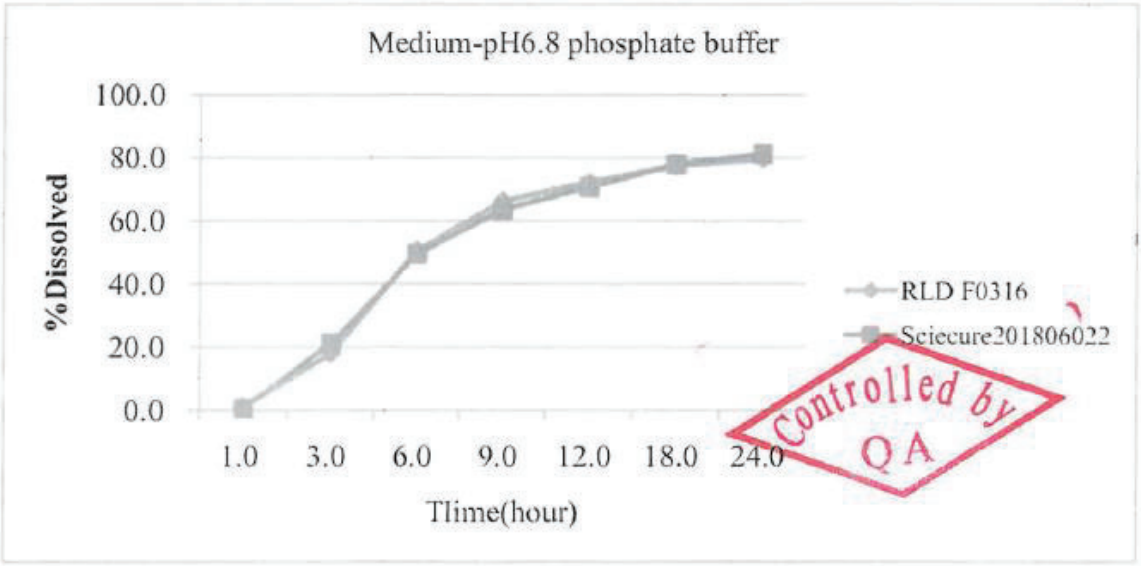
图 7 参比制剂与待测样品 200 mg 溶出曲线比较图（pH 4.5）



pH 6.8 Phosphate Buffer

Figure 8 Dissolution Curve Comparison (pH 6.8) for RLD and Test Product of 200 mg

图 8 参比制剂与待测样品 200 mg 溶出曲线比较图（pH 6.8）



400 mg

Figure 9 Dissolution Curve Comparison (Water) for RLD and Test Product of 400 mg

图 9 参比制剂与待测样品 400 mg 溶出曲线比较图（水）

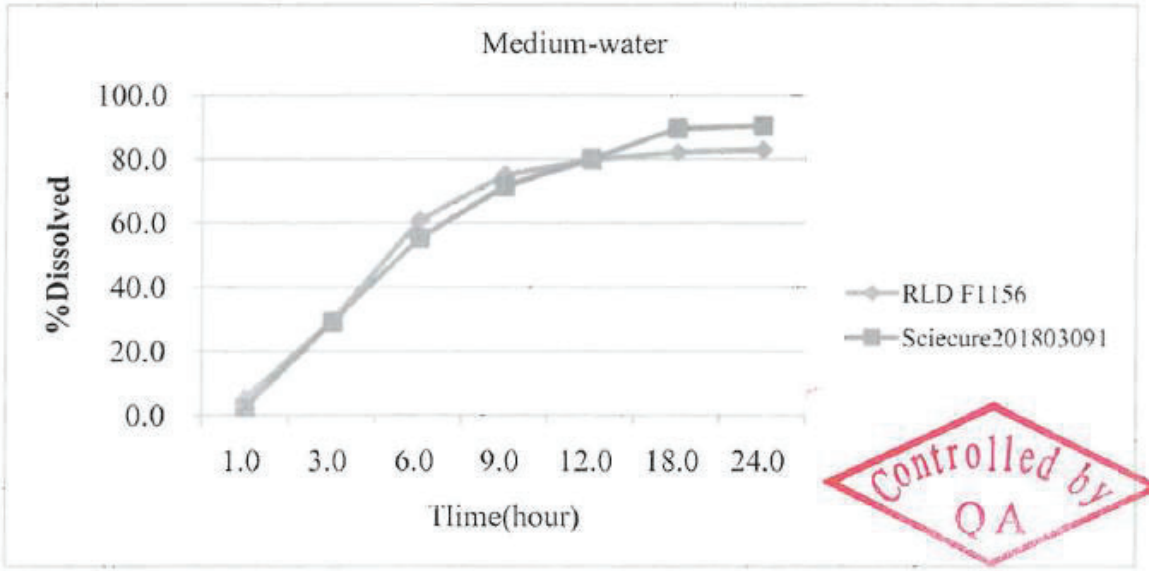


Figure 10 Dissolution Curve Comparison (pH 1.2) for RLD and Test Product of 400 mg

图 10 参比制剂与待测样品 400 mg 溶出曲线比较图（pH 1.2）

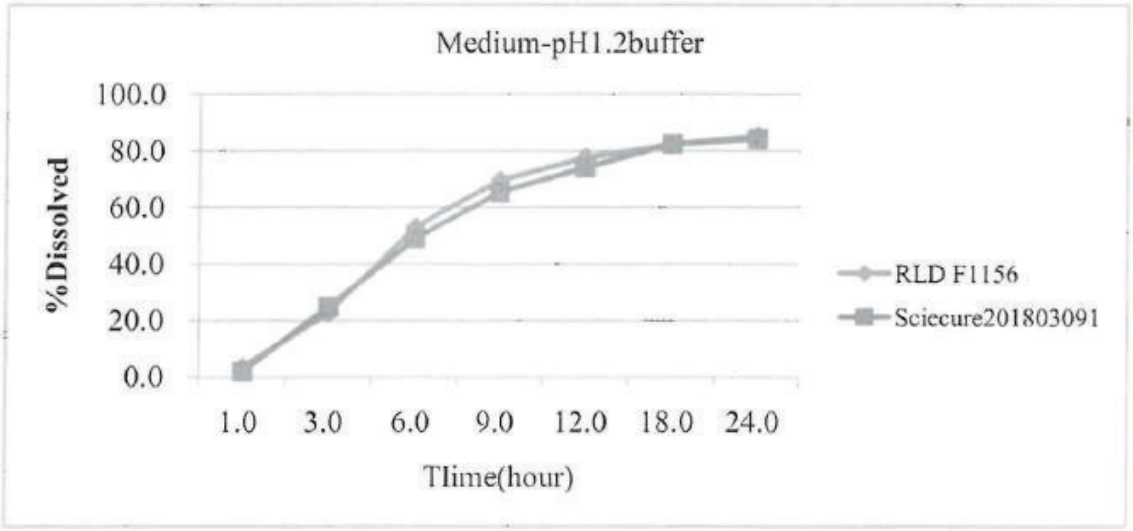


Figure 11 Dissolution Curve Comparison (pH 4.5) for RLD and Test Product of 400 mg

图 11 参比制剂与待测样品 400 mg 溶出曲线比较图（pH 4.5）

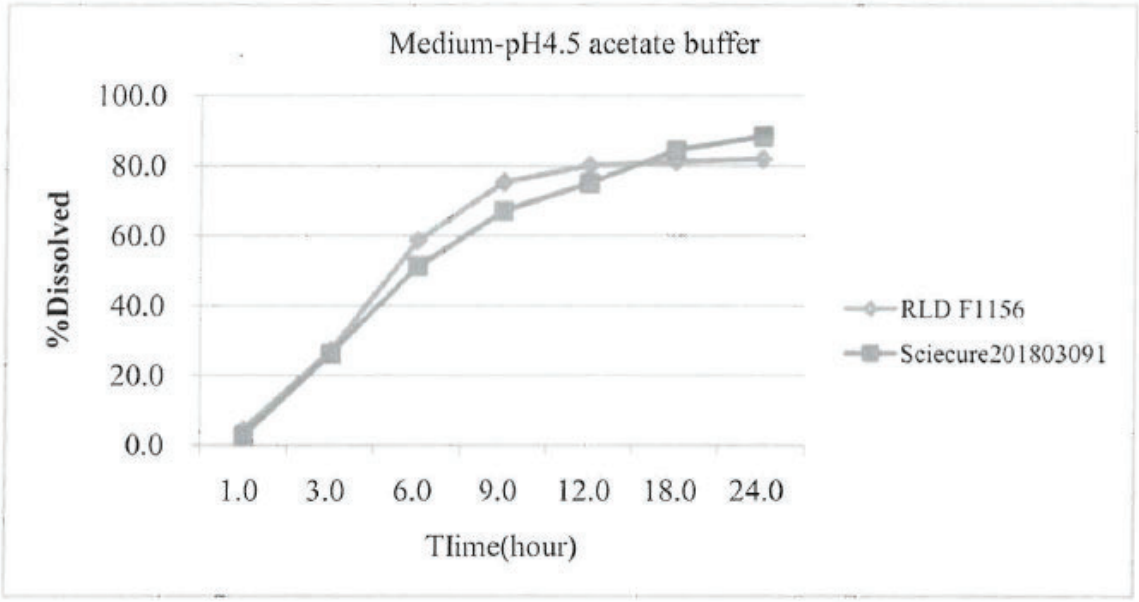
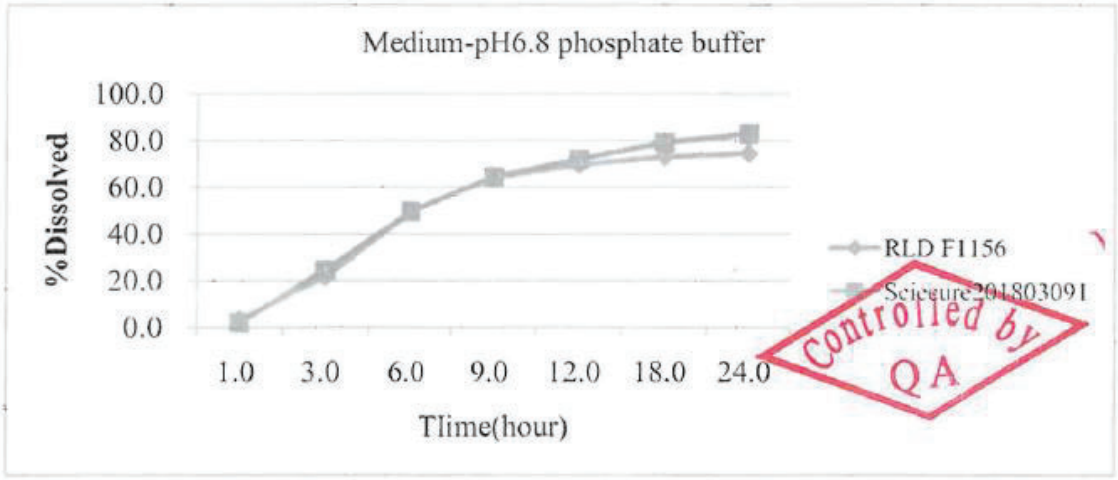


Figure 12 Dissolution Curve Comparison (pH 6.8) for RLD and Test Product of 400 mg

图 12 参比制剂与待测样品 400 mg 溶出曲线比较图（pH 6.8）



Alcohol dose dumping

Figure 13 RLD Dissolution Profiles for 100 mg (Dose Dumping in Alcohol)

图 13 参比制剂 100 mg 溶出曲线图（乙醇倾泻）

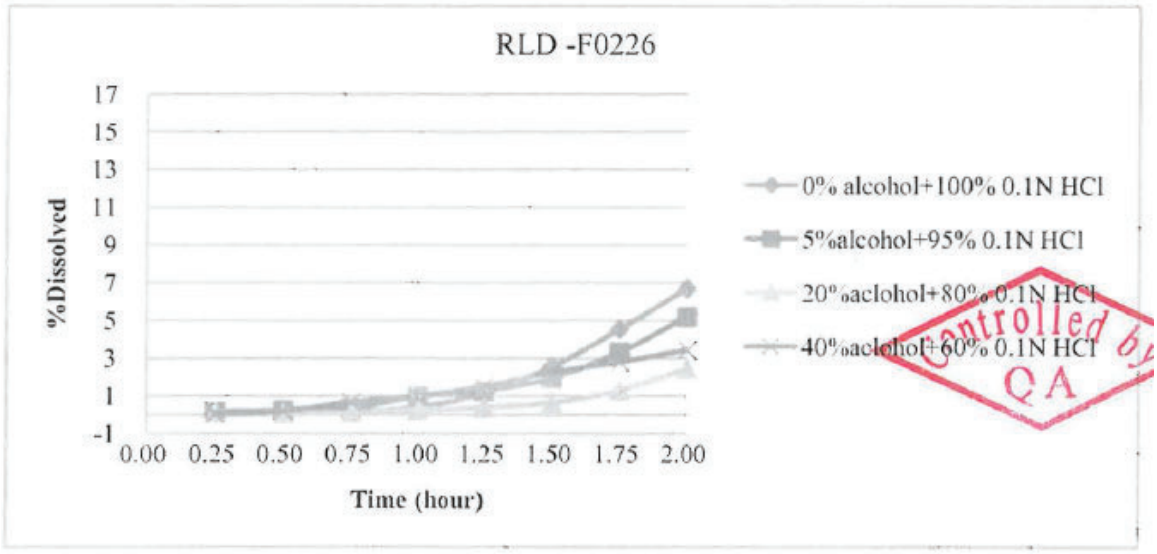


Figure 14 Dissolution Profiles of Test Product for 100 mg (Dose Dumping in Alcohol)

图 14 待测样品 100 mg 的溶出曲线图（乙醇倾泻）

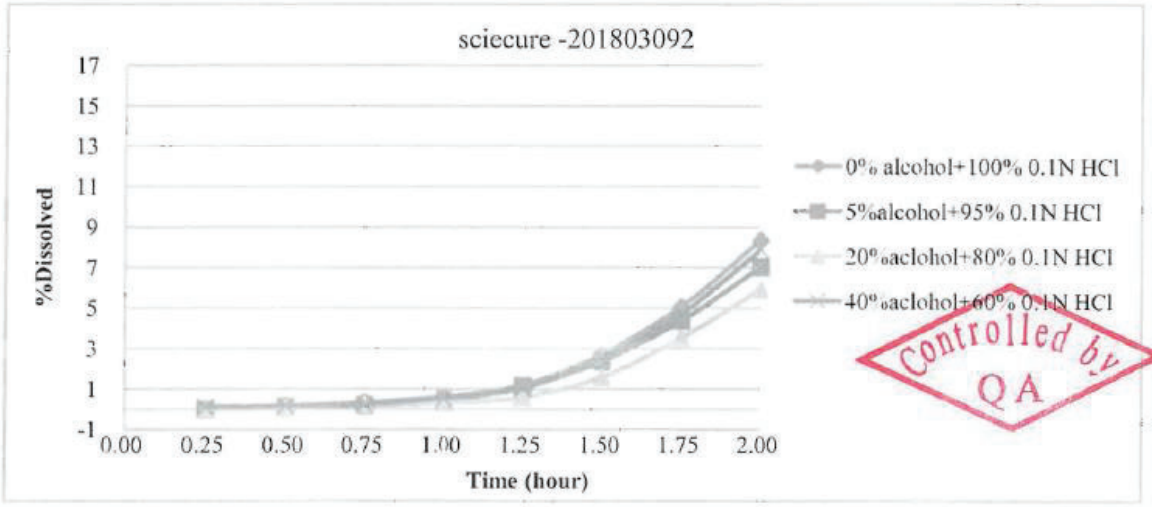


Figure 15 Dissolution Profile Comparison of 100 mg ERT for RLD/Test Products in 0% Alcohol in 0.1 N HCl

图 15 在 0%乙醇 0.1 N HCl 中参比制剂/被测药 100 mg 缓释片的溶出曲线比较图

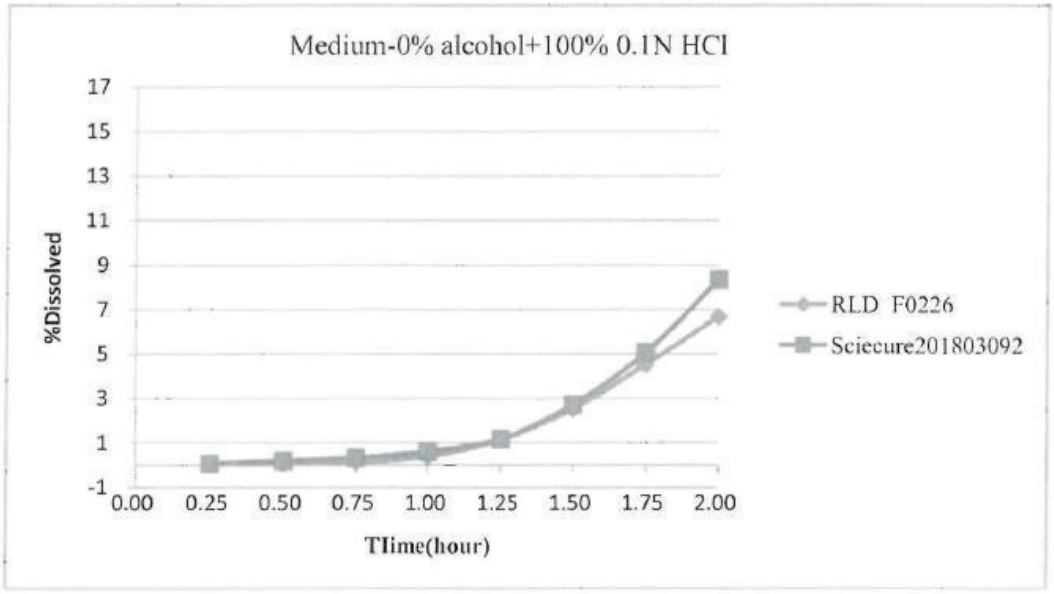


Figure 16 Dissolution Profile Comparison of 100 mg ERT for RLD/Test Products in 5% Alcohol in 0.1 N HCl

图 16 在 5%乙醇 0.1 N HCl 中参比制剂/被测药 100 mg 缓释片的溶出曲线比较图

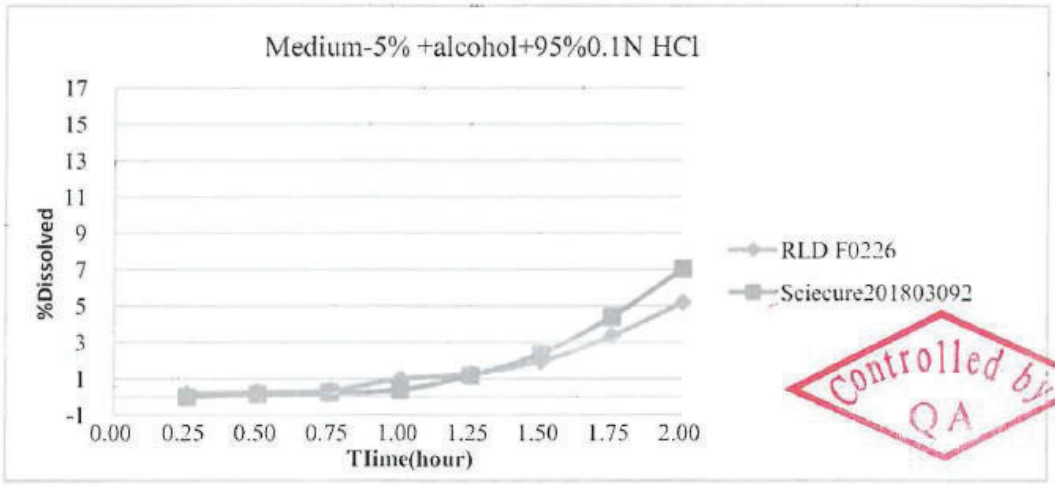


Figure 17 Dissolution Profile Comparison of 100 mg ERT for RLD/Test Products in 20% Alcohol in 0.1 N HCl

图 17 在 20%乙醇 0.1 N HCl 中参比制剂/被测药 100 mg 缓释片的溶出曲线比较图

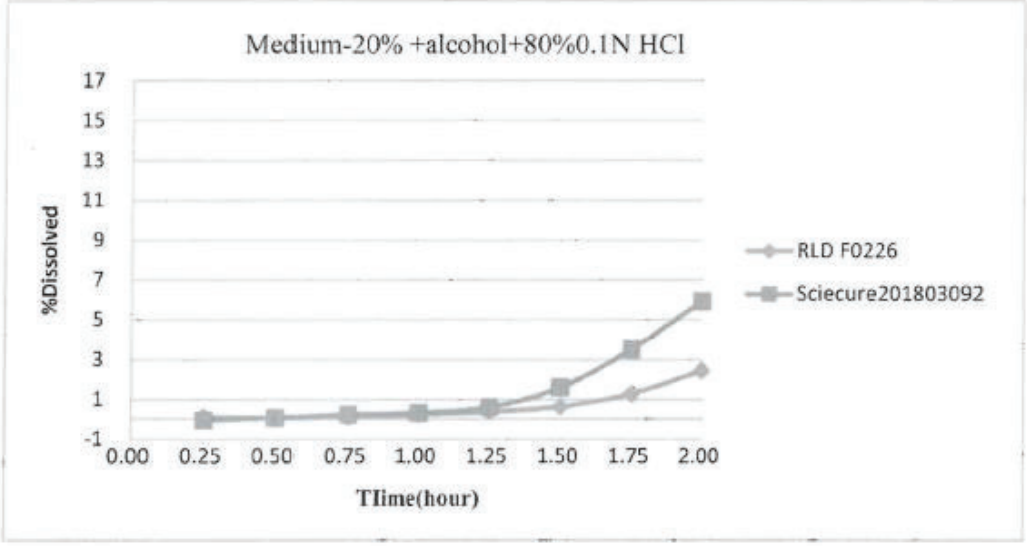
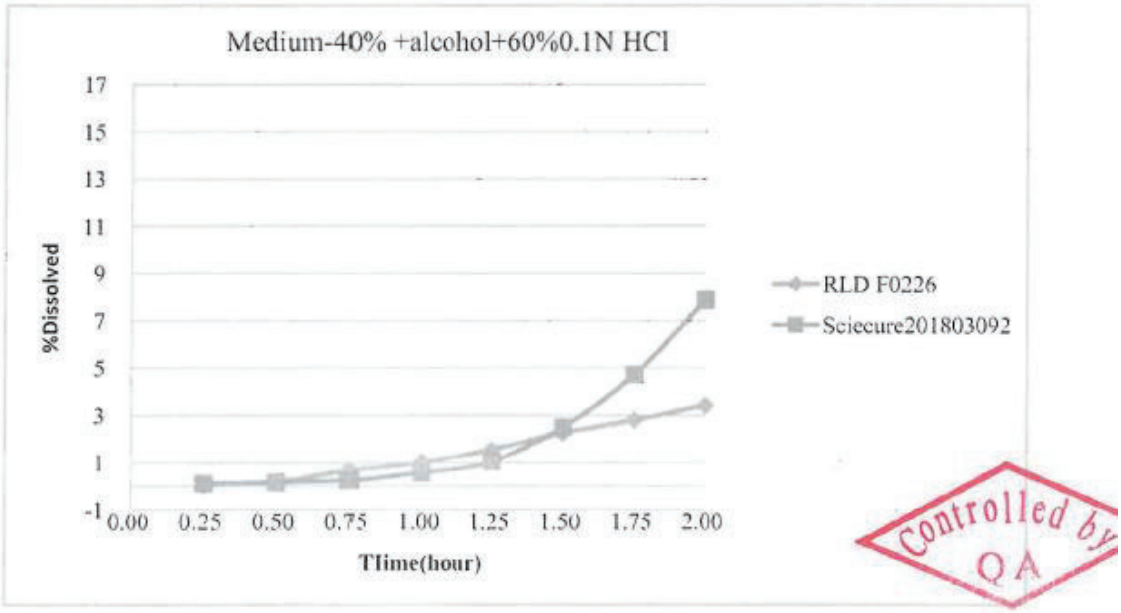


Figure 18 Dissolution Profile Comparison of 100 mg ERT for RLD/Test Products in 40% Alcohol in 0.1 N HCl

图 18 在 40%乙醇 0.1 N HCl 中参比制剂/被测药 100 mg 缓释片的溶出曲线比较图



200 mg

Figure 19 Dissolution Profiles of RLD for 200 mg (Dose Dumping in Alcohol)

图 19 RLD 200 mg 的溶出曲线图（乙醇倾泻）

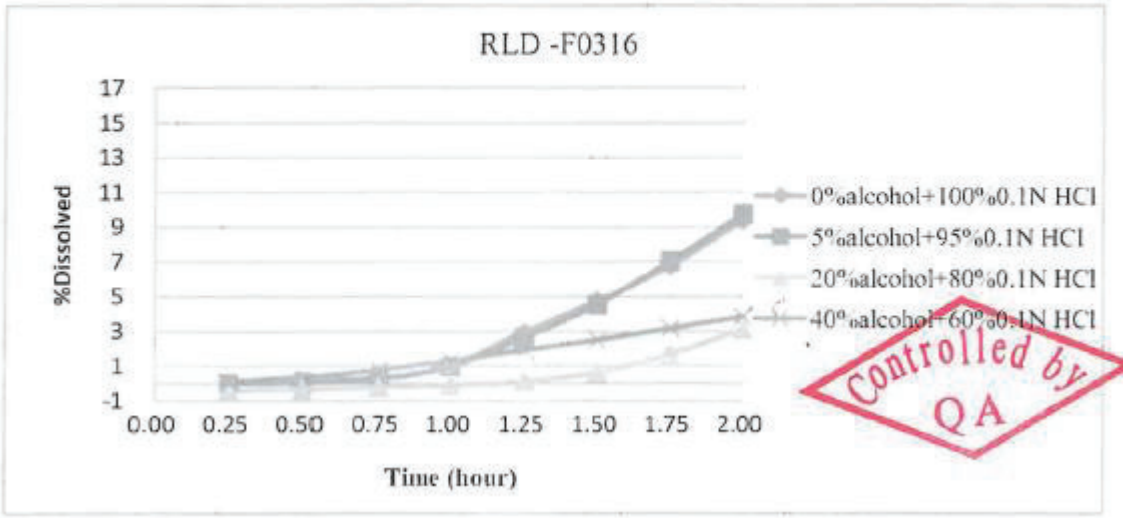


Figure 20 Dissolution Profiles of Test Product for 200 mg (Dose Dumping in Alcohol)

图 20 待测样品 200 mg 的溶出曲线图（乙醇倾泻）

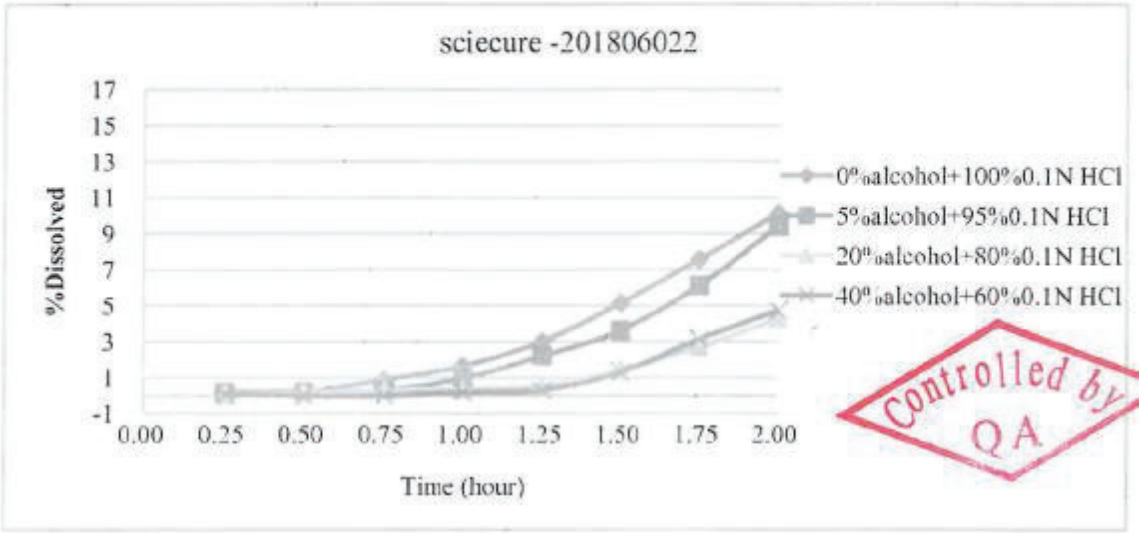


Figure 21 Dissolution Profile Comparison of 200 mg ERT for RLD/Test Products in 0% Alcohol in 0.1 N HCl

图 21 在 0%乙醇 0.1 N HCl 中参比制剂/被测药 200 mg 缓释片的溶出曲线比较图

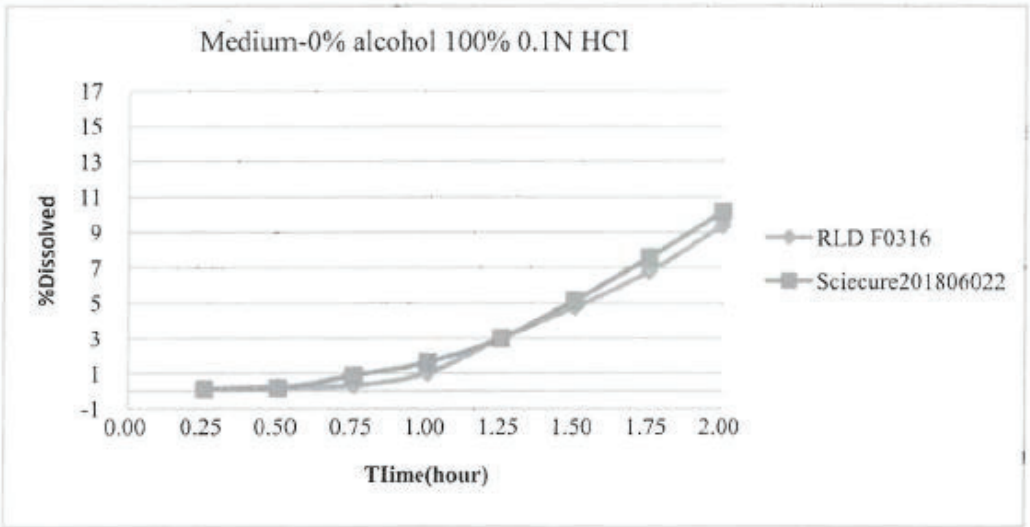


Figure 22 Dissolution Profile Comparison of 200 mg ERT for RLD/Test Products in 5% Alcohol in 0.1 N HCl

图 22 在 5%乙醇 0.1 N HCl 中参比制剂/被测药 200 mg 缓释片的溶出曲线比较图

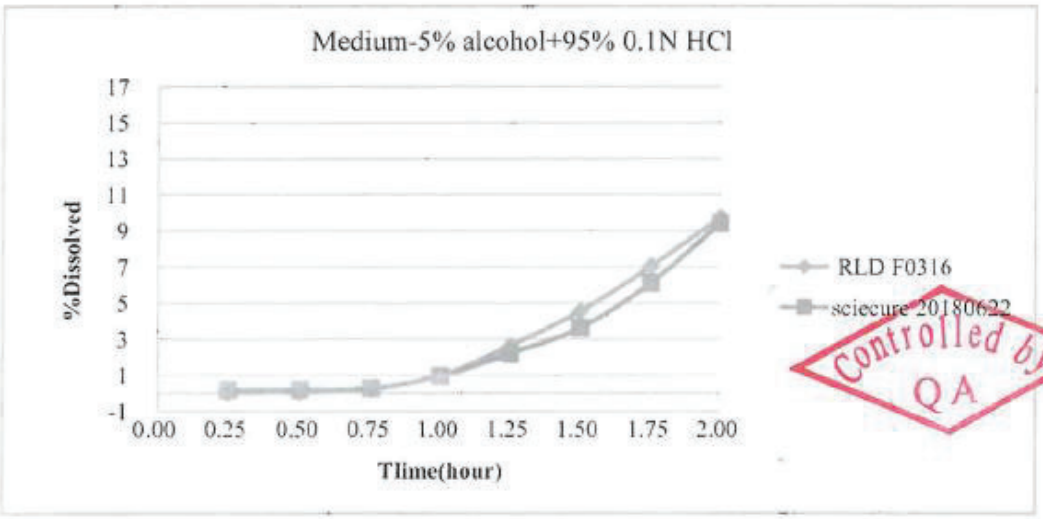


Figure 23 Dissolution Profile Comparison of 200 mg ERT for RLD/Test Products in 20% Alcohol in 0.1 N HCl

图 23 在 20%乙醇 0.1 N HCl 中参比制剂/被测药 200 mg 缓释片的溶出曲线比较图

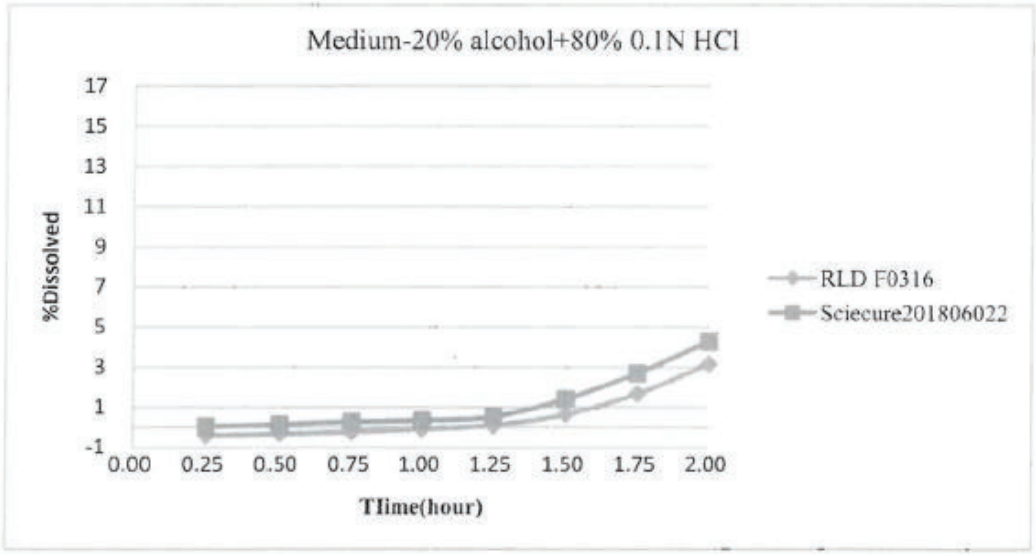
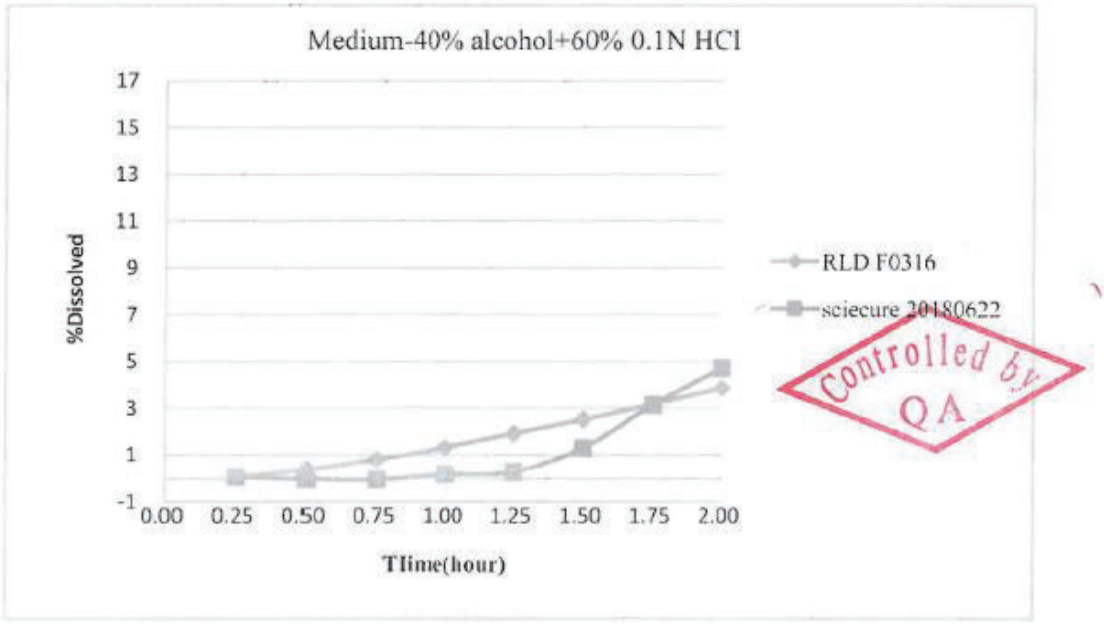


Figure 24 Dissolution Profile Comparison of 200 mg ERT for RLD/Test Products in 40% Alcohol in 0.1 N HCl

图 24 在 40%乙醇 0.1 N HCl 中参比制剂/被测药 200 mg 缓释片的溶出曲线比较图



400 mg

Figure 25 Dissolution Profiles of RLD for 400 mg (Dose Dumping in Alcohol)

图 25 RLD 400 mg 的溶出曲线图（乙醇倾泻）

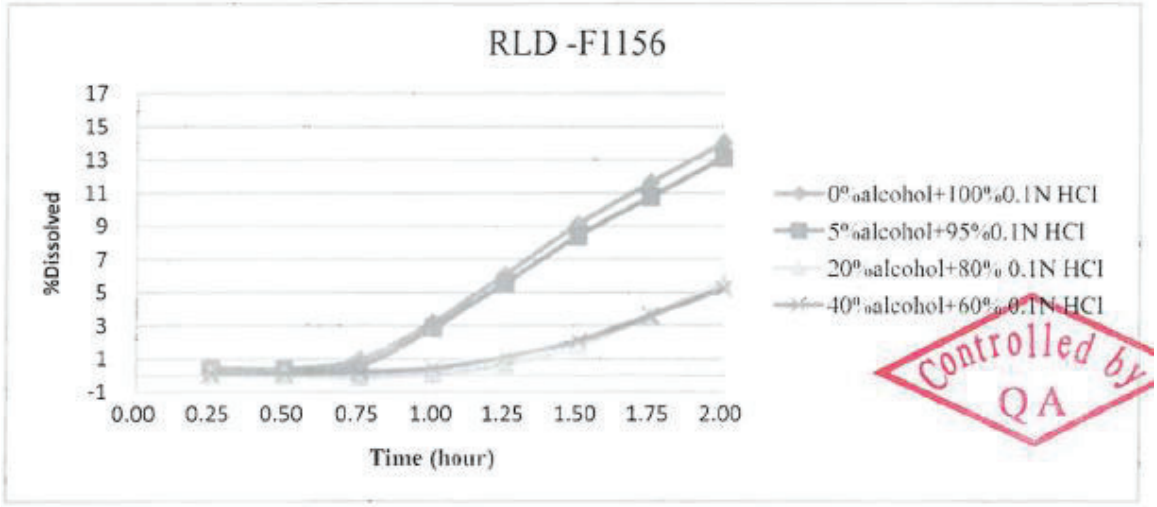


Figure 26 Dissolution Profiles of Test Product for 400 mg (Dose Dumping in Alcohol)

图 26 待测样品 400 mg 的溶出曲线图（乙醇倾泻）

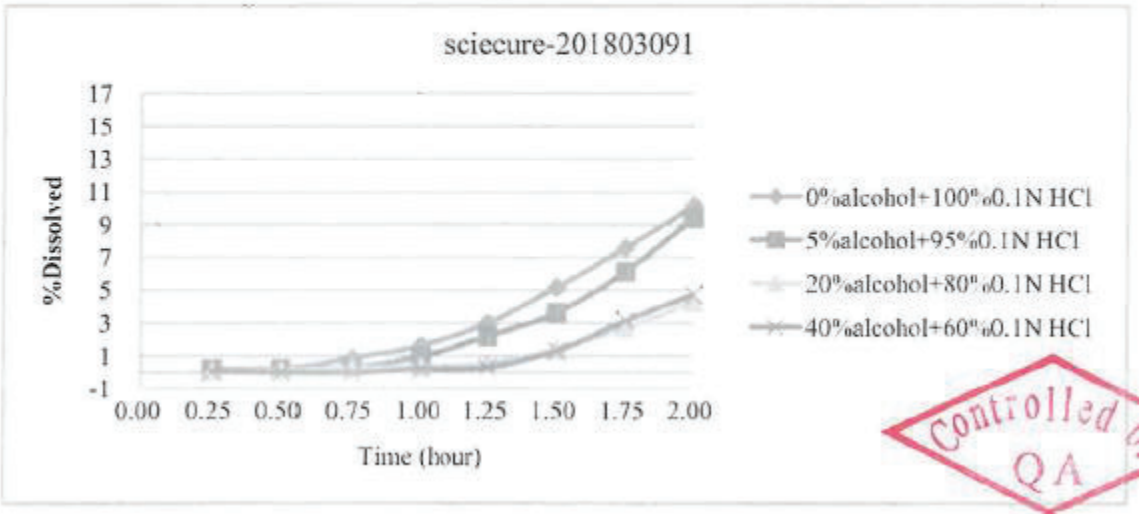


Figure 27 Dissolution Profile Comparison of 400 mg ERT for RLD/Test Products in 0% Alcohol in 0.1 N HCl

图 27 在 0%乙醇 0.1 N HCl 中参比制剂/被测药 400 mg 缓释片的溶出曲线比较图

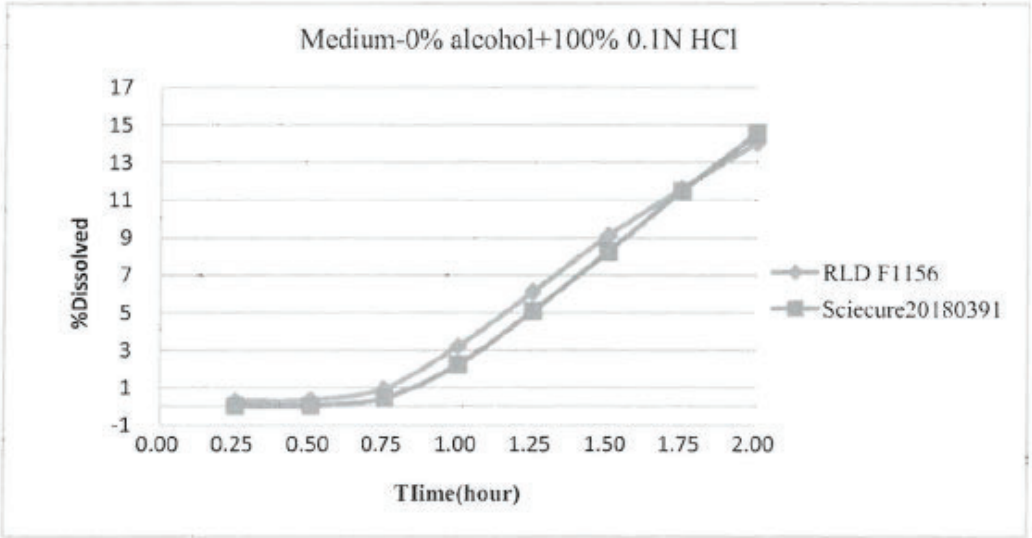


Figure 28 Dissolution Profile Comparison of 400 mg ERT for RLD/Test Products in 5% Alcohol in 0.1 N HCl

图 28 在 5%乙醇 0.1 N HCl 中参比制剂/被测药 400 mg 缓释片的溶出曲线比较图

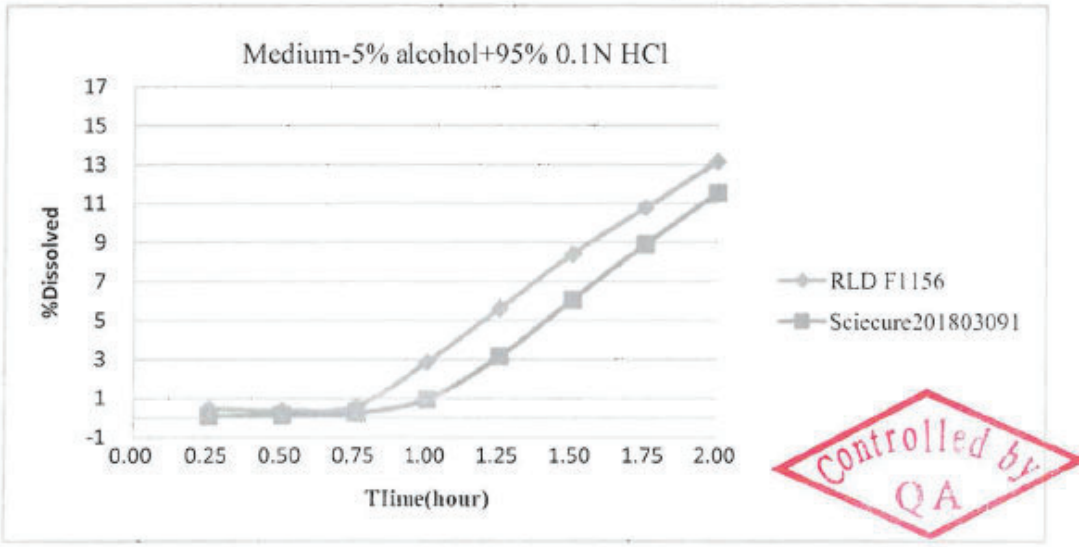


Figure 29 Dissolution Profile Comparison of 400 mg ERT for RLD/Test Products in 20% Alcohol i

0.1 N HCl

图 29 在 20%乙醇 0.1 N HCl 中参比制剂/被测药 400 mg 缓释片的溶出曲线比较图

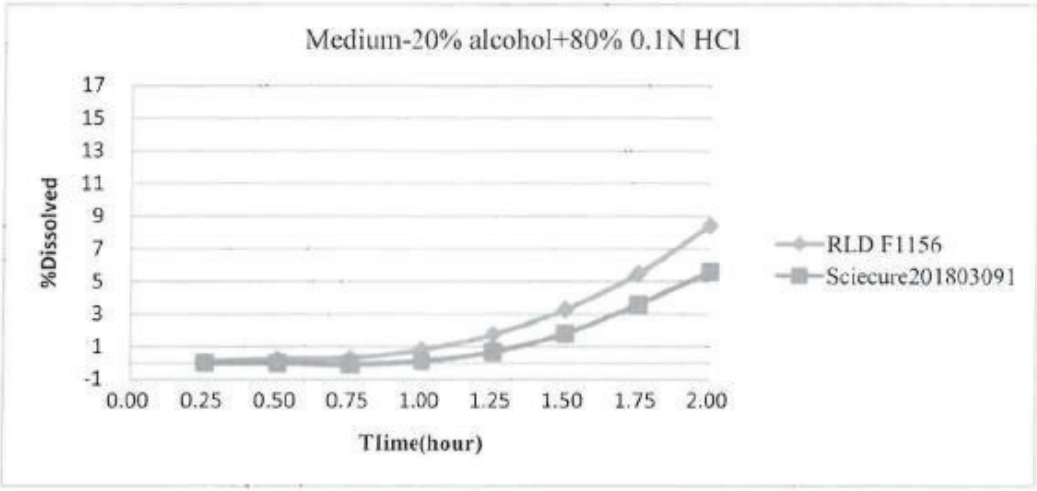
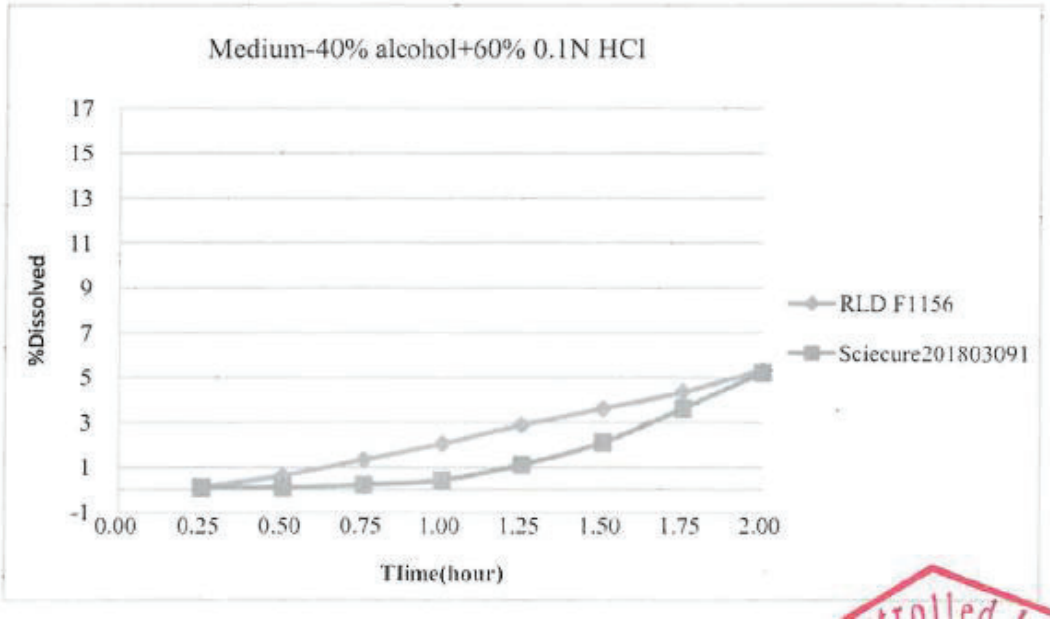


Figure 30 Dissolution Profile Comparison of 400 mg ERT for RLD/Test Products in 40% Alcohol

图 30 在 40%介质中参比制剂/被测药 400 mg 缓释片的溶出曲线比较图



4.3.3 F2 Metric

F2 metric calculated?	☒ Yes ☐ No
If no, reason why F2 not calculated	N/A

Please comment on whether dissolution data are Adequate to support requests submitted under 21 CFR 320.24(b)(6).	Yes

F2 metric, biostudy strengths compared to other strengths of test product

Biostudy Strength	Other Strength	QC media - Water	pH 1.2 Hydrochloric Acid	pH 4.5 Acetate Buffer	pH 6.8 Phosphate Buffer
400 mg (201803091)	200 mg (201806022)	86	70	78	85
400 mg (201803091))	100 mg (201803092)	82	72	78	86

F2 metric, Test strengths compared to other strengths of reference product - (for information purpose only)

Strength	QC media - Water	pH 1.2 Hydrochloric Acid	pH 4.5 Acetate Buffer	pH 6.8 Phosphate Buffer
100 mg (201803092)	96	95	87	85
200 mg (201806022)	74	60	65	84
400 mg (201803091)	68	76	63	68

Alcohol Dose Dumping

% Carbamazepine Dissolved in 0% Ethanol at 2 Hours			
	100 mg	**200 mg**	**400 mg**
Test Product	8 (b) (4)	7 (b) (4)	15 (b) (4)
Reference Product	7	9	14
% Carbamazepine Dissolved in 5% Ethanol at 2 Hours			
	100 mg	**200 mg**	**400 mg**
Test Product	7 (b) (4)	9 (b) (4)	12 (b) (4)
Reference Product		1	13
% Carbamazepine Dissolved in 20% Ethanol at 2 Hours			
	100 mg	**200 mg**	**400 mg**
Test Product	6 (b) (4)	4 (b) (4)	6 (b) (4)

Reference Product	2 (b) (4)	3 (b) (4)	8 (b) (4)
% Carbamazepine Dissolved in 40% Ethanol at 2 Hours			
	100 mg	**200 mg**	**400 mg**
Test Product	8 (b) (4)	5 (b) (4)	5 (b) (4)
Reference Product	3	4	5

Overall Comments:

- There is a USP dissolution method for this drug product.[5] The applicant conducted dissolution testing using the USP dissolution method [900 mL (for the 100 mg and 200 mg strengths) or 1800 mL (for the 400 mg strength) of Water using USP Apparatus I (basket) at 100 rpm]. The applicant's QC dissolution method and data are assessed separately by Biopharmaceutics Assessment team (status: Information Request sent out on August 5, 2021)[44]**.** The tablet sizes are relatively same for the test and reference products. Carbamazepine (API) has low solubility and is classified as BCS-II drug substance. Based on the dissolution profiles, the complete release (i.e., >80% dissolution) of carbamazepine tablets occurs in about 24 hours. Because of low solubility, the dissolution media volume (QC media and multi-media) is higher (1800 mL) for the 400 mg strength in comparison to the low volume (900 mL) for the 100 mg and 200 mg strengths. The dissolution profiles are comparable for all strengths in QC media and multi-media.

- The applicant conducted QC and multimedia dissolution testing comparing three test batches for each strength to the corresponding strengths of the RLD product. The Assessor conducted f2 calculation comparing test batches from each strength (100 mg, 200 mg, and 400 mg) to the corresponding RLD-batches. The f2 values for the test product (test product vs. RLD for 100 mg and 200 mg 400 mg) are greater than 50.

- In the QC media (water), the f_2 values for the test product (100 mg and 200 mg vs. bio-strength 400 mg) are greater than 50. However, the calculated f2 values are for information only as the dissolution testing methods are different (for example, volume of medium used for 100 mg and 200 mg strengths in 900 mL while for 400 mg strength in 1800 mL). The assessor found that the dissolution profiles for the 100 mg and 200 mg strengths are comparable to that for the bio-strength, 400 mg in the QC media.

- The applicant also conducted comparative multimedia dissolution testing using USP Apparatus I at 100 rpm in three (3) media: pH 1.2 Hydrochloric Acid Buffer, pH 4.5 Acetate Buffer, and pH 6.8 Phosphate Buffer for all strengths of the test and reference products as per PSG. When comparing 100 mg and 200 mg strengths (in 900 mL medium) to the 400 mg (bio-strength) (in 1800 mL medium) for the test product, the

[44] GDRP: 216235; https://panorama.fda.gov/project/view?ID=60aba3bc00a137245f8c5679a6384f82; document name: A216235BioPharm_IR.pdf

f2 values in all 3 media are greater than 50. However, the calculated f2 values are for information only as the dissolution testing methods are different (for example, volume of medium used for 100 mg and 200 mg strengths in 900 mL while for 400 mg strength in 1800 mL). The assessor found that the dissolution profiles are comparable for all strengths in multi-media.

- Additionally, the applicant conducted *in vitro* alcohol dose dumping study in 0.1N HCl containing 0%, 5%, 20% and 40% alcohol using USP apparatus I at 100 rpm. Per the PSG for Carbamazepine ER Tablets, *in vitro* alcohol dose dumping study is not required.[2] For each strength of the test product, the percent dissolved of carbamazepine at 120 minutes in 0.1 N HCl containing 0%, 5%, 20%, and 40% alcohol are comparable to that of the reference product. Both the test and the RLD products are robust to alcohol. Therefore, the applicant's *in vitro* alcohol dose dumping study is acceptable.

- The dissolution data are **adequate** with respect to deeming the 100 mg and 200 mg strengths of the test product bioequivalent to the corresponding strengths of the reference product under 21 CFR 320.24 (b) (6).

4.4 Attachments

4.4.1 Additional Studies

Are there any additional studies? (e.g. pilot, failed) **If yes, please provide the location of report (complete/summary).**	☐ Yes ☒ No

4.4.2 SAS Output

Study	SAS Data	SAS Code	SAS Stat	SAS Output/Table
Fasting	Fasting_carbamazepine_conc_pk.xlsx	**ANDA216235 NTI_fasting study.sa**	216235_Fasting_stat_carbamazepine.do	216235-ANALYSIS.doc
Fed	Fed_carbamazepine_conc_pk.xlsx	**ANDA216235 NTI_fed study.sas**	216235_Fed_stat_carbamazepine.doc	216235-ANALYSIS.doc

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	216235
APPLICANT:	Sciecure Pharma Inc.
DRUG PRODUCT:	Carbamazepine Extended-Release Tablets, USP, 100 mg, 200 mg, and 400 mg

The Division of Bioequivalence I (DBI) 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,

Utpal Munshi, Ph.D.
Acting Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.5 Outcome Page

COMPLETED ASSIGNMENT FOR 216235 ID: 46458

Reviewer:	Pabba, Santhosh	**Date Completed:**
Verifier:	,	**Date Verified:**
Division:	Division of Bioequivalence	
Description:	Original assessment - Carbamazepine Extended-Release Tablets, USP; multimedia dissolution, alcohol dose dumping studies	

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
46458	5/21/2021	BIO	ANDA Original [1]	1	1
46458	5/21/2021	Parallel	Fasting Study [1]	1	1
46458	5/21/2021	Parallel	Fed Study [1]	1	1
46458	5/21/2021	Parallel	Dissolution-Based Waiver (MR) (For all waiver strengths) [0.5]	0.5	0.5
46458	5/21/2021	Parallel	In-Vitro Dose-Dumping in Alcohol (For all strengths) [0.5]	0.5	0.5
				Total:	4

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA020965Orig1s015

PRODUCT QUALITY REVIEW (s)

ANDA Executive Summary

1. Application/Product Information

ANDA Number.	216235		
Review Cycle #	2		
Applicant Name	Sciecure Pharma Inc.		
Drug Product Name	Carbamazepine Extended-Release Tablets USP, 100 mg, 200 mg, 400 mg		
Dosage Form. (click (+) for more than one)	Tablet, extended release		
Proposed Strength(s)	100 mg, 200 mg, 400 mg		
Route of Administration (click (+) for more than one)	Oral		
Maximum Daily Dose	**1600 mg**		
Rx/OTC Dispensed	Rx		
Proposed Indication	Indicated for the treatment of pain associated with trigeminal neuralgia and therapeutic relief of epilepsy.		
Drug Product Description	Carbamazepine Extended-Release Tablets USP, 100 mg, 200 mg and 400 mg are bi-convex coated tablets, rounded beveled edges, with one drill hole on one side and printed “2241”, “2242”, “2243” on either side in a top semi-circle shape around the center for 100 mg, 200 mg and 400 mg strengths, respectively.		
Co-packaged product information	HDPE bottles		
Device information, if any:	N/A		
Storage Temperature/ Conditions	Storage: Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from moisture. Dispense in a tight container		
Review Team	**Discipline**	**Primary**	**Secondary**

	Drug Substance	DMF Team	Ben Lim
	Drug Product/ Labeling	Nathaniel Iloanusi	Shankar Saha
	Manufacturing	Vladimir Dragan	Sudipan Karmakar
	Biopharmaceutics	N/A	Tapash Ghosh
	Microbiology	N/A	N/A
	Other (specify):		
	RBPM	Stefen McMillan	
	ATL	Shankar Saha	

Consults	**Discipline Consulted**	**Recommendation**	**Date**
	N/A		

2. Submission Document(s) Reviewed

Submission(s) Assessed		**Documents Date**	**Disciplines Affected**
New ANDA	SD 1	5/21/2021	Quality
Quality IR	SD 3	9/10/2021	Quality
Quality IR	SD 4	9/17/2021	Quality
Quality DRL	SD 6	1/8/2022	Quality
Resubmission	SD 7	5/31/2022	Quality
Quality IR	SD 8	12/7/2022	Quality

2. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b) (4)	II	(b) (4)	Carbamazepine, USP	AQ	8/1/2019	Claude Theophin
	III		(b) (4)			
	III					
	III					
	III					
	III					
	III					
	III					
	III					

(b) (4)		(b) (4)			
	III				
	III				
	III				
	III				

b. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
RLD	N020234	Tegretol® XR (carbamazepine extended release tablets) 100 mg, 200 mg and 400 mg

4. Final Overall recommendation – Approval

Deficiencies (if applicable):

Overall Quality Deficiencies - Optional *(Deficiencies that affect multiple sub-disciplines; for subheadings use the format shown, for all deficiencies.)*

Drug Substance Deficiencies: None

Drug Product Deficiencies: None

Labeling Deficiencies *(Please contact OGD if you identify any Labeling deficiencies with your comments): N/A*

Manufacturing Deficiencies: None

Biopharmaceutics Deficiencies: None

Microbiology Deficiencies: N/A

Other Deficiencies *(Specify discipline, such as Environmental. For consults such as Biostatistics, PharmTox, CDRH, Clinical, etc., include consult type and specify Quality discipline – example: **Pharm/Tox consult for Drug Product**)*

Additional Comments:

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response:

5. Basis for Recommendation

a. Summary of Rationale for Recommendation:
(Include summary of issues and benefit-risk considerations according to recommendation. Not intended to be a summary of review.)

Refer to Risk Assessment in DPQ review

b. Recommendation by Subdiscipline:

Drug Substance: ADEQUATE

Drug Product: ADEQUATE

Quality Labeling: ADEQUATE

Manufacturing: ADEQUATE

Biopharmaceutics: ADEQUATE

Microbiology: N/A

Environmental: N/A

6. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

FDA recommends that the product Life Cycle document (PLCM) document be provided in tabular format in eCTD section 3.2.R, with specific references to the submission, sequence, eCTD section number, and page number where each EC's scientific justification can be found
No such information is available in 3.2R

Comparability Protocols (PACMP): No
Comments:

Not applicable as per module 3.2R

Additional Comments:

Not applicable as per module 3.2R

Shankar Saha

Digitally signed by Shankar Saha
Date: 1/12/2023 02:39:55PM
GUID: 508da703000288a6f78d9a1cd9612534

Knowledge-aided Assessment and Structured Application
OLDP Product Overview

ANDA Basic Information	
ANDA No.	216235
RLD/RS No.	020234
Applicant	SCIECURE PHARMA INC
Dosage	Tablet ER
Route	Oral
DP Name	CARBAMAZEPINE
Primary Assessor	Nathaniel Iloanusi
Secondary Assessor	Shankar Saha

Discipline Executive Summary

The DS is compendial and a BCS II molecule. (b) (4) . The drug substance specifications are consistent with USP monograph. (b) (4) (b) (4) (b) (4) The firm provided updated stability data for the three exhibit batches, 24 months stability data for all three strengths. All submitted results met the drug product specifications.

Drug Substance(s) and Drug Product

	DS Name	Strength Name (Active Moiety or Salt)	USP Monograph	DMF#	Status	Date of Complete
1	CARBAMAZEPINE	Carbamazepine	Compendial	(b) (4)	Adequate	12/10/2018

USP Monograph for DP	Note
Compendial	TBD. According to Biopharmaceutics review, "The Agency recommended to revise the acceptance criteria based on the bio-batch data which the firm accepted. The firm was requested to petition the USP for the revised acceptance criteria. The submission is adequate from Biopharmaceutics perspective".

DP Strength List	
	DS 1
	mg
Strength 1	100
Strength 2	200
Strength 3	400

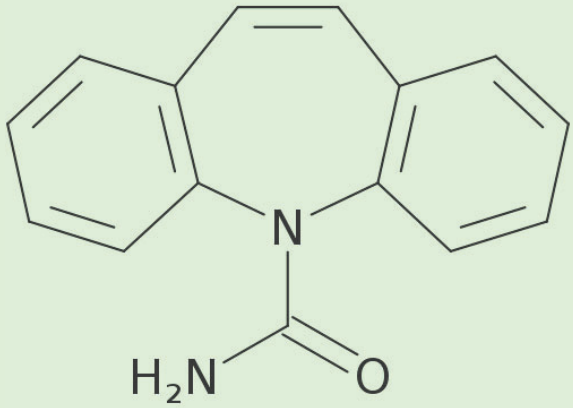
Review Iteration

Review Iteration	Assessor Decision	Date Finalized	Submission(s) To Be Reviewed	Supporting Document	Submission Date

1	Original Review	DRL	11/5/2021	Form 3674; New Filing; Labeling Amendment Correspondence; Quality	1 2 4	5/21/2021 7/6/2021 9/17/2021
2	DRL Response	Inadequate Minor	2/18/2022	Amendment Correspondence; Quality	6	1/10/2022
3	CR Response	Adequate		Amendment Correspondence; Labeling; Quality; Resubmission	7	5/31/2022

Knowledge-aided Assessment and Structured Application

S4. Drug Substance

DMF	(b) (4)	CARBAMAZEPINE
UNII	33CM23913M	
DMF Status	Adequate	

DS Specifications				
Specification	Release	Justification	Evaluation	AD
Description	White to off white odorless crystalline powder		Consistent with DMF	Yes
Solubility	Sparingly soluble in alcohol and in acetone; very slightly soluble in water.	Adopted from DMF	Consistent with DMF	Yes
(b) (4)				Yes
				Yes
				Yes
				Yes
				Yes

(b) (4)	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes
	Yes

Missing DS Specifications	
Does the sponsor's specification monitor all relevant drug substance attributes?	Yes

	(b) (4)

8 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

S.4.5 Reference Standard for Drug Substance

S.4.6 Unique Situations

Knowledge-aided Assessment and Structured Application

P1 Drug Product Description

Tablet ER			
Comparison of Drug Product Design			
RLD/RS Product Design			
Configuration	(b) (4) tablet with tablet coating(s)		
Release Mechanism	Osmotic Pump		
Functional Components			
Components		**Type**	**Brief Description**
#1	Tablet Core	DR	
Coatings	The core tablet is then coated (b) (4) and then a hole is drilled on one side of the tablet.		
CCS	**Counts**		
Bottles	100		
ANDA Product Design			
Configuration	(b) (4) r tablet with tablet coating(s)		
Release Mechanism	Osmotic Pump		
Functional Components			
Components		**Type**	**Description (Optional)**
#1	Tablet Core	DR	
Coatings	The core tablet is then coated (b) (4) and then a hole is drilled on one side of the tablet.		
CCS	**Counts**		
Bottles	100		

AD	Reviewer Evaluation
Yes	The applicant's Carbamazepine Extended-Release Tablets USP, 100 mg, 200 mg, and 400 mg packaging configuration is similar to that of reference listed drug.

DP Component Composition of ANDA Drug Product
ANDA Product Design

Ingredient	Excipient Grade	Function	Quantity	Percentage	Function Location
Strength #1: (b) (4)					
DR Tablet Core					
CARBAMAZEPINE	USP	API	100	(b) (4)	
MANNITOL	USP				
DEXTRATES	NF				
HYPROMELLOSE (b) (4)	USP				
MAGNESIUM STEARATE	USP				
SODIUM LAURYL SULFATE	USO/NF				
HYDROXYETHYL CELLULOSE (b) (4)	NF				
Total:					
(b) (4)					
CELLULOSE ACETATE				(b) (4)	
POLYETHYLENE GLYCOL, (b) (4)					
OPACODE S-1-17823 BLACK					
Total:			(b) (4)	100%	
Strength #2: Carbamazepine 200 mg					
DR Tablet Core					
CARBAMAZEPINE	USP	API	200.00	(b) (4)	
MANNITOL	USP			(b) (4)	
DEXTRATES	NF				
HYPROMELLOSE 2 (b) (4)	USP				
MAGNESIUM STEARATE	USP				
SODIUM LAURYL SULFATE	USO/NF				
HYDROXYETHYL CELLULOSE (b) (4))	NF				
Total:					
(b) (4)					
CELLULOSE ACETATE				(b) (4)	
POLYETHYLENE GLYCOL, UNSPECIFIED					
OPACODE S-1-17823 BLACK					
Total:			(b) (4)	100%	
Strength #3: Carbamazepine 400 mg					
DR Tablet Core					
CARBAMAZEPINE	USP	API	400	(b) (4)	
MAGNESIUM STEARATE	USP			(b) (4)	
HYPROMELLOSE (b) (4)	USP				
SODIUM LAURYL SULFATE	USP/NF				
MANNITOL	USP				
DEXTRATES	NF				
HYDROXYETHYL CELLULOSE (b) (4)	NF				
Total:					

		(b) (4)
CELLULOSE ACETATE	NF	(b) (4)
POLYETHYLENE GLYCOL, UNSPECIFIED	NF	
OPACODE S-1-17823 BLACK		
Total:	(b) (4)	100%

Are there any DMFs with drug product intermediate (DPI)?	No

Overall Evaluation of Components Composition	
Reviewer Evaluation	(b) (4)

Patient-Product Interface		
URL Description	**URL**	**Init. Page**
Side by Side comparison of RLD vs. Generic Information	\\CDSESUB1\evsprod\anda216235\0000\m1\us\112-oth-cor\11212-com-of-gen-dr-and-ref-lis-dr\1-12-12-comparison-generic-drug-reference-listed-drug.pdf	2

Strength #1: Carbamazepine 100 mg		
Property	**RLD**	**ANDA**
Shape	Round 8 mm tablet	Round 8 mm tablet
Strength #2: Carbamazepine 200 mg		
Property	**RLD**	**ANDA**
Shape	10 mm round tablet	10 mm round tablet
Strength #3: Carbamazepine 400 mg		
Property	**RLD**	**ANDA**
Shape	12 mm round tablet	12 mm round tablet

Reviewer Evaluation
Based on above data, the tablet sizes of applicant's carbamazepine extended-release tablets drug products are similar to that of reference listed drug.

Color and Size	
For multiple strength drug products, do all strengths have the same color and size?	No
AD	**Reviewer Evaluation**
Yes	The firm provided a side-by-side comparison of their proposed commercial physical profile of the ANDA drug product Carbamazepine extended-release tablets), 100 mg, 200 mg, and 400 mg to the Reference Listed Drug Tegretol-XR (carbamazepine extended-release tablets), 100 mg, 200 mg, and 400 mg. However, the drug product did not include complete the full physiochemical characterization of RLD drug product with that of the proposed Carbamazepine Extended Release Tablets which is consistent with the information on the finished drug product specification. The firm was asked to update the information. In eCTD 0005 (6), 01/10/2022 amendment submission, the firm provided an updated side-by-side comparison of their proposed commercial physical profile of the ANDA drug product to the Reference Listed Drug product that which is consistent with the information on the finished drug product specification and in compliance with the FDA guidance on Size,

	Shape, and Other Physical Attributes of Generic Tablets and Capsules (June 2015). The response is acceptable.

Tablet Split	
Does the ANDA meet the criteria per the Tablet Scoring Guidance?	N/A

Unique Situations	
Any Unique Situations Not Covered by KASA?	No
Narrative	

Labeling	
Description Section	
Is the information accurate?	Yes

Is the drug product subject of a USP monograph?	Yes

Does the labeling need a special USP statement in the Description?	No

How Supplied Section	
Is the information accurate?	Yes

Are the storage conditions acceptable?	Yes

Dosage and Administration Section	
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	N/A

For Solid Oral Drug Product:		
ANDA Strength	**Length(mm)**	**Imprint Code**
Carbamazepine 100mg	8	2241 on one side only
Carbamazepine 200mg	10	2242 on one side only
Carbamazepine 400mg	12	2243 on one side only
Is the imprint code consistent with the labeling?	Yes	

Any issue(s) sent to and/or received from the OGD Labeling Reviewer?	**No**

Deficiencies

P.1.1 Overall Drug Product Design

P.1.2 Component Composition of ANDA Drug Product

P.1.3 Formulation of Overage Assessment

P.1.4 Patient- Product Interface

Color & Size

Iteration	Status	ID	[Issue Topic]
Original Review	New	1	The drug product comparison table did not include complete full physiochemical characterization of RLD drug product with that of the proposed Carbamazepine Extended Release Tablets which is consistent with the information on the finished drug product specification.
			[Deficiency/IR]
			Please update Table 1 Side by Side comparison of RLD vs. Generic Information (page 2 of 3 in 1.12.12 Comparison between Generic Drug and RLD Report) with the exhibit batches data, including product images, to be consistent with the finished drug product specification, to ensure that your proposed drug product follows FDA Guidance for Industry on Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules June 2015.
			[Summary of the applicant's response and reviewer comment]
			The firm will be asked to update the information.
DRL Response	Solved	1	**[Summary of the applicant's response and reviewer comment]**
			The firm provided the requested information.
			[Deficiency/IR Previous Iteration]

P.1.5 Unique Situations

L.1 Labeling

Knowledge-aided Assessment and Structured Application

P2. Drug Product Development

CARBAMAZEPINE	Tablet ER

Initial Risk Assessment			
DS Physical Properties			
1	**What is the form of the API in the DP? (Please choose Amorphous if not sure)**	Crystalline	Carbamazepine is known to exist in four polymorphic forms. (b) (4) (b) (4)
2	**Do polymorphic forms exist based on prior knowledge?**	Yes	Carbamazepine is known to exist in four polymorphic forms. (b) (b) (4)
3	**Is the most stable form of API used?**	Yes	
4	**Is an unstable crystalline form of API used and solid state crystalline form conversions are well documented (but not theoretical)?**	No	

DS Chemical Properties

1	**Significant trending on stability?**	No	(b) (4)
2	**Does RLD or proposed generic formulation include stabilization agent in formulation?**	No	

DS Dissolution & Drug Release			
1	**What is the release mechanism for the selected API?**	Osmotic System	Osmotic driving agent provides the driving force to push suspended drug substance out of the coating membrane through the drilled hole.
2	**Is this release control mechanism a different design type than the RLD?**	No	
3	**Release controlling unit operation will be scale-up from exhibit batch?**	Yes	
4	**Is tablet scored for splitting and/or labeling allows for sprinkling?**	No	
5	**Is biphasic release applied for drug product design? (delayed release is not biphasic)**	No	
6	**Tablet or capsule contains a mixture of different types of beads or granules?**	No	

Physical Stability	
Initial Risk Ranking	Medium
Comment	

Product Design		
Mitigation Strategies	**Reviewer Evaluation**	**AD**
Supporting data show API form is inherently stable and shows no propensity for crystallization/transformation	Chemical stability is controlled by drug substance specifications meeting USP and ICH requirements, and will not affect tablet physical attributes, assay, content uniformity, or drug release .	Yes

Measurement		
Mitigation Strategies	**Reviewer Evaluation**	**AD**

(b) (4)	Yes

Risk Update:	
Medium	(b) (4)

Chemical Stability	
Initial Risk Ranking	Low
Comment	

Product Design		
Mitigation Strategies	**Reviewer Evaluation**	**AD**
API and Excipient(s) compatibility properly evaluated and used to select excipients that do not show chemical incompatibilities with API	(b) (4)	Yes

Measurement		
Mitigation Strategies	**Reviewer Evaluation**	**AD**
Accelerated and available long term stability data do not show significant changes	The firm provided six (6) months accelerated (40°C ± 2°C/ 75 % RH ± 5 % RH) and 12 months long term (25°C ± 2°C/ 60% RH ± 5% RH) stability data for all three batches of all the strengths. The data demonstrates that all monitored attributes of the drug product were well within the proposed stability specifications of Carbamazepine Extended-Release Tablets, USP 100 mg, 200mg and 400mg.	Yes

Risk Update:	
Low	(b) (4)

In Vitro Dissolution	
Initial Risk Ranking	High
Comment	

Product Design			
Design	**Mitigation Strategies**	**Reviewer Evaluation**	**AD**
		(b) (4)	Yes

Measurement		
Mitigation Strategies	**Reviewer Evaluation**	**AD**
Refer to Biopharmaceutics Assessment	(b) (4)	Yes

Risk Update:	
Low	Based on formula optimization studies, process development and optimization studies, the finished drug product dissolution profile was not negatively impacted by the drug substance solubility classification (BCS II). The applicant conducted dissolution testing using the USP dissolution method [900 mL (for the 100 mg and 200 mg strengths) or 1800 mL (for the 400 mg strength) of Water using USP Apparatus I (basket) at 100 rpm]. The applicant's quality control (QC) dissolution testing will be reviewed by the biopharmaceutical reviewer.

Specialized Dosage Forms			
Attribute	**Rationale**	**Risk Mitigation**	**AD**
Reviewer Evaluation			

Mechanical and Alcohol Dose Dumping			
Does mechanical dose pose a potential risk for the selected drug substance in the drug product?			No
Does alcohol dose dumping pose a potential risk for the selected drug substance in the drug product?			Yes
Drug Substance	**Mitigation Strategy**	**Reviewer Evaluation**	**AD**
CARBAMAZEPINE	In vitro assessments show no significant effect of alcohol on drug release characteristics	(b) (4)	Yes

		(b) (4)

Deficiencies

P.2.1 Physical Stability

Risk Mitigation of Measurements

Iteration	Status	ID	Strategy	[Issue Topic]
Original Review	New	1	(b) (4)	
DRL Response	Solved	1		

P.2.2 Chemical Stability

P.2.3 In-Vitro Dissolution

P.2.4 Specialized Dosage Forms

P.2.5 Mechanical and Alcohol Dose Dumping

Shankar Saha

Digitally signed by Shankar Saha
Date: 12/02/2022 11:23:15AM
GUID: 508da703000288a6f78d9a1cd9612534

Nathaniel Iloanusi

Digitally signed by Nathaniel Iloanusi
Date: 12/02/2022 11:29:06AM
GUID: 5a26cd00004ac42d8bf182c5a62c7c28

Manufacturing Integrated Assessment

Overview

ANDA Basic Information	
ANDA No.	216235
Drug Product Name	CARBAMAZEPINE
Drug Product Strength(s)	CARBAMAZEPINE 400 mg CARBAMAZEPINE 200 mg CARBAMAZEPINE 100 mg
RLD/RS Number.	020234
Applicant Name	SCIECURE PHARMA INC
Dosage Form	Tablet ER
Administration Route	Oral
Indication	Indicated for the treatment of pain associated with trigeminal neuralgia and therapeutic relief of epilepsy.
Primary Assessor	Vladimir Dragan
Secondary Assessor	Sudipan Karmakar

I. Manufacturing Summary	
Facility Assessment Recommendation	Adequate
Process Assessment Recommendation	Adequate

Discipline Assessment Summary

(b) (4)

Drug Substance(s) and Drug Product				
Drug Substance Name		**Strength Name (Active Moiety or Salt)**	**DMF#**	**Note for Convenience**
1	CARBAMAZEPINE	CARBAMAZEPINE	(b) (4)	

Drug Product Strength List		
	DS 1	
	mg	
Strength 1	400	
Strength 2	200	
Strength 3	100	

Review Iteration

Review Iteration		Process	Facility	Date Finalized	Submission(s) To Be Reviewed	Supporting Document	Submission Date
1	Original Review	Inadequate Minor	Pending	11/29/2021	Form 3674; New Amendment Correspondence; Quality Amendment Correspondence; Quality	1 3 4	5/21/2021 9/10/2021 9/17/2021
2	DRL Response	Inadequate Minor	Inadequate Major	12/22/2022			
3	CR Response	Adequate	Adequate				

Highlight Key Issues from Last Cycle and Their Resolution
(b) (4)

Concise Description of Outstanding Issues
None

Lifecycle Management Considerations	
Post-approval inspection?	No
Lifecycle Consideration	No

Facilities Table

Facilities
(b) (4)

19 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Sudipan Karmakar

Digitally signed by Sudipan Karmakar
Date: 12/28/2022 08:53:57AM
GUID: 5140967f0006d934848600b6e1a55e35

Knowledge-Aided Assessment and Structured Application Biopharmaceutics Assessment

Overview

ANDA Basic Information	
ANDA No.	216235
DP Name	CARBAMAZEPINE
RLD/RS No.	020234
Applicant	SCIECURE PHARMA INC
Dosage	Tablet ER
Route	Oral
Primary Assessor	Kalpana Paudel
Secondary Assessor	NA

Biopharmaceutics Executive Summary	
The Biopharmaceutics review focused on the assessment of proposed dissolution method, dissolution acceptance criteria, and the in-vitro in-vivo correlation (IVIVC) data. The Applicant proposed USP monograph dissolution method (Test 1) for carbamazepine ER tablets which is acceptable based on the method development report and submitted data. The proposed dissolution acceptance criteria are permissive for the drug product and not acceptable. The Applicant submitted an IVIVC report to demonstrate that revised USP dissolution acceptance criteria will be able to reject product that is not bioequivalent to the reference-target drug product. The IVIVC study, however, was deemed not acceptable because of incomplete data/justification provided. Therefore, the Agency recommended to revise the acceptance criteria based on the bio-batch data which the Applicant has accepted. The Applicant was requested to petition the USP for the revised acceptance criteria which the applicant has initiated. The submission is adequate from Biopharmaceutics perspective.	
Has OGD deemed the drug product BE to the RLD?	Yes

Drug Substance(s) and Drug Product				
	DS Name	**Strength Name (Active Moiety or Salt)**	**Therapeutic Area**	**Therapeutic Sub-Category**
1	CARBAMAZEPINE	CARBAMAZEPINE	Neurology 2	Epilepsy

DP Strength List		
	DS 1	
	mg	
Strength 1	400	
Strength 2	100	
Strength 3	200	

Review Iteration						
	Review Iteration	**Assessor Decision**	**Date Finalized**	**Submission(s) To Be Reviewed**	**Supporting Document**	**Submission Date**
1	Original Review	DRL	11/3/2021	Amendment Correspondence; Quality Form 3674; New	3 1	9/10/2021 5/21/2021
2	DRL Response	Inadequate Minor	3/2/2022	Amendment Correspondence; Quality	6	1/10/2022

3	CR Response	Adequate	12/8/2022	Amendment Correspondence; Labeling; Quality; Resubmission	7	5/31/2022

In Vitro Release Specification						
CARBAMAZEPINE - Tablet ER						
Strength		**Apparatus**	**Rotation Speed**	**Temperature**	**Medium / Volume (ml)**	**Acceptance Criteria**
1	100mg,200mg	1-Basket	100	37	Water (Degassed) - Volume: 900 ml	3 hr; Range - 18-38% 6 hr; Range - 46-66% 12 hr; Range - 70-90% 24 hr; NLT - 80%
2	400mg	1-Basket	100	37	Water (Degassed) - Volume: 1800 ml	3 hr; Range - 18-38% 6 hr; Range - 46-66% 12 hr; Range - 70-90% 24 hr; NLT - 80%

Reference Biopharmaceutics Properties

RLD Basic Information	
NDA No.	020234
Non-proprietary DP Name	CARBAMAZEPINE
Proprietary DP Name	TEGRETOL-XR

RLD Reference Information	
Dosage and Administration	Please see the label below for details.
Equilibrium Solubility	NA
pKa	NA
Bioavailability	The relative bioavailability of the product is 89 % compared to oral suspension.
Pharmacokinetics	Carbamazepine is 76% bound to the plasma proteins in blood. Plasma levels of Carbamazepine are variable and may range from 0.5 µg/mL to 25 µg/mL, with no apparent relationship to the daily intake of the drug. Carbamazepine is metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of Carbamazepine-10, 11-epoxide from Carbamazepine.
BCS Classification	The BCS classification of the RLD is not provided in the submission.
DS/DP Characterization	The RLD product was designed as an osmotic delivery system.
Other Relevant Biopharm Information	NA

Reference Documents		
URL Description	**URL**	**Init. Page**
Description and composition of the RLD drug product (page 4)	\\CDSESUB1\evsprod\nda020234\0087\m3\32-body-data\32p-drug-prod\tegretol-xr extended-release-tablets-01\32p1-desc-comp\description-and-composition.pdf	4

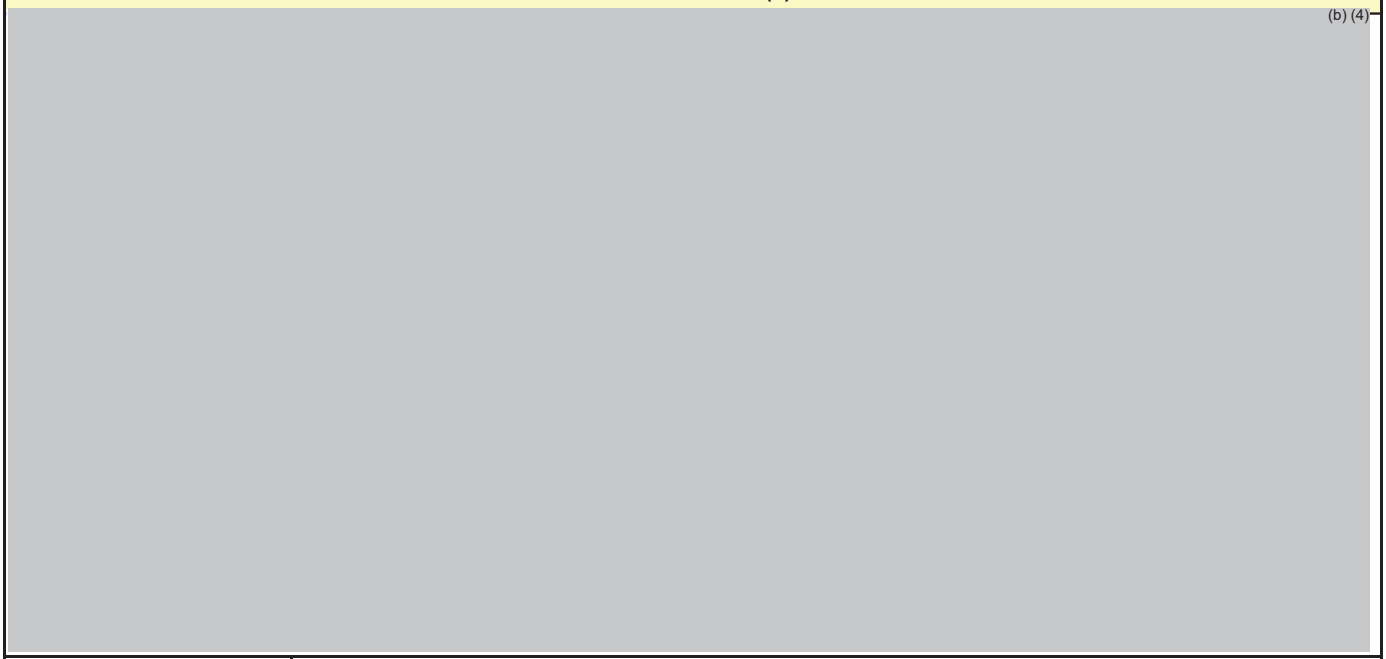
RLD Drug Substance(s) and Drug Product		
	DS Name	**Strength Name (Active Moiety or Salt)**
1	CARBAMAZEPINE	Carbamazepine

RLD DP Strength List		
	DS 1	
	mg	
Strength 1	100	
Strength 2	200	
Strength 3	400	

Pilot BE Studies

Are there any submitted pilot studies evaluating the BE of several formulation variants for the test product?	Yes
Has an IVIVC or IVIVR (e.g. physiological based model with virtual BE) been established?	No
Pertinent BE / Clinical Evaluations Perspective	The data are not adequate to build a safe space
Reviewer Evaluation	The applicant conducted an IVIVC study using the dissolution data generated by the selected dissolution method and pharmacokinetics data from a pilot bioequivalence study. The IVIVC data was submitted to demonstrate that revised acceptance criteria for the dissolution method will reject product that is not bioequivalent to the reference-target drug product. The IVIVC study is deemed not acceptable at this time. Please refer to the IVIVC section below for details.

Drug Substance Information

CARBAMAZEPINE (ER)	
Drug Substance Information	
High Risk drug substance	Yes
BCS Solubility	Low
BCS Class Reported by Applicant	II
Dissolution Plot(s)	
(b) (4) 	
Reviewer Evaluation	The complete release (i. (b) (4) % dissolution) of carbamazepine tablets occurs in about 24 hours.; Dissolution profiles of biobatch and exhibit batches in QC and multi media
Are there supportive BE studies (i.e. pilot BE studies evaluating formulation variants) to support the in vivo relevance of the dissolution test?	Yes
Reviewer Evaluation	The applicant submitted IVIVC data from Pilot BE studies to propose a revised acceptance criteria that will reject product that is not bioequivalent to the reference-target drug product.

Initial Risk Assessment

CARBAMAZEPINE (ER) / BCS Solubility: Low	
Is in vitro dissolution independent of test condition (e.g., medium pH, rotation speed)?	No
Could Critical Bioavailability Attribute(s) be clearly identified, detected and controlled?	Yes
Initial Risk Ranking	Medium

Mitigation Strategies

CARBAMAZEPINE (ER) / BCS Solubility: Low / Initial Risk: Medium			
Recommended Biopharmaceutics Mitigation Strategies (Pertinent Critical Bioavailability Attribute(s) CBAs)			
Attributes	**Strength(s)**	**Proposed Control Limit**	**Comment**
(b) (4)			
Mitigated Biopharmaceutics Risk Level		**Reviewer Evaluation**	
Low		Adequate	

Drug Substance Dissolution Methods and Acceptance Criteria

CARBAMAZEPINE (Tablet ER)						
Proposed Dissolution Methods and Acceptance Criteria						
Strength	**Apparatus**	**Rotation Speed**	**Temp (°C)**	**Medium/Volume (mL)**	**Acceptance Criteria**	**Adequate**
100mg; 200mg	1-Basket	100 rpm	37	Water (Degassed) - Volume: 900 ml	3 hr, Range - 18-38%; 6 hr, Range - 46-66%; 12 hr, Range - 70-90%; 24 hr, NLT - 80%	Yes
400mg	1-Basket	100 rpm	37	Water (Degassed) - Volume: 1800 ml	3 hr, Range - 18-38%; 6 hr, Range - 46-66%; 12 hr, Range - 70-90%; 24 hr, NLT - 80%	Yes

Reviewer Evaluation	The Biopharmaceutics review focused on the dissolution method development, dissolution data, dissolution acceptance criteria, and IVIVC data. The parameters of the proposed dissolution method for the routine QC testing of the proposed generic drug product are the same as those specified in the USP Monograph of the carbamazepine extended-release tablets with the exception of the use of a 10-mesh size of the basket. Note that the FDA Dissolution Methods Database refers to USP. For the study, one tablet is placed into basket with hole side facing down, and then a cage sinker is loaded into basket to cover the tablet. The Applicant's proposed dissolution acceptance criteria is same as USP test 1. Based on the submitted in vitro dissolution profile data, the proposed in vitro dissolution acceptance criteria are permissive and not acceptable. Applicant's submitted IVIVC study also does not support the proposed acceptance criteria as the model is deemed inadequate. Therefore, applicant will be requested to revise the acceptance criteria based on the bio-batch data. If the proposed dissolution method is ultimately deemed to be adequate for QC testing purposes, the Applicant should be reminded to submit a USP petition to request incorporation of their approved dissolution method and (if applicable) acceptance criteria in the drug product's official monograph. IVIVC study: The applicant also submitted an IVIVC study using the dissolution data generated by the selected dissolution method and pharmacokinetics data from a pilot bioequivalence study to propose that a revised dissolution acceptance criteria (mentioned below) will be able to reject product that is not bioequivalent to the reference-target drug product with the USP dissolution specification. However, the IVIVC study is deemed not acceptable at this time because of the incomplete data and justifications submitted. Please refer to the IVIVC IR for details. 3 hr (b) (4) % 6 hr (b) (4) % 12 hr (b) (4) % 24 hr (b) (4) % ; IVIVC report
Unique Situations	
Any unique situations not covered by KASA?	No
Adequate	Yes
Reviewer Evaluation	
Proposed Dissolution Testing	
FDA Dissolution Database	
Is the dissolution analytical quantification method acceptable to OLDP assessors?	Yes
Reviewer Evaluation	
Description of Links for Dissolution Methods	**URL Link**
Dissolution method validation	\\CDSESUB1\evsprod\anda216235\0001\m3\32-body-data\32p-drug-prod\beij-carb-abl\32p5-contr-drug-prod\32p53-val-analyt-proc\tmvr-03-an1-2016-37-dissolution.pdf
Dissolution method validation	\\CDSESUB1\evsprod\anda216235\0001\m3\32-body-data\32p-drug-prod\beij-carb-abl\32p5-contr-drug-prod\32p53-val-analyt-proc\tmvr-03-an1-2016-37-a1-dissolution-addendum.pdf
Variability in the dissolution results meet the recommendations (e.g. %CV < 20% at early time points (<15 minutes) and <10% at other time points)	Yes
Reviewer Evaluation	
Number of units tested meets the requirements (e.g. 12 units)	Yes

Reviewer Evaluation	
Source of Dissolution Test Method	USP Monograph
Does the proposed drug product meet the USP Monograph standards?	No
Actions requested of the Applicant	Initiate USP Monograph revision
Reviewer Evaluation	

Deficiencies

Proposed Dissolution Methods and Acceptance Criteria

Iteration	Status	ID	[Issue Topic]
Original Review	Solved	1	Method development report and justification for the selection of 10-mesh basket
			[Deficiency/IR]
			Provide in vitro dissolution method development report supporting the selection of the proposed dissolution test conditions including the justification for the selection of 10-mesh basket.
			[Summary of the applicant's response and reviewer comment]
			In the Response to the Biopharmaceutics Information, the Applicant reported that the final phase of the dissolution was greatly impacted by the mesh size of the basket used in the method. The method using baskets with larger opening (i.e., 10 mesh) produced (b) (4) dissolution while the method using baskets with smaller opening (b) (4) produced incomplete release (b) (4)%) at 24 hour timepoint. Note that the Applicant did not provide data with (b) (4) basket which is the standard size for basket. For the study, one tablet is placed into basket with hole side facing down and then a cage sinker is placed in the basket to cover the tablet. In the method validation report, the applicant noted that original test process (without cage sinker) and the new test process (with cage sinker) had equivalent detection capabilities. The Applicant explored other dissolution conditions such as by varying the basket rotation speed, the pH of the media and surfactant. The agitation speed from 50 rpm, 100 rpm, and 150 rpm produced similar dissolution profiles and therefore has no impact on dissolution profiles. Similar dissolution profiles were observed at pH 1.2 and pH 4.5 media to that of Water while pH 6.8 medium produced slower and incomplete dissolution profile at 24 hour timepoint. Similarly, addition of different amount of the surfactant (SDS) at 0.5, 1, and 2% level (1800 mL) did not improve the drug release. Rather, the drug release rate decreased with increasing SDS concentration. ; IR response
Iteration	**Status**	**ID**	**[Issue Topic]**
DRL Response	Solved	2	method development report with the bio-batch
			[Deficiency/IR]
			In your response letter dated September 10, 2021, we noted that you have explored all the dissolution method conditions and discriminating ability with RLD as the target drug product. You should explore the dissolution method conditions with your proposed drug product. Accordingly, we request that you submit data obtained with the proposed product. In addition, for discriminating ability testing, your reference batch should be reference target product (e.g., bio-batch).
			[Summary of the applicant's response and reviewer comment]
			It is noted that the applicant explored all the dissolution method conditions with RLD. The applicant will be recommended to explore all the method conditions with the applicant's proposed product.
CR Response	Solved	2	**[Summary of the applicant's response and reviewer comment]**
			The Applicant submitted data exploring the dissolution method conditions with their proposed drug product. In addition, the applicant provided data for discriminating ability comparing with the bio-batch. (b) (4) The Applicant's response is acceptable. ; Dissolution method development
			[Deficiency/IR Previous Iteration]
Iteration	**Status**	**ID**	**[Issue Topic]**
Original Review	Solved	3	List of CMAs, CPPs, and formulation variables
			[Deficiency/IR]
			Provide a list of the critical material attributes (CMAs), critical formulation variables and critical process attributes (CPAs) affecting dissolution.
			[Summary of the applicant's response and reviewer comment]
			The Applicant provided the requested information.
Iteration	**Status**	**ID**	**[Issue Topic]**
Original	Solved	4	Discriminating ability

Review			**[Deficiency/IR]**
			Provide data supporting the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations in the most relevant critical material attributes, critical formulation variables, and critical process parameters (i.e., ± 10-20% change to the specification-ranges of these variables). Submit the dissolution profile data and similarity testing results obtained with appropriate statistical test (e.g., f2 values) comparing the test and reference drug products. In addition, if available, submit data showing that the selected dissolution method is able to reject product that is not bioequivalent to the reference-target drug product.
			[Summary of the applicant's response and reviewer comment]
			In response to the Biopharmaceutics Information Request (see the link above), the Applicant provided data to show that the USP method is discriminating (b) (4) , based on the comparative dissolution profile data of the three batches of 400 mg strength tablets (b) (4) Not only were the dissolution profiles of two batches different compared to the target, but the profiles among the batches were also different based on similarity factor (f2). The applicant will be requested to provide all the dataset in excel format to verify the f2 calculations.
Iteration	**Status**	**ID**	**[Issue Topic]**
DRL Response	Solved	5	IVIVC issues
			[Deficiency/IR]
			You submitted an in-vitro in-vivo correlation (IVIVC) study to support that revised USP acceptance criteria for the selected dissolution method will be able to reject product that is not bioequivalent to the reference-target drug product. However, your IVIVC study is deemed not acceptable at this time because of the insufficient data/justification provided. As outlined in the FDA Guidance for Industry Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations three or more formulations with different release rates are recommended to define an IVIVC. Exceptions to this may be considered for formulations for which in vitro dissolution is independent of the dissolution test conditions (e.g., medium, agitation, pH, volume). Please submit the following information/data to aid in the regulatory decision making in terms of the acceptability of the proposed IVIVC model, if you still want to pursue the model: a. A modeling summary report, which provides an overview of the modeling strategy and details of the modeling procedures, including model development, model verification/modification, and model application in a step-by-step process. Inclusion of a flow chart, decision tree, or other similar representation is preferred for clarity. b. Demonstrate that the dissolution of the proposed drug product is dependent or independent of dissolution conditions. c. As part of the validation steps, follow the “leave-one out” cross validation approach in the construction and validation of your model to challenge its robustness. d. Provide side by side comparative formulation composition for all batches used in the model development and external predictions. e. Submit the executable project files (e.g., .phxproj, .xlsx or .xls, .sas) for the IVIVC model development and internal/external validation. Provide all relevant input including complete in vitro and in vivo data (i.e., individual, mean, % CV, profiles, in .csv, .xlsx or .xls, or .xpt format) and output files used in the construction and validation of the IVIVC model. f. Provide definition file(s) listing all input and output files, and the use or purpose of each of this files in an appropriate format (e.g., .pdf, .xpt, .xls). In addition, provide the hyperlinks for each data file and instructions for extracting these files. g. Provide the IVIVC predictions including the output files and summary table supporting your revised dissolution acceptance criteria, if any. Note that the FDA’s final decision regarding the acceptability of the IVIVC model will be made based on the totality of the supportive data and relevant information provided in the submission, which should include demonstration of a robust model predictability.
			[Summary of the applicant's response and reviewer comment]
CR Response	Solved	5	**[Summary of the applicant's response and reviewer comment]**
			The Applicant chose not to pursue the IVIVC model and adapt the dissolution acceptance criteria recommended by the Agency.
			[Deficiency/IR Previous Iteration]
Iteration	**Status**	**ID**	**[Issue Topic]**
Original	Solved	6	Dissolution profile data for all exhibit data in excel format

Review			**[Deficiency/IR]**
			Provide the complete dissolution profile data (n=12, individual data, range, mean, % CV, and mean dissolution profiles) for all exhibit batches of 100 mg, 200 mg, and 400 mg strengths of your proposed drug product in Microsoft Excel ".xls or .xlsx" format. Also provide the details on manufacturing date, site, size and the dissolution test date.
			[Summary of the applicant's response and reviewer comment]
			The Applicant provided the requested information.
Iteration	**Status**	**ID**	**[Issue Topic]**
DRL Response	Solved	7	Revise dissolution acceptance criteria based on the bio-batch
			[Deficiency/IR]
			Based on the submitted in vitro dissolution profile data, your proposed in vitro dissolution acceptance criteria are permissive for your drug product and not acceptable. Note that per the current Agency's guideline for proper setting of the dissolution specification, drug product acceptance criteria are set primarily based on the performance of the bio-batch/exhibit batches at release. In addition, selection of the in vitro drug dissolution acceptance criteria ranges is based on mean target value (b) (4) % for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved IVIVC model, physiologically based absorption and pharmacokinetic model, safe space etc. Since your submitted IVIVC model is not acceptable at this time, we recommend the following acceptance criteria for the proposed generic drug product based on the bio-batch data: 3 hr 18-38% 6 hr 46-66% 12 hr 70-90% 24 hr NLT 80% We request that you acknowledge your acceptance of the recommended acceptance criteria for all the strengths of your drug product at release and on stability and update your drug product release and stability specifications accordingly. In addition, please be advised that all proposed exhibit batches are expected to meet the revised dissolution specification in your stability program through your proposed expiry period. Be reminded that if stability failure occurs at Level 1 (L1), Level 2 (L2) testing and Level 3 (L3) testing should be conducted. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.
			[Summary of the applicant's response and reviewer comment]
CR Response	Solved	7	**[Summary of the applicant's response and reviewer comment]**
			The Applicant accepted Agency's recommended dissolution acceptance criteria for all the strengths of drug product at release and on stability.
			[Deficiency/IR Previous Iteration]

Recommended Dissolution Acceptance Criteria

Iteration	**Status**	**ID**	**[Issue Topic]**
CR Response	Solved	1	Petition the USP
			[Deficiency/IR]
			[Summary of the applicant's response and reviewer comment]
			The applicant noted in the response that they have initiated the revision process to the official USP monograph for carbamazepine tablets following the USP Pending Monograph Process.

Drug Product Exhibit Batch Dissolution Testing

Commercial batch size is within a factor of ten times the size of the biobatch	Yes
Reviewer Evaluation	
Testing was conducted using unexpired and/or fresh lots	Yes
Reviewer Evaluation	
Is the RLD drug product scored?	No

Deficiencies

No deficiencies to display

Kalpana Paudel

Digitally signed by Kalpana Paudel
Date: 12/08/2022 06:54:07PM
GUID: 562e1e15002f200f35c6ccac959cdb34

Shankar Saha

Digitally signed by Shankar Saha
Date: 1/13/2023 02:43:50PM
GUID: 508da703000288a6f78d9a1cd9612534

Stefen Mcmillan

Digitally signed by Stefen Mcmillan
Date: 1/12/2023 03:03:35PM
GUID: 5c79670400f0b4ced48918c2bd217435

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Complete Response-Minor
☐ Complete Response-Minor + Travel Comment
☒ Complete Response-Major
☐ Complete Response-Major + Travel Comment
☐ Complete Response-Major-Facilities Only
☐ Complete Response-Deferred-Travel Restriction-COVID19 *Choose this option when both of the following apply:* • *Quality is Adequate except for inspection deferred due to travel restriction AND* • *OGD has deficiencies (e.g., Bioequivalence, Labeling, etc.)*

U.S. FOOD & DRUG ADMINISTRATION

ANDA 216235
Assessment 1

Drug Product Name	Carbamazepine Extended-Release Tablets USP, 100 mg, 200 mg & 400 mg
Dosage Form	Tablet
Strength	100 mg, 200 mg & 400 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Sciecure Pharma Inc. 11 Deer Park Drive Monmouth Junction NJ 08852
US agent, if applicable	N/A

Submission(s) Assessed		Document Date	Discipline(s) Affected
New ANDA	SD 1	5/21/2021	Quality
Quality IR	SD 3	9/10/2021	Quality
Quality IR	SD 4	9/17/2021	Quality
Quality DRL	SD 6	1/8/2022	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance*	DMF Team	Benjamin Lim
Drug Product	Nathaniel Iloanusi	Shankar Saha
Manufacturing	Vladimir Dragan	Sudipan Karmakar
Microbiology	N/A	N/A
Biopharmaceutics	Kalpana Paudel	Tapash Ghosh
Regulatory Business Process Manager	Stefen McMillan	
Application Technical Lead	Shankar Saha	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

*If Active Pharmaceutical Ingredient (API) data is provided as part of ANDA submission, list Division of Lifecycle API (DLAPI) Assessor

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the ANDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Assessor/ Comments
(b) (4)	II	(b) (4)	Carbamazepine, USP	AQ	8/1/2019	Claude Theophin
	III		(b) (4)			
	III					
	III					
	III					
	III					
	III					
	III					

(b) (4)	III	(b) (4)			
	III				
	III				
	III				
	III				

B. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
RLD	020234	Tegretol® XR (carbamazepine extended release tablets) 100 mg, 200 mg and 400 mg

2. CONSULTS: N/A

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

U.S. FOOD & DRUG ADMINISTRATION

ABBREVIATED EXECUTIVE SUMMARY (CR ONLY)

For more details about the items in this template, please see the Abbreviated Executive Summary (CR Only) chapter of the ANDA IQA Guide

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Complete Response-Major

{Include a summary paragraph outlining reasons for OPQ action recommendation}

The OPQ do not recommend the approval of this ANDA in this cycle. The OPQ issues a CR-major due to major in facility.

II. QUALITY ASSESSMENT OVERVIEW

III. A. DP OVERALL RECOMMENDATION: Inadequate-Minor

Drug Substance: **Adequate**
Drug Product: Inadequate-Minor
Labeling: Adequate

B. Manufacturing:

a. **Process: Inadequate-Minor**
b. **Facilities: Inadequate-Major**

1. Provide Justification, if **Major**: *(Click link to view Justification Statements)*

The facilities deficiencies have been classified as MAJOR because one or more facilities were found inadequate at the time of action due to inspectional deficiencies as noted in Appendix A, Section A(6)(a) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Note that after the deficiencies have been purportedly resolved, FDA must assess the resolution of the cited deficiencies during the next review cycle. This assessment, upon receipt of an amendment responding to this deficiency, in FDA's judgement, will require substantial expenditure of FDA resources.

C. Biopharmaceutics: Inadequate-Minor

D. Microbiology: Choose an item.

Not Applicable

E. List of Deficiencies for Complete Response

Overall Quality Deficiencies - Optional *(Deficiencies that affect multiple*

Drug Substance Deficiencies:

None

Drug Product Deficiencies

1. Please provide all available stability data to further support the proposed 24 months expiration date for your finished drug products.

2. We acknowledge that you have provided stability data to support your proposed Holding Times for the various intermediates of your proposed drug product and are more than 30 days in some cases. Please note that the computation of the expiration date of the drug product should be based on the date of quality control release of the batch. The date of release should generally not exceed thirty days from the production date. If the date of quality control release is later than thirty days following the production date, the production date should be used to calculate the expiration date. The production date (Manufacture date) is defined as the date that the first step of manufacture is performed which involves the combining of the drug substance, antioxidant, or preservative, with excipients in the production of a dosage form

Labeling Deficiencies *(Please contact OGD if you identify any Labeling deficiencies with your comments)*

None

Manufacturing Deficiencies

1. (b) (4)

2.

(b) (4)

Biopharmaceutics Deficiencies

1. In your response letter dated September 10, 2021, we noted that you have explored all the dissolution method conditions and discriminating ability with RLD as the target drug product. You should explore the dissolution method conditions with your proposed drug product. Accordingly, we request that you submit data obtained with the proposed product. In addition, for discriminating ability testing, your reference batch should be reference target product (e.g., bio-batch).

2. You submitted an in-vitro in-vivo correlation (IVIVC) study to support that revised USP acceptance criteria for the selected dissolution method will be able to reject product that is not bioequivalent to the reference-target drug product. However, your IVIVC study is deemed not acceptable at this time because of the insufficient data/justification provided.
   As outlined in the FDA Guidance for Industry Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations three or more formulations with different release rates are recommended to define an IVIVC. Exceptions to this may be considered for formulations for which in vitro dissolution is independent of the dissolution test conditions (e.g., medium, agitation, pH, volume).
   Please submit the following information/data to aid in the regulatory decision making in terms of the acceptability of the proposed IVIVC model, if you still want to pursue the model:

   a. A modeling summary report, which provides an overview of the modeling strategy and details of the modeling procedures, including model development, model verification/modification, and model application in a step-by-step process. Inclusion of a flow chart, decision tree, or other similar representation is preferred for clarity.
   b. Demonstrate that the dissolution of the proposed drug product is dependent or independent of dissolution conditions.
   c. As part of the validation steps, follow the “leave-one out” cross validation approach in the construction and validation of your model to challenge its robustness.
   d. Provide side by side comparative formulation composition for all batches used in the model development and external predictions.
   e. Submit the executable project files (e.g., .phxproj, .xlsx or .xls, .sas) for the IVIVC model development and internal/external validation. Provide all relevant input including complete in vitro and in vivo data (i.e., individual, mean, % CV, profiles, in .csv, .xlsx or .xls, or .xpt format) and output files used in the construction and validation of the IVIVC model.
   f. Provide definition file(s) listing all input and output files, and the use or purpose of each of this files in an appropriate format (e.g., .pdf, .xpt, .xls). In addition, provide the hyperlinks for each data file and instructions for extracting these files.
   g. Provide the IVIVC predictions including the output files and summary table supporting your revised dissolution acceptance criteria, if any.

   Note that the FDA’s final decision regarding the acceptability of the IVIVC model will be made based on the totality of the supportive data and relevant information provided in the submission, which should include demonstration of a robust model predictability.

3. Based on the submitted in vitro dissolution profile data, your proposed in vitro dissolution acceptance criteria are permissive for your drug product and not acceptable. Note that per the current Agency’s guideline for proper setting of the dissolution specification, drug product acceptance criteria are set primarily based on the performance of the bio-batch/exhibit batches at release. In addition, selection of the in vitro drug dissolution acceptance criteria ranges is based on mean target value ±10% and >80% for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved IVIVC model, physiologically based absorption and pharmacokinetic model, safe space etc. Since your submitted IVIVC model is not acceptable at this time, we recommend the following acceptance criteria for the proposed generic drug product based on the bio-batch data:

3 hr 18-38%
6 hr 46-66%
12 hr 70-90%
24 hr NLT 80%

We request that you acknowledge your acceptance of the recommended acceptance criteria for all the strengths of your drug product at release and on stability and update your drug product release and stability specifications accordingly. In addition, please be advised that all proposed exhibit batches are expected to meet the revised dissolution specification in your stability program through your proposed expiry period. Be reminded that if stability failure occurs at Level 1 (L1), Level 2 (L2) testing and Level 3 (L3) testing should be conducted. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

Microbiology Deficiencies

None

Other Deficiencies *(Specify discipline, such as Environmental. For consults such as Biostatistics, PharmTox, CDRH, Clinical, etc., include consult type and specify Quality discipline – example:* ***Pharm/Tox consult for Drug Product****)*

None

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response:

Application Technical Lead Name and Date: Shankar Saha, 03/04/2022

Shankar Saha

Digitally signed by Shankar Saha
Date: 3/04/2022 04:20:01PM
GUID: 508da703000288a6f78d9a1cd9612534

Manufacturing Integrated Assessment

Overview

ANDA Basic Information	
ANDA No.	216235
Drug Product Name	CARBAMAZEPINE
Drug Product Strength(s)	CARBAMAZEPINE 400 mg CARBAMAZEPINE 200 mg CARBAMAZEPINE 100 mg
RLD/RS Number.	020234
Applicant Name	SCIECURE PHARMA INC
Dosage Form	Tablet ER
Administration Route	Oral
Indication	Indicated for the treatment of pain associated with trigeminal neuralgia and therapeutic relief of epilepsy.
Primary Assessor	Vladimir Dragan
Secondary Assessor	Sudipan Karmakar

I. Manufacturing Summary	
Facility Assessment Recommendation	Adequate
Process Assessment Recommendation	Adequate

Discipline Assessment Summary
(b) (4)

Drug Substance(s) and Drug Product				
	Drug Substance Name	**Strength Name (Active Moiety or Salt)**	**DMF#**	**Note for Convenience**
1	CARBAMAZEPINE	CARBAMAZEPINE	(b) (4)	

Drug Product Strength List	
	DS 1
	mg
Strength 1	400
Strength 2	200
Strength 3	100

Review Iteration

Review Iteration		Process	Facility	Date Finalized	Submission(s) To Be Reviewed	Supporting Document	Submission Date
1	Original Review	Inadequate Minor	Pending	11/29/2021	Form 3674; New Amendment Correspondence; Quality Amendment Correspondence; Quality	1 3 4	5/21/2021 9/10/2021 9/17/2021
2	DRL Response	Inadequate Minor	Inadequate Major	12/22/2022			
3	CR Response	Adequate	Adequate				

Highlight Key Issues from Last Cycle and Their Resolution
(b) (4)

Concise Description of Outstanding Issues
None

Lifecycle Management Considerations	
Post-approval inspection?	No
Lifecycle Consideration	No

Facilities Table

(b) (4)

II. Drug Product Manufacturing

1. Batch Formula

Batch Formula				
Strength	**Max Exhibit Batch Size**	**Commercial Batch Size**	**Scale-Up Factor**	**URL**
CARBAMAZEPINE 400mg	110.25 kg	147 kg	1.33	\\CDSESUB1\evsprod\anda216235\0000\m3\32-body-data\32p-drug-prod\beij-carb-abl\32p3-manuf\batch-formula\32p32-batch-formula.pdf
CARBAMAZEPINE 200mg	68.04 kg	151.2 kg	2.22	\\CDSESUB1\evsprod\anda216235\0000\m3\32-body-data\32p-drug-prod\beij-carb-abl\32p3-manuf\batch-formula\32p32-batch-formula.pdf
CARBAMAZEPINE 100mg	34.34 kg	152.64 kg	4.44	\\CDSESUB1\evsprod\anda216235\0000\m3\32-body-data\32p-drug-prod\beij-carb-abl\32p3-manuf\batch-formula\32p32-batch-formula.pdf

Assessment of Batch Formula	
Did the applicant provide adequate information of Batch Formula and is overall scale up in a reasonable range?	Yes
Reviewer Evaluation	(b) (4) [redacted]

2. Commercial Process Flow Diagram

Manufacturing Flow Diagram
(b) (4) [redacted]

18 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Sudipan Karmakar

Digitally signed by Sudipan Karmakar
Date: 12/28/2022 08:53:57AM
GUID: 5140967f0006d934848600b6e1a55e35

Knowledge-aided Assessment and Structured Application
OLDP Product Overview

ANDA Basic Information	
ANDA No.	216235
RLD/RS No.	020234
Applicant	SCIECURE PHARMA INC
Dosage	Tablet ER
Route	Oral
DP Name	CARBAMAZEPINE
Primary Assessor	Nathaniel Iloanusi
Secondary Assessor	Shankar Saha

Discipline Executive Summary
The DS is compendial and a BCS II molecule. (b) (4) (b) (4)

Drug Substance(s) and Drug Product						
	DS Name	**Strength Name (Active Moiety or Salt)**	**USP Monograph**	**DMF#**	**Status**	**Date of Complete**
1	CARBAMAZEPINE	Carbamazepine	USP-43	(b) (4)	Adequate	12/10/2018

USP Monograph for DP	Note
USP-43	TBD

DP Strength List	
	DS 1
	mg
Strength 1	100
Strength 2	200
Strength 3	400

Review Iteration						
	Review Iteration	**Assessor Decision**	**Date Finalized**	**Submission(s) To Be Reviewed**	**Supporting Document**	**Submission Date**
1	Original Review	DRL		Form 3674; New Filing; Labeling	1 2 4	5/21/2021 7/6/2021 9/17/2021

				Amendment Correspondence; Quality		

Knowledge-aided Assessment and Structured Application

S4. Drug Substance

DMF	(b) (4)	**CARBAMAZEPINE**
DMF Status	**Adequate**	

(b) (4)

S.4.4 Key Analytical Methods

S.4.5 Reference Standard for Drug Substance

S.4.6 Unique Situations

Knowledge-aided Assessment and Structured Application

P1 Drug Product Description

Tablet ER			
Comparison of Drug Product Design			
RLD/RS Product Design			
Configuration	(b) (4) tablet with tablet coating(s)		
Release Mechanism	Osmotic Pump		
Functional Components			
Components		**Type**	**Brief Description**
#1	Tablet Core	DR	
Coatings	The core tablet is then coated (b) (4) and then a hole is drilled on one side of the tablet.		
CCS	**Counts**		
Bottles	100		
ANDA Product Design			
Configuration	(b) (4) tablet with tablet coating(s)		
Release Mechanism	Osmotic Pump		
Functional Components			
Components		**Type**	**Description (Optional)**
#1	Tablet Core	DR	
Coatings	The core tablet is then coated (b) (4) and then a hole is drilled on one side of the tablet.		
CCS	**Counts**		
Bottles	100		

AD	Reviewer Evaluation
Yes	The applicant's Carbamazepine Extended-Release Tablets USP, 100 mg, 200 mg, and 400 mg packaging configuration is similar to that of reference listed drug.

DP Component Composition of ANDA Drug Product
ANDA Product Design

Ingredient	Excipient Grade	Function	Quantity	Percentage	Function Location
Strength #1: Carbamazepine 100 mg					
DR Tablet Core					
CARBAMAZEPINE	USP	API	100		
MANNITOL	USP				
DEXTRATES	NF				
HYPROMELLOSE (b) (4)	USP				
MAGNESIUM STEARATE	USP				
SODIUM LAURYL SULFATE	USO/NF				
HYDROXYETHYL CELLULOSE (b) (4)	NF				
Total:					
CELLULOSE ACETATE					
POLYETHYLENE GLYCOL, UNSPECIFIED					
OPACODE S-1-17823 BLACK					
Total:					
Strength #2: Carbamazepine 200 mg					
DR Tablet Core					
CARBAMAZEPINE	USP	API	200.00		
MANNITOL	USP				
DEXTRATES	NF				
HYPROMELLOSE (b) (4)	USP				
MAGNESIUM STEARATE	USP				
SODIUM LAURYL SULFATE	USO/NF				
HYDROXYETHYL CELLULOSE (b) (4)	NF				
Total:					
CELLULOSE ACETATE					
POLYETHYLENE GLYCOL, UNSPECIFIED					
OPACODE S-1-17823 BLACK					
Total:					
Strength #3: Carbamazepine 400 mg					
DR Tablet Core					
CARBAMAZEPINE	USP	API	400		
MAGNESIUM STEARATE	USP				
HYPROMELLOSE (b) (4)	USP				
SODIUM LAURYL SULFATE	USP/NF				
MANNITOL	USP				
DEXTRATES	NF				
HYDROXYETHYL CELLULOSE (b) (4)	NF				
Total:				100%	

Knowledge-aided Assessment and Structured Application
OLDP Product Overview

ANDA Basic Information	
ANDA No.	216235
RLD/RS No.	020234
Applicant	SCIECURE PHARMA INC
Dosage	Tablet ER
Route	Oral
DP Name	CARBAMAZEPINE
Primary Assessor	Nathaniel Iloanusi
Secondary Assessor	Shankar Saha

Discipline Executive Summary
The DS is compendial and a BCS II molecule. (b) (4) (b) (4) (b) (4). The firm provided updated stability data for the three exhibit batches, 24 months stability data for all three strengths. All submitted results met the drug product specifications.

Drug Substance(s) and Drug Product						
	DS Name	**Strength Name (Active Moiety or Salt)**	**USP Monograph**	**DMF#**	**Status**	**Date of Complete**
1	CARBAMAZEPINE	Carbamazepine	USP-43	(b) (4)	Adequate	12/10/2018

USP Monograph for DP	Note
USP-43	TBD. According to Biopharmaceutics review, The proposed dissolution acceptance criteria are same as USP test 1. The Applicant also submitted IVIVC data to demonstrate that revised USP dissolution acceptance criteria will be able to reject product that is not bioequivalent to the reference-target drug product. However, the IVIVC study is deemed not acceptable because of incomplete data/justification provided. The proposed dissolution method and acceptance criteria are not acceptable.

DP Strength List	
	DS 1
	mg
Strength 1	100
Strength 2	200
Strength 3	400

Review Iteration

Review Iteration		Assessor Decision	Date Finalized	Submission(s) To Be Reviewed	Supporting Document	Submission Date
1	Original Review	DRL	11/5/2021	Form 3674; New Filing; Labeling Amendment Correspondence; Quality	1 2 4	5/21/2021 7/6/2021 9/17/2021
2	DRL Response	Inadequate Minor		Amendment Correspondence; Quality	6	1/10/2022

Knowledge-aided Assessment and Structured Application

S4. Drug Substance

DMF	(b) (4)	**CARBAMAZEPINE**
DMF Status	**Adequate**	

(b) (4)

S.4.5 Reference Standard for Drug Substance

S.4.6 Unique Situations

Knowledge-aided Assessment and Structured Application

P1 Drug Product Description

Tablet ER			
Comparison of Drug Product Design			
RLD/RS Product Design			
Configuration	(b) (4) tablet with tablet coating(s)		
Release Mechanism	Osmotic Pump		
Functional Components			
Components		**Type**	**Brief Description**
#1	Tablet Core	DR	
Coatings	The core tablet is then coated (b) (4) and then a hole is drilled on one side of the tablet.		
CCS	**Counts**		
Bottles	100		
ANDA Product Design			
Configuration	(b) (4) tablet with tablet coating(s)		
Release Mechanism	Osmotic Pump		
Functional Components			
Components		**Type**	**Description (Optional)**
#1	Tablet Core	DR	
Coatings	The core tablet is then coated (b) (4) and then a hole is drilled on one side of the tablet.		
CCS	**Counts**		
Bottles	100		

AD	Reviewer Evaluation
Yes	The applicant's Carbamazepine Extended-Release Tablets USP, 100 mg, 200 mg, and 400 mg packaging configuration is similar to that of reference listed drug.

DP Component Composition of ANDA Drug Product
ANDA Product Design

Ingredient	Excipient Grade	Function	Quantity	Percentage	Function Location
Strength #1: Carbamazepine 100 mg					
DR Tablet Core					
CARBAMAZEPINE	USP	API	100	(b) (4)	(b) (4)
MANNITOL	USP				
DEXTRATES	NF				
HYPROMELLOSE (b) (4)	USP				
MAGNESIUM STEARATE	USP				
SODIUM LAURYL SULFATE	USO/NF				
HYDROXYETHYL CELLULOSE (b) (4)	NF				
Total:					
(b) (4)					
CELLULOSE ACETATE					
POLYETHYLENE GLYCOL, UNSPECIFIED					
OPACODE S-1-17823 BLACK					
Total:			(b) (4)	100%	
Strength #2: Carbamazepine 200 mg					
DR Tablet Core					
CARBAMAZEPINE	USP	API	200.00	(b) (4)	
MANNITOL	USP				
DEXTRATES	NF				
HYPROMELLOSE 2 (b) (4)	USP				
MAGNESIUM STEARATE	USP				
SODIUM LAURYL SULFATE	USO/NF				
HYDROXYETHYL CELLULOSE (b) (4)	NF				
Total:			(b) (4)	100%	
(b) (4)					
CELLULOSE ACETATE					
POLYETHYLENE GLYCOL, UNSPECIFIED					
OPACODE S-1-17823 BLACK					
Total:			(b) (4)	100%	
Strength #3: Carbamazepine 400 mg					
DR Tablet Core					
CARBAMAZEPINE	USP	API	400	(b) (4)	
MAGNESIUM STEARATE	USP				
HYPROMELLOSE (b) (4)	USP				
SODIUM LAURYL SULFATE	USP/NF				
MANNITOL	USP				
DEXTRATES	NF				
HYDROXYETHYL CELLULOSE (b) (4)	NF				
Total:			(b)	100%	

CELLULOSE ACETATE	NF	(b) (4)	
POLYETHYLENE GLYCOL, UNSPECIFIED	NF		
OPACODE S-1-17823 BLACK			
Total:		(b) (4)	100%
Are there any DMFs with drug product intermediate (DPI)?			No

Overall Evaluation of Components Composition

Reviewer Evaluation	(b) (4)

Patient-Product Interface		
URL Description	**URL**	**Init. Page**
Side by Side comparison of RLD vs. Generic Information	\\CDSESUB1\evsprod\anda216235\0000\m1\us\112-oth-cor\11212-com-of-gen-dr-and-ref-lis-dr\1-12-12-comparison-generic-drug-reference-listed-drug.pdf	2

Strength #1: Carbamazepine 100 mg		
Property	**RLD**	**ANDA**
Shape	Round 8 mm tablet	Round 8 mm tablet

Strength #2: Carbamazepine 200 mg		
Property	**RLD**	**ANDA**
Shape	10 mm round tablet	10 mm round tablet

Strength #3: Carbamazepine 400 mg		
Property	**RLD**	**ANDA**
Shape	12 mm round tablet	12 mm round tablet

Reviewer Evaluation
Based on above data, the tablet sizes of applicant's carbamazepine extended-release tablets drug products are similar to that of reference listed drug.

Color and Size	
For multiple strength drug products, do all strengths have the same color and size?	No
AD	**Reviewer Evaluation**
Yes	The firm provided a side-by-side comparison of their proposed commercial physical profile of the ANDA drug product Carbamazepine extended-release tablets), 100 mg, 200 mg, and 400 mg to the Reference Listed Drug Tegretol-XR (carbamazepine extended-release tablets), 100 mg, 200 mg, and 400 mg. However, the drug product did not include complete the full physiochemical characterization of RLD drug product with that of the proposed Carbamazepine Extended Release Tablets which is consistent with the information on the finished drug product specification. The firm was asked to update the information. In eCTD 0005 (6), 01/10/2022 amendment submission, the firm provided an updated side-by-side comparison of their proposed commercial physical profile of the ANDA drug product to the Reference Listed Drug product that which is consistent with the information on the finished drug product specification and in compliance with the FDA guidance on Size,

	Shape, and Other Physical Attributes of Generic Tablets and Capsules (June 2015). The response is acceptable.

Tablet Split	
Does the ANDA meet the criteria per the Tablet Scoring Guidance?	N/A

Unique Situations	
Any Unique Situations Not Covered by KASA?	No
Narrative	

Labeling	
Description Section	
Is the information accurate?	Yes

Is the drug product subject of a USP monograph?	Yes

Does the labeling need a special USP statement in the Description?	No

How Supplied Section	
Is the information accurate?	Yes

Are the storage conditions acceptable?	Yes

Dosage and Administration Section	
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	N/A

For Solid Oral Drug Product:		
ANDA Strength	**Length(mm)**	**Imprint Code**
Carbamazepine 100mg	8	2241 on one side only
Carbamazepine 200mg	10	2242 on one side only
Carbamazepine 400mg	12	2243 on one side only
Is the imprint code consistent with the labeling?	Yes	

Any issue(s) sent to and/or received from the OGD Labeling Reviewer?	**No**

Deficiencies

P.1.1 Overall Drug Product Design

P.1.2 Component Composition of ANDA Drug Product

P.1.3 Formulation of Overage Assessment

P.1.4 Patient- Product Interface

Color & Size

Iteration	Status	ID	[Issue Topic]
Original Review	New	1	The drug product comparison table did not include complete full physiochemical characterization of RLD drug product with that of the proposed Carbamazepine Extended Release Tablets which is consistent with the information on the finished drug product specification.
			[Deficiency/IR]
			Please update Table 1 Side by Side comparison of RLD vs. Generic Information (page 2 of 3 in 1.12.12 Comparison between Generic Drug and RLD Report) with the exhibit batches data, including product images, to be consistent with the finished drug product specification, to ensure that your proposed drug product follows FDA Guidance for Industry on Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules June 2015.
			[Summary of the applicant's response and reviewer comment]
			The firm will be asked to update the information.
DRL Response	Solved	1	**[Summary of the applicant's response and reviewer comment]**
			The firm provided the requested information.
			[Deficiency/IR Previous Iteration]

P.1.5 Unique Situations

L.1 Labeling

Knowledge-aided Assessment and Structured Application

P2. Drug Product Development

CARBAMAZEPINE	Tablet ER

Initial Risk Assessment			
DS Physical Properties			
1	**What is the form of the API in the DP? (Please choose Amorphous if not sure)**	Crystalline	Carbamazepine is known to exist in four polymorphic forms. (b) (4) (b) (4)
2	**Do polymorphic forms exist based on prior knowledge?**	Yes	Carbamazepine is known to exist in four polymorphic forms. (b) (4) (b) (4)
3	**Is the most stable form of API used?**	Yes	
4	**Is an unstable crystalline form of API used and solid state crystalline form conversions are well documented (but not theoretical)?**	No	

DS Chemical Properties

1	**Significant trending on stability?**	No	(b) (4)
2	**Does RLD or proposed generic formulation include stabilization agent in formulation?**	No	

DS Dissolution & Drug Release			
1	**What is the release mechanism for the selected API?**	Osmotic System	(b) (4)
2	**Is this release control mechanism a different design type than the RLD?**	No	
3	**Release controlling unit operation will be scale-up from exhibit batch?**	Yes	
4	**Is tablet scored for splitting and/or labeling allows for sprinkling?**	No	
5	**Is biphasic release applied for drug product design? (delayed release is not biphasic)**	No	
6	**Tablet or capsule contains a mixture of different types of beads or granules?**	No	

Physical Stability	
Initial Risk Ranking	Medium
Comment	

Product Design		
Mitigation Strategies	**Reviewer Evaluation**	**AD**
Supporting data show API form is inherently stable and shows no propensity for crystallization/transformation	Chemical stability is controlled by drug substance specifications meeting USP and ICH requirements, and will not affect tablet physical attributes, assay, content uniformity, or drug release .	Yes

Measurement		
Mitigation Strategies	**Reviewer Evaluation**	**AD**

Form verified in multiple drug product batches through final product testing at release and/or shelf life	(b) (4)	Yes

Risk Update:	
Medium	(b) (4)

Chemical Stability	
Initial Risk Ranking	Low
Comment	

Product Design		
Mitigation Strategies	**Reviewer Evaluation**	**AD**
API and Excipient(s) compatibility properly evaluated and used to select excipients that do not show chemical incompatibilities with API	(b) (4)	Yes

Measurement		
Mitigation Strategies	**Reviewer Evaluation**	**AD**
Accelerated and available long term stability data do not show significant changes	The firm provided six (6) months accelerated (40°C ± 2°C/ 75 % RH ± 5 % RH) and 12 months long term (25°C ± 2°C/ 60% RH ± 5% RH) stability data for all three batches of all the strengths. The data demonstrates that all monitored attributes of the drug product were well within the proposed stability specifications of Carbamazepine Extended-Release Tablets, USP 100 mg, 200mg and 400mg.	Yes

Risk Update:	
Low	Stability data for assay and degradation products showing no significant degradation, the risk remains low.

In Vitro Dissolution	
Initial Risk Ranking	High
Comment	

Product Design			
Design	**Mitigation Strategies**	**Reviewer Evaluation**	**AD**
		(b) (4)	Yes

Measurement		
Mitigation Strategies	**Reviewer Evaluation**	**AD**
Refer to Biopharmaceutics Assessment	Carbamazepine is a low soluble drug substance, the API particle size is controlled in micronized range to provide sufficient drug solubility and by an appropriate three tier specification, i.e., D10, D50, D90. With the API particle size controlled by the three-tier specification and in the micronized ranges, the risk of the drug substance particle size affecting the drug release rate of the finished product can be well controlled. (b) (4) . These optimized ER coating levels will be controlled for our drug products to assure drug release performance.	Yes

Risk Update:	
Low	Based on formula optimization studies, process development and optimization studies, the finished drug product dissolution profile was not negatively impacted by the drug substance solubility classification (BCS II). The applicant conducted dissolution testing using the USP dissolution method [900 mL (for the 100 mg and 200 mg strengths) or 1800 mL (for the 400 mg strength) of Water using USP Apparatus I (basket) at 100 rpm]. The applicant's quality control (QC) dissolution testing will be reviewed by the biopharmaceutical reviewer.

Specialized Dosage Forms			
Attribute	**Rationale**	**Risk Mitigation**	**AD**
Reviewer Evaluation			

Mechanical and Alcohol Dose Dumping			
Does mechanical dose pose a potential risk for the selected drug substance in the drug product?			No
Does alcohol dose dumping pose a potential risk for the selected drug substance in the drug product?			Yes
Drug Substance	**Mitigation Strategy**	**Reviewer Evaluation**	**AD**
CARBAMAZEPINE	In vitro assessments show no significant effect of alcohol on drug release characteristics	(b) (4)	Yes

		(b) (4)	

Deficiencies

P.2.1 Physical Stability

Risk Mitigation of Measurements

Iteration	Status	ID	Strategy	[Issue Topic]
Original Review	New	1	Form verified in multiple drug product batches through final product testing at release and/or shelf life	The XRD spectra show that the DS manufacturer consistently produces the same form of drug substance. However, the firm has not demonstrated that the drug substance remains in crystalline form through the manufacturing process and drug product storage. The firm will be asked to demonstrate that the Carbamazepine drug substance crystalline form does not change throughout the manufacturing process.
				[Deficiency/IR]
				You stated that the crystalline form of the Carbamazepine drug substance is stable in the solid state. Please provide supporting data to demonstrate that the Carbamazepine drug substance crystalline form does not change during drug product manufacturing process and storage.
				[Summary of the applicant's response and reviewer comment]
				The firm will be asked to demonstrate that the Carbamazepine drug substance crystalline form does not change throughout the manufacturing process.
DRL Response	Solved	1	Form verified in multiple drug product batches through final product testing at release and/or shelf life	**[Summary of the applicant's response and reviewer comment]**
				The firm provided the requested information. No further action is required.
				[Deficiency/IR]

P.2.2 Chemical Stability

P.2.3 In-Vitro Dissolution

P.2.4 Specialized Dosage Forms

P.2.5 Mechanical and Alcohol Dose Dumping

Knowledge-aided Assessment and Structured Application

P.4.1 Control of Excipients

(b) (4)

Shankar Saha

Digitally signed by Shankar Saha
Date: 2/18/2022 10:37:22AM
GUID: 508da703000288a6f78d9a1cd9612534

Nathaniel Iloanusi

Digitally signed by Nathaniel Iloanusi
Date: 2/18/2022 01:03:08PM
GUID: 5a26cd00004ac42d8bf182c5a62c7c28

(b) (4)	
Are there any DMFs with drug product intermediate (DPI)?	No
Overall Evaluation of Components Composition	
Reviewer Evaluation	(b) (4)

Patient-Product Interface		
URL Description	**URL**	**Init. Page**
Side by Side comparison of RLD vs. Generic Information	\\CDSESUB1\evsprod\anda216235\0000\m1\us\112-oth-cor\11212-com-of-gen-dr-and-ref-lis-dr\1-12-12-comparison-generic-drug-reference-listed-drug.pdf	2

Strength #1: Carbamazepine 100 mg		
Property	**RLD**	**ANDA**
Shape	Round 8 mm tablet	Round 8 mm tablet
Strength #2: Carbamazepine 200 mg		
Property	**RLD**	**ANDA**
Shape	10 mm round tablet	10 mm round tablet
Strength #3: Carbamazepine 400 mg		
Property	**RLD**	**ANDA**
Shape	12 mm round tablet	12 mm round tablet

Reviewer Evaluation
Based on above data, the tablet sizes of applicant's carbamazepine extended-release tablets drug products are similar to that of reference listed drug.

Color and Size	
For multiple strength drug products, do all strengths have the same color and size?	No
AD	**Reviewer Evaluation**
No	The firm provided a side-by-side comparison of their proposed commercial physical profile of the ANDA drug product Carbamazepine extended-release tablets), 100 mg, 200 mg, and 400 mg to the Reference Listed Drug Tegretol-XR (carbamazepine extended-release tablets), 100 mg, 200 mg, and 400 mg. However, the drug product did not include complete the full physiochemical characterization of RLD drug product with that of the proposed Carbamazepine Extended Release Tablets which is consistent with the information on the finished drug product specification. The firm was asked to update the information.
Tablet Split	
Does the ANDA meet the criteria per the Tablet Scoring Guidance?	N/A

Unique Situations	
Any Unique Situations Not Covered by KASA?	No
Narrative	

Labeling	
Description Section	
Is the information accurate?	Yes

Is the drug product subject of a USP monograph?	Yes

Does the labeling need a special USP statement in the Description?	No

How Supplied Section	
Is the information accurate?	Yes

Are the storage conditions acceptable?	Yes

Dosage and Administration Section	
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	N/A

For Solid Oral Drug Product:		
ANDA Strength	**Length(mm)**	**Imprint Code**
Carbamazepine 100mg	8	2241 on one side only
Carbamazepine 200mg	10	2242 on one side only
Carbamazepine 400mg	12	2243 on one side only
Is the imprint code consistent with the labeling?	Yes	

Any issue(s) sent to and/or received from the OGD Labeling Reviewer?	**No**

Deficiencies

P.1.1 Overall Drug Product Design

P.1.2 Component Composition of ANDA Drug Product

P.1.3 Formulation of Overage Assessment

P.1.4 Patient- Product Interface

Color & Size

Iteration	Status	ID	[Issue Topic]
Original Review	New	1	The drug product comparison table did not include complete full physiochemical characterization of RLD drug product with that of the proposed Carbamazepine Extended Release Tablets which is consistent with the information on the finished drug product specification.
			[Deficiency/IR]
			Please update Table 1 Side by Side comparison of RLD vs. Generic Information (page 2 of 3 in 1.12.12 Comparison between Generic Drug and RLD Report) with the exhibit batches data, including product images, to be consistent with the finished drug product specification, to ensure that your proposed drug product follows FDA Guidance for Industry on Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules June 2015.
			[Summary of the applicant's response and reviewer comment]
			The firm will be asked to update the information.

P.1.5 Unique Situations

L.1 Labeling

Knowledge-aided Assessment and Structured Application

P2. Drug Product Development

CARBAMAZEPINE	Tablet ER

Initial Risk Assessment			
DS Physical Properties			
1	**What is the form of the API in the DP? (Please choose Amorphous if not sure)**	Crystalline	Carbamazepine is known to exist in four polymorphic forms. (b) (4) (b) (4)
2	**Do polymorphic forms exist based on prior knowledge?**	Yes	Carbamazepine is known to exist in four polymorphic forms. (b) (b) (4)
3	**Is the most stable form of API used?**	Yes	
4	**Is an unstable crystalline form of API used and solid state crystalline form conversions are well documented (but not theoretical)?**	No	

DS Chemical Properties

1	**Significant trending on stability?**	No	(b) (4)
2	**Does RLD or proposed generic formulation include stabilization agent in formulation?**	No	

DS Dissolution & Drug Release			
1	**What is the release mechanism for the selected API?**	Osmotic System	(b) (4)
2	**Is this release control mechanism a different design type than the RLD?**	No	
3	**Release controlling unit operation will be scale-up from exhibit batch?**	Yes	
4	**Is tablet scored for splitting and/or labeling allows for sprinkling?**	No	
5	**Is biphasic release applied for drug product design? (delayed release is not biphasic)**	No	
6	**Tablet or capsule contains a mixture of different types of beads or granules?**	No	

Physical Stability	
Initial Risk Ranking	Medium
Comment	

Product Design		
Mitigation Strategies	**Reviewer Evaluation**	**AD**
Supporting data show API form is inherently stable and shows no propensity for crystallization/transformation	Chemical stability is controlled by drug substance specifications meeting USP and ICH requirements, and will not affect tablet physical attributes, assay, content uniformity, or drug release .	Yes

Measurement		
Mitigation Strategies	**Reviewer Evaluation**	**AD**
Form verified in multiple drug product batches through final product testing at release and/or shelf life	There are different polymorphs of Carbamazepine drug substance. (b) (4) (b) (4)	No

Risk Update:	
Medium	(b) (4)

Chemical Stability	
Initial Risk Ranking	Low

Comment	

Product Design		
Mitigation Strategies	**Reviewer Evaluation**	**AD**
API and Excipient(s) compatibility properly evaluated and used to select excipients that do not show chemical incompatibilities with API	(b) (4)	Yes

Measurement		
Mitigation Strategies	**Reviewer Evaluation**	**AD**
Accelerated and available long term stability data do not show significant changes	The firm provided six (6) months accelerated (40°C ± 2°C/ 75 % RH ± 5 % RH) and 12 months long term (25°C ± 2°C/ 60% RH ± 5% RH) stability data for all three batches of all the strengths. The data demonstrates that all monitored attributes of the drug product were well within the proposed stability specifications of Carbamazepine Extended-Release Tablets, USP 100 mg, 200mg and 400mg.	Yes

Risk Update:	
Low	(b) (4)

In Vitro Dissolution	
Initial Risk Ranking	High
Comment	

Product Design			
Design	**Mitigation Strategies**	**Reviewer Evaluation**	**AD**
		(b) (4)	Yes

Measurement		
Mitigation Strategies	**Reviewer Evaluation**	**AD**
Refer to Biopharmaceutics Assessment	Carbamazepine is a low soluble drug substance, the API particle size is controlled in micronized range to provide sufficient drug solubility and by an appropriate three tier specification, i.e., D10, D50, D90. With the API particle size controlled by the three-tier specification and in the micronized ranges, the risk of the drug substance particle size affecting the drug release rate of the finished product can be well controlled. The core tablet contains osmotic agents that creates osmotic pressure inside a semi-permeable membrane surrounded the core. These optimized ER coating levels will be controlled for our drug products to assure drug release performance.	Yes

Risk Update:	
Low	Based on formula optimization studies, process development and optimization studies, the finished drug product dissolution profile was not negatively impacted by the drug substance solubility classification (BCS II). The applicant conducted dissolution testing using the USP dissolution method [900 mL (for the 100 mg and 200 mg strengths) or 1800

	mL (for the 400 mg strength) of Water using USP Apparatus I (basket) at 100 rpm]. The applicant's quality control (QC) dissolution testing will be reviewed by the biopharmaceutical reviewer.

Specialized Dosage Forms			
Attribute	**Rationale**	**Risk Mitigation**	**AD**
Reviewer Evaluation			

Alcohol Dumping			
Risk assessment if alcohol-dumping is a potential risk for the selected drug substance?			Yes
Drug Substance	**Mitigation Strategy**	**Reviewer Evaluation**	**AD**
CARBAMAZEPINE	In vitro assessments show no significant effect of alcohol on drug release characteristics	(b) (4)	Yes

Deficiencies

P.2.1 Physical Stability

Risk Mitigation of Measurements

Iteration	Status	ID	Strategy	[Issue Topic]
Original Review	New	1	Form verified in multiple drug product batches through final product testing at release and/or shelf life	(b) (4) **[Deficiency/IR]** (b) (4) t **[Summary of the applicant's response and reviewer comment]** (b) (4)

P.2.2 Chemical Stability

P.2.3 In-Vitro Dissolution

P.2.4 Specialized Dosage Forms

P.2.5 Alcohol Dumping

Knowledge-aided Assessment and Structured Application

P.4.1 Control of Excipients

(b) (4)

[redacted]

Reviewer Evaluation

13 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Knowledge-aided Assessment and Structured Application

K.R.1 Comparability Protocol

Comparability Protocol					
Total number of CPs approved:	0				
ID	**Topic**	**Reporting Category**	**Description of Comparability Protocol**	**Status**	**AD**
1					

Deficiencies

K.R.1 Comparability Protocol

Knowledge-Aided Assessment and Structured Application

DEFICIENCIES

Nathaniel Iloanusi

Digitally signed by Nathaniel Iloanusi
Date: 11/08/2021 09:59:34AM
GUID: 5a26cd00004ac42d8bf182c5a62c7c28

Shankar Saha

Digitally signed by Shankar Saha
Date: 11/08/2021 10:06:08AM
GUID: 508da703000288a6f78d9a1cd9612534

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA216235Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Approval Type: ☒ **FULL APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL AP or TA (NEW STRENGTH)**

RPM and TL: Daniil Marchuk and Joe Shin

ANDA #: 216235 Applicant: Sciecure Pharma Inc.
Established Product Name: Carbamazepine Extended-Release Tablets USP, 100 mg, 200 mg, and 400 mg

Basis of Submission (BOS)/RLD (Application#/Proprietary Name/Applicant): NDA 020234 / Tegretol XR Extended-Release Tablets, 100 mg, 200 mg, and 400 mg / Novartis Pharmaceuticals Corporation

If BOS discontinued: [insert hyperlink to FRN] ☐ Safety/effectiveness FRN pending

Select, as applicable:

☒ RX ☐ OTC

☐ History of tentative or split approval action

☐ Shared Bio Studies (list ANDA number(s)) ☐ Shared Labeling (list ANDA number(s) _____)

☐ Memo uploaded for PAL item or OGDP confirmation

Priority: ☐ First Generic Approval (i.e., no other generics approved) ☐ Drug Shortage ☐ PEPFAR ☐ CGT

☐ Other priority _____

Misc: ☐ REMS ☐ Combination product ☐ Suitability Petition ☐ 180-day language ☐ MOU ☐ PEPFAR

☒ ***RPM Has Verified the Following:*** **Date: 1/4/2023**

1. ANDA number, NDA/RLD, Drug product and strength(s) are correct on all discipline/subdiscipline reviews
2. All submissions have been reviewed: Relevant disciplines are adequate and finalized/archived in the appropriate system of record
3. Most recent BE guidance is included in the review or a memo has been uploaded
4. No RLD updates or changes to exclusivity/patents impact endorsed labeling
5. 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). (Not applicable to supplements)
6. OSIS Clinical Endpoint and Bioequivalence Site Inspections acceptable or not applicable
7. No blocking legal or regulatory issue (refer to Policy Alert Tracker)
8. OGD Communications has been notified if Priority Approval (First generic, Drug Shortage, PEPFAR, CGT, other OGD Communications priorities)
9. OMIR is Approve with no new facility alerts and a DP and API manufacturer listed in Submission Facility Status View
10. No open issues or tasks in Platform
11. No pending consults
12. Filing review completed for NSA or reformulation
13. PNR review is current
14. Correct language, format and content in action letter (e.g., relevant contact from 356h form)
15. Endorsements are within 29 days

Discipline Completion Dates:

Bioequivalence **11/10/2021** Labeling **2/17/2023** Clinical **N/A**	Integrated Quality Assessment: **1/13/2023** If there is no IQA, provide the applicable date(s): • Chemistry _____ • Microbiology N/A • Biopharmaceutics/Dissolution DMF No(s). (b) (4) Date(s) Acceptable 12/20/2018

Additional Notes (if applicable)

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 2/22/2023
Name: HS

Patent/Exclusivity Certification: ☐ **No Relevant Patents** ☒ **PI** ☐ **PII** ☐ **PIII** ☐ **PIV** ☐ **section viii** Reminders: - Check the policy alert list for any pending exclusivity determinations - Verify in the Orange Book there are no unexpired ODE's that cover the active moiety - Confirm the ANDA is not blocked by other ANDA's eligibility for 180-day CGT exclusivity - Confirm S/E determination completed for RLDs in the discontinued section of the OB	RLD = **Tegretol XR** NDA# **20234** ☒ **RX or** ☐ **OTC** Date Checked in Orange Book#**: 2/22/2023** **Type of Letter:** ☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL AP or TA (NEW STRENGTH)
Forfeiture Information - Confirm whether the first applicant remains eligible for 180-day exclusivity (i.e., that a forfeiture event under section 505(j)(5)(D) has not occurred) and document the determination Is a forfeiture memo needed for the first applicant: Yes ☐ No ☐ If yes, the date forfeiture memo was completed Date _____ ANDA # _____ **Competitive Generic Therapy 75 Day Special Forfeiture Rule:** First Applicant: ANDA # _____ Date of Approval: _____ 75 Day Date: _____	**180 Day Exclusivity Information** Is applicant eligible for H-W 180 day exclusivity Yes ☐ No ☐ ☐ Sole ☐ Shared Is applicant eligible for CGT 180 day exclusivity Yes ☐ No ☐ ☐ Sole ☐ Shared Is applicant blocked by a triggered CGT 180 day exclusivity Yes ☐ No ☐ If no, the date and time checked for notification of commercial marketing: Date _____ Time: _____
Comments: ANDA submitted on 5/21/2021. BOS = Tegretol, NDA 20234. PI certification provided. ANDA ack for filing on 5/21/2021 (LO date 7/9/2021) This ANDA is eligible for immediate full approval. There are no unexpired patents or exclusivities protecting the RLD or other legal barriers to approval.	
180 Day/CGT Exclusivity Status/Landscape: drug product does not appear on CGT tracker If known, impact on pending exclusivity determinations: none, reviewed PAL If Tentative Approval, if known, anticipated full approval date: n/a	

2. Final Decision

Date: 3/2/2023
Name: CAP

☒ 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 in DARRTS since the Labeling Endorsement
5. No new 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 received since Quality Endorsement
9. No new 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****

(b) (4)

Endorsement Signatures (To be provided by endorsees in the event of Platform unavailability):

- Division of Legal and Regulatory Support Endorsement
  - Sign & Date_____
- Paragraph IV Evaluation
  - Sign & Date_____
- REMS Endorsement
  - Sign & Date_____
- Quality Endorsement
  - Sign & Date_____
- Bioequivalence Endorsement
  - Sign & Date_____
- Clinical-Bioequivalence Endorsement
  - Sign & Date_____
- Labeling Endorsement
  - Sign & Date_____
- RPM Team Leader Endorsement
  - Sign & Date_____
- ORO IO Endorsement
  - Sign & Date_____

REFERENCES / ASSOCIATED DOCUMENTS

Reference Name
4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

REVISION HISTORY

Author	Role	Version	Change Date	Summary of Changes
Heather Strandberg	Author	1.0	2014-10-01	New Form
Kevin Denny	Reviser	2.0	2017-10-03	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
Kevin Denny	Reviser	3.0	2018-01-14	Update Final Decision section
Joe Shin	Reviser	4.0	2019-03-04	Changes made: 1) "No Relevant Patents" checkbox added to patent types; 2) Basis of Submission was updated to include (NDA#/Proprietary Name/Applicant); 3) Removed "(CR)" from the second checkbox in the RPM Evaluation section; 4) Added "Shared BE studies..." and "Shared Labeling..." bullets to the review date section; 5) Added a not applicable checkbox for the MMA question; 6) Sentence revised to include not applicable cases in the OSIS question
John Ibrahim/QM Team	Reviser/QM	5.0	2021-08-18	• Update page 1 (revisted ANDA information section, RPM checklist, and discipline completion dates) • QM Team updated Header, document #, & title to conform to OGD Controlled Documents Program naming conventions & formatting standards • QM Team updated Footer to conform to ISO 8601 – International Time & Date Standards

ANDA 216235

DISCIPLINE REVIEW LETTER
LABELING

Sciecure Pharma Inc
11 Deer Park Drive
Unit 120
Monmouth Junciton, NJ 08852
Attention: Nuo (Nolan) Wang
CTO

Dear Nuo (Nolan) Wang:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on May 31, 2022, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Carbamazepine Extended-Release Tablets USP, 100 mg, 200 mg, and 400 mg.

The following comments have been identified by the Division of Labeling Review (DLR) based on your submissions on May 31, 2022, and December 7, 2022. Prior to final approval, the proposed labeling should be clear and precise (grammar, spelling, and formatting) for end users, and accurately reflect the Reference Listed Drug (RLD) information to comply with FDA policies, laws, regulations (i.e., 21 CFR 314.94(a)(8)), official compendia, and relevant guidance.

1. PRESCRIBING INFORMATION
    a. DOSAGE AND ADMINISTRATION, **Dosage Information** table
        1. Row 6-12 yr; Column Subsequent Dose, Extended-Release Tablets: Revise [redacted] (b) (4) "Add 100 mg..." to be consistent with the RLD labeling.
        2. Widen the cell to ensure the word "day" is not wrapped to the next line for better readability (see yellow highlighted text in the table below).

Dosage Information

Indication	Initial Dose			Subsequent Dose			Maximum Daily Dose		
	Tablet*	Extended-Release Tablets^	Suspension	Tablet*	Extended-Release Tablets^	Suspension	Tablet*	Extended-Release Tablets^	Suspension
Epilepsy Under 6 yr	10-20 mg/kg/day twice a day or 3 times a day		10-20 mg/kg/day 4 times a day	Increase weekly to achieve optimal clinical response, 3 times a day or 4 times a day		Increase weekly to achieve optimal clinical response, 3 times a day or 4 times a day	35 mg/kg/24 hr (see Dosage and Administration section above)		35 mg/kg/24 hr (see Dosage and Administration section above)

LABELING

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.

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 Orange Book are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than February 6, 2023. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING
MINOR

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2022 (GDUFA III)[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. If your submission is a response to a Major DRL received by the due date (or any agreed-upon extension), FDA may classify the response as Major and assign an appropriate goal date for that amendment.

2. If you do not respond by the requested due date, FDA may defer review of your response.

3. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.

4. If you are responding to a late cycle DRL[2], the goal date may be extended based upon the major or minor deficiencies included upon receipt of the response.

5. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as a major or minor amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

As described in FDA's draft guidance for industry *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, please contact Juliette Larmie-Gyamfi, Labeling Project Manager, at Juliette.Larmie-Gyamfi@fda.hhs.gov or .

Sincerely,

{See appended electronic signature page}

Juliette Larmie-Gyamfi
Labeling Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027 (available at:https://www.fda.gov/media/153631/download).
[2] Late cycle defined as IRs or DRLs issued after the mid-cycle of an original ANDA or IRs or DRLs issued less than 90 days from the goal date of an ANDA amendment

Juliette Larmie-Gyamfi

Digitally signed by Juliette Larmie-Gyamfi
Date: 2/01/2023 01:44:32PM
GUID: 5508755d000926ebceca6d5de2d276c5

ANDA 216235

DISCIPLINE REVIEW LETTER
LABELING

Sciecure Pharma Inc
11 Deer Park Drive
Unit 120
Monmouth Junciton, NJ 08852
Attention: Nuo (Nolan) Wang
CTO

Dear Nuo (Nolan) Wang:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on May 31, 2022, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Carbamazepine Extended-Release Tablets USP, 100 mg, 200 mg, and 400 mg.

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

The following comments have been identified by the Division of Labeling Review (DLR) based on your submissions on May 31, 2022, and December 7, 2022. Prior to final approval, the proposed labeling should be clear and precise (grammar, spelling, and formatting) for end users, and accurately reflect the Reference Listed Drug (RLD) information to comply with FDA policies, laws, regulations (i.e., 21 CFR 314.94(a)(8)), official compendia, and relevant guidance.

1. GENERAL COMMENTS

(b) (4)

2. PRESCRIBING INFORMATION
    a. DOSAGE AND ADMINISTRATION, **Dosage Information** table

i. Row 6-12 yr; Column Subsequent Dose, Extended-Release Tablets: (b) (4) to "Add 100 mg..." to be consistent with the RLD labeling.
ii. Widen the cell to ensure the word "day" is not wrapped to the next line for better readability (see yellow highlighted text in the table below).

Dosage Information

	Initial Dose			Subsequent Dose			Maximum Daily Dose		
Indication	Tablet*	Extended-Release Tablets^	Suspension	Tablet*	Extended-Release Tablets^	Suspension	Tablet*	Extended-Release Tablets^	Suspension
Epilepsy Under 6 yr	10-20 mg/kg/day twice a day or 3 times a day		10-20 mg/kg/day 4 times a day	Increase weekly to achieve optimal clinical response, 3 times a day or 4 times a day		Increase weekly to achieve optimal clinical response, 3 times a day or 4 times a day	35 mg/kg/24 hr (see Dosage and Administration section above)		35 mg/kg/24 hr (see Dosage and Administration section above)

LABELING

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.

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 Orange Book are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than January 17, 2023. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING
MINOR

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2022 (GDUFA III)[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. If your submission is a response to a Major DRL received by the due date (or any agreed-upon extension), FDA may classify the response as Major and assign an appropriate goal date for that amendment.

2. If you do not respond by the requested due date, FDA may defer review of your response.

3. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.

4. If you are responding to a late cycle DRL[2], the goal date may be extended based upon the major or minor deficiencies included upon receipt of the response.

5. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by

FDA, FDA may classify the response as a major or minor amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

As described in FDA's draft guidance for industry *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, please contact Juliette Larmie-Gyamfi, Labeling Project Manager, at Juliette.Larmie-Gyamfi@fda.hhs.gov or .

Sincerely,

{See appended electronic signature page}

Juliette Larmie-Gyamfi
Labeling Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023-2027 (available at:https://www.fda.gov/media/153631/download).
[2] Late cycle defined as IRs or DRLs issued after the mid-cycle of an original ANDA or IRs or DRLs issued less than 90 days from the goal date of an ANDA amendment

Juliette Larmie-Gyamfi

Digitally signed by Juliette Larmie-Gyamfi
Date: 1/06/2023 08:02:37AM
GUID: 5508755d000926ebceca6d5de2d276c5

ANDA 216235

INFORMATION REQUEST
QUALITY

Sciecure Pharma Inc
11 Deer Park Drive
Unit 120
Monmouth Junciton, NJ 08852
Attention: Nuo (Nolan) Wang
CTO

Dear Nuo (Nolan) Wang:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on May 31, 2022, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Carbamazepine Extended-Release Tablets USP, 100 mg, 200 mg & 400 mg.

We are reviewing the Quality section of your submission and request the following additional information/clarification and/or have the following comments:

QUALITY

A. Biopharmaceutics

1. We acknowledge that the dissolution acceptance criteria for your drug product differs from the USP. Please initiate a revision to the official USP monograph for carbamazepine tablets under the USP Pending Monograph Process. Until your product is in alignment with the dissolution specifications (method and acceptance criteria) in the USP monograph, include the following statement at the end of the DESCRIPTION section of the prescribing information: *FDA approved dissolution test specifications differ from USP*.

We request a complete written response, no later than December 8, 2022 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. If you are responding to a late cycle information request[1], the goal date may be extended based upon the major or minor deficiencies included upon receipt of the response. The goal

date assigned to the amendment may extend the review goal date for your current submission.

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
MINOR

If you do not submit a complete written response by December 8, 2022, the listed information requests may be incorporated in a discipline review letter or complete response letter.

As described in FDA's draft guidance for industry *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, please contact CDR Stefen McMillan, MSN FNP-BC, Regulatory Business Process Manager, at stefen.mcmillan@fda.hhs.gov or (301) 796 - 3018.

Sincerely,

{See appended electronic signature page}

CDR Stefen McMillan, MSN FNP-BC
Regulatory Business Process Manager
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

[1] Late cycle defined as IRs or DRLs issued after the mid-cycle of an original ANDA or less than 90 days from the goal date for any ANDA amendment.

Stefen Mcmillan

Digitally signed by Stefen Mcmillan
Date: 12/02/2022 02:46:04PM
GUID: 5c79670400f0b4ced48918c2bd217435

ANDA 216235

DISCIPLINE REVIEW LETTER
QUALITY

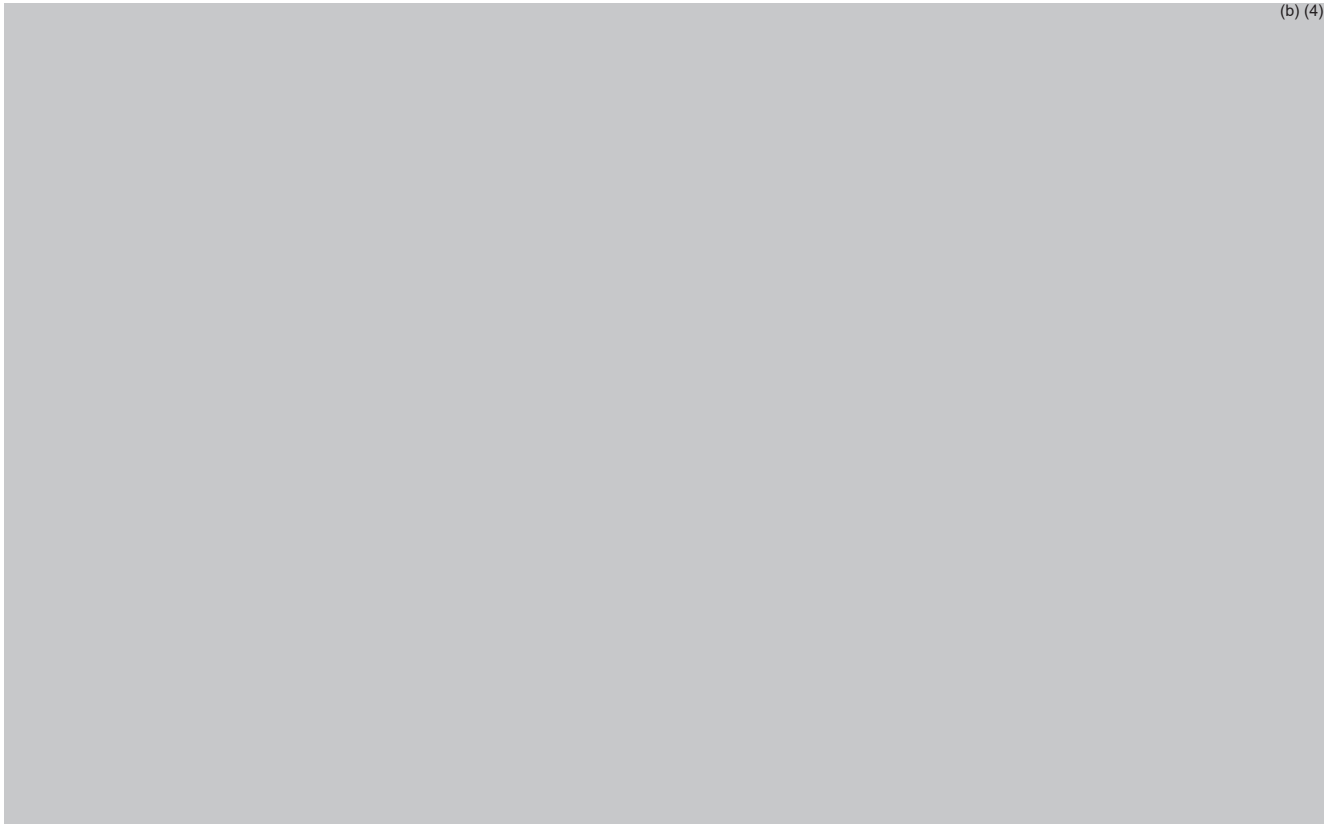
Sciecure Pharma Inc.
11 Deer Park Drive
Unit 120
Monmouth Junction, NJ 08852
Attention: Nuo (Nolan) Wang
CTO

Dear Nuo (Nolan) Wang:

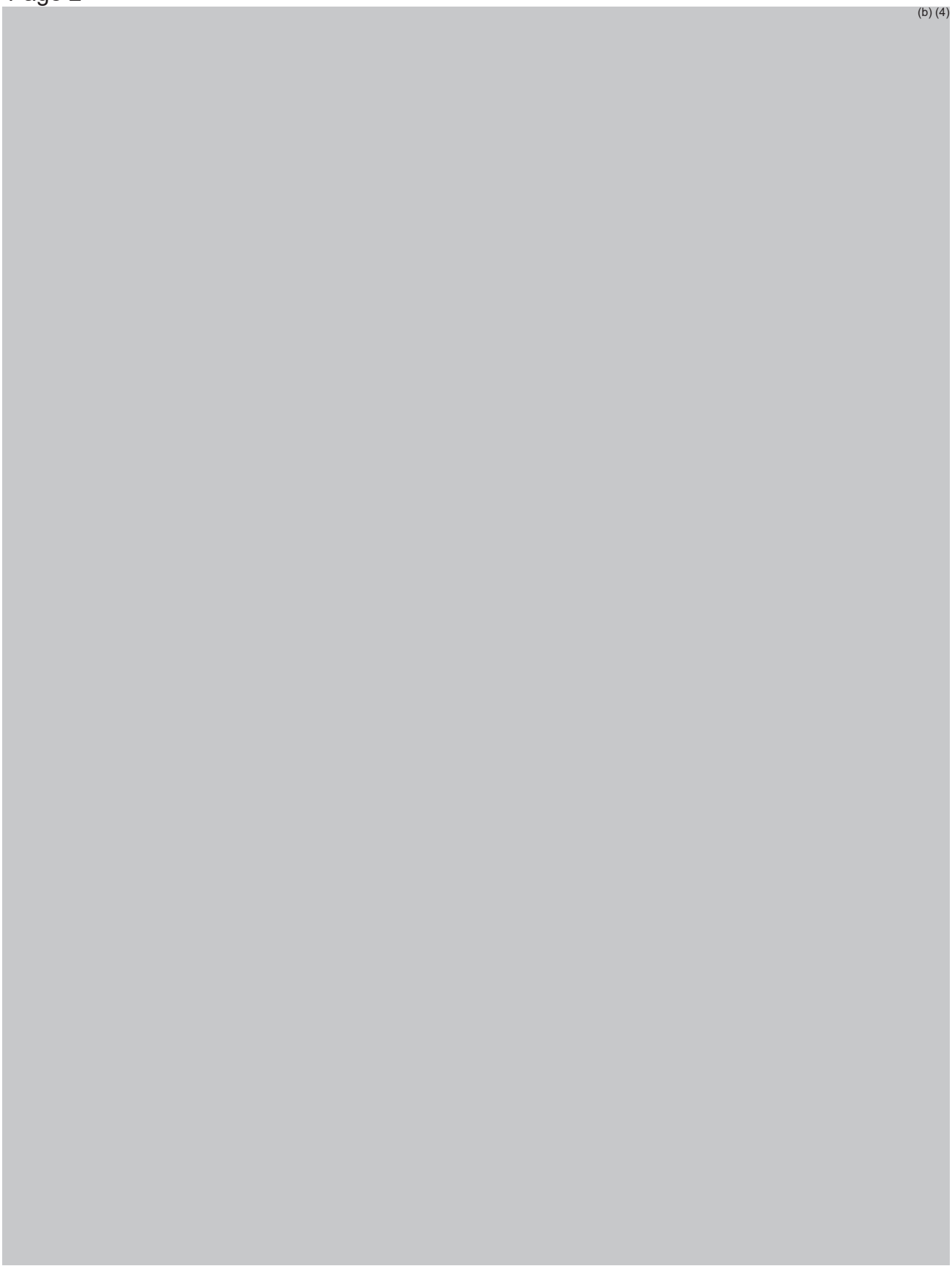
This letter is in reference to your abbreviated new drug application (ANDA) received for review on May 21, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Carbamazepine Extended-Release Tablets USP, 100mg, 200mg, 400mg.

The following possible deficiencies have been identified by the Office of Pharmaceutical Quality:

(b) (4)



(b) (4)



B. Biopharmaceutics

1. We acknowledge your response (dated September 10, 2021) to Biopharmaceutics questions**.** Please provide all the dissolution data from Tables 1-4, and Tables 8-14 in *Microsoft Excel ".xls or .xlsx" format*.

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than December 8, 2021. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not

process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
QUALITY

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified, or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.

2. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

If you have any questions, please contact CDR Stefen McMillan, MSN FNP-BC, Regulatory Business Process Manager, at stefen.mcmillan@fda.hhs.gov or (301) 796 - 3018.

Sincerely,

{See appended electronic signature page}

CDR Stefen McMillan, MSN FNP-BC
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at:https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

Stefen Mcmillan

Digitally signed by Stefen Mcmillan
Date: 11/08/2021 09:58:50AM
GUID: 5c79670400f0b4ced48918c2bd217435

ANDA 216235

DISCIPLINE REVIEW LETTER
LABELING

Sceicure Pharma Inc
11 Deer Park Drive Unit 120
Monmouth Junction, New Jersey 08852
Attention: Nuo Wang
CEO

Dear Sir or Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on July 6, 2021 and May 21, 2021, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Carbamazepine Extended-Release Tablets USP, 100 mg, 200 mg, and 400 mg.

The following possible deficiencies have been identified by LABELING:

Labeling deficiencies based on your submissions received May 21, 2021, and July 6, 2021:

1. GENERAL COMMENTS
    a. Ensure to provide your revised Prescribing Information and Medication Guide in an editable Word document.
2. CONTAINER LABEL
    a. Relocate the net quantity statement (**100 Tablets**) to the bottom of the PDP or decrease the prominence, so that it does not compete with the most critical information (e.g., established name and strength) on the PDP.
    b. Ensure that you complete the National Drug Code (NDC) number in a linear bar code prior to the submission of the final printed labeling per 21 CFR 201.25(c).
    c. Use a method to increase the prominence of the precautionary statement, "Carbamazepine Extended-Release Tablets must be swallowed whole and never crushed or chewed.", on the PDP (e.g., boxing, contrasting colors, and/or some other means).
3. PRESCRIBING INFORMATION
    a. Revise your established name in accordance with the USP monograph for your drug product titled "Carbamazepine Extended-Release Tablets".
    b. Limit the use of the "USP" descriptor to the Quality sections of the Prescribing Information (DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED).

c. Ensure references to the drug substance (carbamazepine) and drug product (Carbamazepine Extended-Release Tablets) are consistent throughout the Prescribing Information. Ensure to use the established name, carbamazepine extended-release tablets (i.e., dosage form included), when referring to the drug product.
d. Conduct editorial revisions throughout your Prescribing Information for punctuation and spacing errors. For example (note: not inclusive of all the necessary revisions),
    1. Boxed Warning, last paragraph and sentence: Add punctuation at the end of the last sentence, such as "...BONE MARROW DEPRESSION DEVELOPS."
    2. CLINICAL PHARMACOLOGY: Extra spacing between words throughout this section.
e. DESCRIPTION
    1. 3rd paragraph, second sentence: Revise the dosage form from (b) (4) to "extended-release tablet". For example, revise (b) (4) to "In addition, each extended-release tablet contains..."
    2. Last sentence: Remove the last sentence, (b) (4)
f. DOSAGE AND ADMINISTRATION: Carve out the tablet (chewable and conventional) and oral suspension dosage form information, as your proposed labeling is only for the extended-release tablets.
g. DOSAGE AND ADMINISTRATION, Table (Dosage Information)
    1. Expand the columns and/or rows so that all the text in each cell is visible to the reader to ensure important information is easily accessible.
    2. Header row, 2nd column: Revise (b) (4) to "Subsequent Dose" to be consistent with the RLD labeling.
    3. 1st column, last row: Widen the cell so the words "Trigeminal Neuralgia" are not wrapped to the next line for better readability.
h. HOW SUPPLIED: Comment and/or revise your product description (e.g., shape, color, scoring, coating, and imprint code) to be in accordance with the information in your submission, as required per 21 CFR 201.57(c)(17).

4. MEDICATION GUIDE
    a. Ensure a sufficient number of Medication Guides is available for dispensing and distribution to patients receiving a prescription for your drug product per 21 CFR 208.24.
    b. Revise your proposed pronunciation of the non-proprietary name to conform to the phonetic pronunciation in the current USP Dictionary of USAN and International Drug Names. For example,

    „ (kar″ ba maz′ e peen) „.

c. Remove the USP descriptor in the title of your established name.
d. **What is the most important information I should know about Carbamazepine Extended-Release Tablets?**: Revise and increase the indenting of the subsections and bullets throughout this section for better readability and to be consistent with the RLD labeling.
e. **What are Carbamazepine Extended-Release Tablets?**, 2nd bullet, last sentence: Relocate the last sentence ("Carbamazepine extended-release tablets are not a regular pain medicine and should not be used for aches or pains.") to the next line to be consistent with the RLD labeling.
f. **Do not take Carbamazepine Extended-Release Tablets if you:**, 2nd bullet, 1st sentence: Reference the drug substance in the first instance of this sentence to be consistent with the RLD labeling. For example, revise (b) (4) to "are allergic to carbamazepine or any of the ingredients in carbamazepine extended-release tablets."
g. **What should I tell my healthcare provider before taking Carbamazepine Extended-Release Tablets?**: Reference the drug substance in the instances specified below.
    1. 11th bullet, 2nd sentence: Revise (b) (4) ." to "Carbamazepine may harm your unborn baby."
    2. last bullet, 2nd sentence: Revise (b) (4) to "Carbamazepine passes into breast milk."
h. **How should I take Carbamazepine Extended-Release Tablets?** (5th, 6th, and 7th bullets): Bold the text of the 5th bullet and increase the indenting of the 6th and 7th bullets to be consistent with the RLD labeling.
i. **How should I store Carbamazepine Extended-Release Tablets?**, 1st bullet: Remove (b) (4)]. Protect from Moisture" to be consistent with the RLD labeling.
j. **General Information about Carbamazepine Extended-Release Tablets**, last sentence: Resolve the hyperlink error in your PDF document (received on July 6, 2021). Note that your Word document (received on May 21, 2021) does not include a hyperlink.

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.

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 Orange Book are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than September 29, 2021. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit

[1] GDUFAD Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.

2. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

If you have any questions, please contact Juliette Larmie-Gyamfi, Labeling Project Manager, at Juliette.Larmie-Gyamfi@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Juliette Larmie-Gyamfi, PharmD, PMP
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Juliette Larmie-Gyamfi

Digitally signed by Juliette Larmie-Gyamfi
Date: 9/15/2021 09:12:11AM
GUID: 5508755d000926ebceca6d5de2d276c5

ANDA 216235

INFORMATION REQUEST

Sciecure Pharma Inc
11 Deer Park Drive
Unit 120
Monmouth Junction, NJ 08852

Attention: Nuo (Nolan) Wang
CEO

Dear Nuo (Nolan) Wang:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on May 21, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Carbamazepine Tablets, Extended Release USP, 100 mg, 200 mg, 400 mg..

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. Biopharmaceutics

1. Provide in vitro dissolution method development report supporting the selection of the proposed dissolution test conditions including the justification for the selection of 10-mesh basket.

2. Provide a list of the critical material attributes (CMAs), critical formulation variables and critical process attributes (CPAs) affecting dissolution.

3. Provide data supporting the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations in the most relevant critical material attributes, critical formulation variables, and critical process parameters (i.e., ± 10-20% change to the specification-ranges of these variables). Submit the dissolution profile data and similarity testing results obtained with appropriate statistical test (e.g., f2 values) comparing the test and reference drug products. In addition, if available, submit data showing that the selected dissolution method is able to reject product that is not bioequivalent to the reference-target drug product.

4. Provide the complete dissolution profile data (n=12, individual data, range, mean, % CV, and mean dissolution profiles) for all exhibit batches of 100 mg, 200 mg, and 400 mg strengths of your proposed drug product in *Microsoft Excel ".xls or .xlsx" format*. Also provide the details on manufacturing date, site, size and the dissolution test date.

We request a prompt written response, no later than August 19, 2021 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

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 CDR Stefen McMillan, MSN FNP-BC, Regulatory Business Process Manager, at stefen.mcmillan@fda.hhs.gov or (301) 796 - 3018.

Sincerely,

{See appended electronic signature page}

CDR Stefen McMillan, MSN FNP-BC
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Stefen Mcmillan

Digitally signed by Stefen Mcmillan
Date: 8/05/2021 12:11:03PM
GUID: 5c79670400f0b4ced48918c2bd217435

ANDA 216235

INFORMATION REQUEST

Sciecure Pharma Inc.
11 Deer Park Drive
Unit 120
Monmouth Junction, NJ 08852
Attention: Nuo (Nolan) Wang
CEO

Dear Nuo (Nolan) Wang:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on May 21, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Carbamazepine Tablets, Extended Release USP, 100 mg, 200 mg, 400 mg.

We are reviewing the Quality section of your submission and have the following comments and information requests:

(b) (4)

We request a prompt written response, no later than August 18, 2021 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

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 CDR Stefen McMillan, MSN FNP-BC, Regulatory Business Process Manager, at stefen.mcmillan@fda.hhs.gov or (301) 796 - 3018.

Sincerely,

{See appended electronic signature page}

CDR Stefen McMillan, MSN FNP-BC
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Stefen Mcmillan

Digitally signed by Stefen Mcmillan
Date: 8/04/2021 01:05:04PM
GUID: 5c79670400f0b4ced48918c2bd217435

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: 8/2/2021

TO: Office of Bioequivalence
Office of Generic Drugs

FROM: Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: ANDA 216235

The Division of Generic Drug Study Integrity (DGDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) inspected the site in May 2019, which falls within the surveillance interval. The inspection was conducted under the following submissions: ANDA 212883 and (b) (4)

The final classification for the inspection was No Action Indicated (NAI).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Accutest Research Laboratories Pvt., Ltd..	1st & 2nd Floor, Synergy Square Complex, Krishna Industrial Estate, BIDC Gorwa, Vadodara, Gujarat, India

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: 8/12/2021

TO: Office of Bioequivalence
Office of Generic Drugs

FROM: Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: ANDA 216235

The Division of Generic Drug Study Integrity (DGDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS inspected the site in November 2018, which falls within the surveillance interval. The inspection was conducted under the following submissions: (b) (4)

The final classification for the inspection was No

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
		(b) (4)