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**VIA ELECTRONIC SUBMISSION**
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

# CITIZEN PETITION

On behalf of Zydus Pharmaceuticals (USA) Inc. ("Zydus"), we respectfully submit this Citizen Petition pursuant to Section 505 of the Federal Food, Drug, and Cosmetic Act (the "FD&C Act") and 21 C.F.R. §§ 10.20, 10.25, 10.30, and 10.31 to request that the Commissioner of Food and Drugs require the holder of any pending or approved abbreviated new drug application ("ANDA") for Carbamazepine Extended Release Tablets that references Tegretol XR® Tablets (NDA 020234) fully comply with the bioequivalence recommendations set out in the product specific guidance issued by the Food and Drug Administration ("FDA") in 2015 (hereinafter, the "March 2015 Guidance").[1] These recommendations include scaling of bioequivalence limits to the variability of the reference product and comparison of within-subject variability for test and reference products.

As described more fully herein, older bioequivalence parameters for Carbamazepine Extended Release Tablets are inadequate to assure the safety and effectiveness of generic versions of this "Narrow Therapeutic Index (NTI)" drug product, and FDA has revised these parameters to ensure equivalent clinical effect for generic NTI drugs. Yet, it appears that an approved generic product on the market may not comply with the revised parameters set out in the March 2015 Guidance. Until holders of approved ANDAs have submitted a passing bioequivalence study conducted in accordance with the March 2015 Guidance (as Zydus has done), FDA should change the current therapeutic equivalence ("TE") code published in the *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") from AB to BX for such ANDAs to protect public health and prevent serious adverse events.

In addition, it appears that a generic product is being marketed with a size and shape that is significantly different than the reference listed drug ("RLD") Tegretol XR® Tablets. These differences are particularly important given that Carbamazepine is an NTI drug indicated for the chronic disease epilepsy, where optimum and regular dosing is critical. Such differences are significant and pose safety and patient compliance issues.

## I. ACTIONS REQUESTED

We respectfully request that FDA take the following actions:

[1] *See* FDA, Draft Guidance on Carbamazepine (rev'd March 2015), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/psg/Carbamazepine_ER%20tab_020234_RV03-15.pdf.

(1) To ensure bioequivalence between the RLD and ANDAs for Carbamazepine Extended Release Tablets, require pending and approved ANDAs to meet the rigorous bioequivalence standard that Zydus's ANDA has met by submitting a passing bioequivalence study with a fully replicated crossover design that has scaled bioequivalence limits to the variability of the reference product and compared the within-subject variability of test and reference products, in compliance with the March 2015 Guidance;

(2) Downgrade the TE code of any approved ANDA currently listed as "AB" in the Orange Book to "BX" unless and until such a study has been provided to FDA;

(3) Assess whether the size and shape differences between approved ANDA products and the RLD pose patient safety and compliance issues; and

(4) Downgrade the TE code of any approved ANDA currently listed as "AB" in the Orange Book to "BX" if FDA concludes that the differences pose safety and compliance issues.

## II. STATEMENT OF GROUNDS

### A. Carbamazepine Drug Products are Widely Used to Treat Epilepsy

Epilepsy is a chronic neurological condition characterized by recurrent seizures. The U.S. Centers for Disease Control and Prevention estimates that in 2015, 1.2% of the U.S. population had active epilepsy. These 3.4 million people with epilepsy nationwide consist of approximately 3 million adults and 470,000 children.[2]

Carbamazepine is an anticonvulsant that was first marketed as a drug to treat epilepsy and trigeminal neuralgia in Switzerland in 1963 under the brand name Tegretol®. Tegretol® was first approved for use in the United States in 1968 in the form of immediate release tablets. Although the exact mechanism of action remains unknown, carbamazepine appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation.[3]

Carbamazepine is widely prescribed in the United States. FDA has approved carbamazepine for epilepsy – specifically for partial seizures with complex symptomatology (psychomotor, temporal lobe), generalized tonic-clonic seizures (grand mal), and mixed seizure patterns – and trigeminal neuralgia, as well as acute manic and mixed episodes in bipolar I disorder.[4]

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[2] Ctrs. for Disease Control & Prevention, *Epilepsy Data and Statistics*, https://www.cdc.gov/epilepsy/data/index.html (last visited June 13, 2019).

[3] Tegretol® Prescribing Information (March 2018), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/016608s115_018281_s058_018927s055_020234_s047.pdf.

[4] Zydus's Carbamazepine Extended Release Tablets (ANDA No. 205571) are approved by FDA solely for use in epilepsy and trigeminal neuralgia. *See* Zydus Pharmaceuticals (USA) Inc., DailyMed Drug Label, https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c5e4a25a-0137-4327-96f5-15735891ad5c (last visited June 17, 2019).

FDA has classified carbamazepine as a narrow therapeutic index ("NTI") drug. NTI drugs are "drugs where small differences in dose or blood concentration may lead to serious therapeutic failures and/or adverse drug reactions that are life-threatening or result in persistent or significant disability or incapacity."[5] Because there is a short interval between the dose resulting in therapeutic and unwanted toxic effects, even minor alterations in dosing with such a drug could lead to significant consequences.

B. Tegretol-XR® Development and Approval History

Tegretol-XR® (Carbamazepine Extended Release Tablets) was first approved by FDA on March 25, 1996. This dosage form offered meaningful benefits over the immediate release formulation, which exhibits extreme variability in performance as related to drug absorption and shows large fluctuations in peak-trough concentrations.[6] Absorption of carbamazepine after oral ingestion is quite variable with $T_{max}$ values that are formulation dependent.[7] Further, to maintain plasma concentrations within the target therapeutic plasma concentration range of 4-12 µg/mL requires multiple daily dosing with immediate release tablets up to a total of 1600 mg/day.[8] Clearly, decreasing the dosing frequency benefits patients on chronic therapy by simplifying their treatment regimens.

To address these challenges, an extended release formulation of carbamazepine was developed and approved under NDA No. 020234 as Tegretol-XR®. Tegretol-XR® is a controlled release formulation that approximates zero order release for several hours. This extended release formulation also prolongs the dosing interval such that dosing frequency can be minimized, enhancing patient adherence. The extended release formulation thereby offers significant advantages and improved absorption over immediate release carbamazepine.

C. Development of Generic Versions of Tegretol-XR®

In February 2008, FDA proposed the first product-specific guidance for carbamazepine extended release tablets (hereinafter, the "February 2008 Guidance").[9] The February 2008 Guidance recommended single-dose, two-treatment, two-sequence, two-period, crossover in vivo studies using an average bioequivalence approach. On March 31, 2009, FDA approved the first ANDA referencing Tegretol-XR® as the RLD pursuant to ANDA No. 078115, which belongs to Taro Pharmaceuticals U.S.A., Inc. ("Taro").[10]

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[5] FDA, *FY2015 Regulatory Science Research Report: Narrow Therapeutic Index Drugs*, https://www.fda.gov/industry/generic-drug-user-fee-amendments/fy2015-regulatory-science-research-report-narrow-therapeutic-index-drugs (last visited June 13, 2019).

[6] P. K. Jensen et al., "Pharmacokinetic comparison of two carbamazepine slow-release formulations," Acta Neurol. Scand. 82:135–13 (1990) (Exhibit A); Summary Basis of Approval, Tegretol-XR® (NDA No. 020234), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/96/020234_complete_Approval_pkg.pdf.

[7] P. Patsalos et al., "Therapeutic Drug Monitoring of Antiepileptic Drugs by Use of Saliva," 35(1) Ther. Drug Monit. 7 (2013) (Exhibit B).

[8] Tegretol® Prescribing Information.

[9] FDA, Draft Guidance on Carbamazepine (recommended February 2008) (Exhibit C).

[10] ANDA No. 078115 Approval Letter (March 31, 2009), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/078115s000ltr.pdf.

1. FDA Revises its Bioequivalence Recommendations

By 2010, issues were being reported in patients who had received generic anticonvulsants and mood stabilizers, including carbamazepine, such as increased seizures, decreased carbamazepine levels, increased toxicity, shorter $C_{max}$, and bio*in*equivalence.[11] By this time, FDA had realized that current criteria to establish the bioequivalence of generic NTI drugs were insufficient and undertook to modernize its criteria for approval of these drugs. At the April 2010 Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, the committee voted that the current bioequivalence standards were insufficient for NTI drugs and that the standards needed to be stricter.[12] The committee also recommended future research.[13]

In a meeting the following year, the advisory committee voted in favor of a two-treatment, four-period, fully replicated, crossover design for bioequivalence studies of NTI drugs that utilizes the reference-scaled average bioequivalence approach.[14] The Office of Generic Drugs announced that it would publish FDA's approach in the individual product-specific bioequivalence guidances for each NTI drug.[15] FDA stated that its new bioequivalence approach for NTI drugs was expected to "bring the US into harmony with other regulatory agencies and improve public confidence in quality and switchability of generic drugs."[16] The Agency also undertook research activities into bioequivalence of NTI drugs in the ensuing years, which gave rise to product-specific bioequivalence recommendations.[17]

For these reasons, FDA revised the February 2008 Guidance and published new bioequivalence requirements in the March 2015 Guidance. The March 2015 Guidance identified carbamazepine as an NTI drug,[18] and incorporated the advisory committee's recommendations for bioequivalence study design.[19] Table 1 compares the guidance drafts:

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[11] Julie E. Desmarais et al., "Switching from Brand-Name to Generic Psychotropic Medications: A Literature Review," CNS Neuroscience & Therapeutics 17 (2011) 750–760 (first published 2010) (Exhibit D).

[12] *See* Dr. Lawrence X. Yu, Office of Generic Drugs, "Quality and Bioequivalence Standards for Narrow Therapeutic Index Drugs," GPhA Fall 2011 Technical Workshop Slides (explaining the advisory committee meeting outcomes), *available at* https://www.fda.gov/media/82940/download.

[13] *Id.*

[14] *Id.* (describing the outcome of the July 2011 Advisory Committee for Pharmaceutical Science and Clinical Pharmacology).

[15] *Id.*

[16] *Id.*

[17] *See, e.g.,* FDA FY2015 Regulatory Science Research Report: Narrow Therapeutic Index Drugs, https://www.fda.gov/industry/generic-drug-user-fee-amendments/fy2015-regulatory-science-research-report-narrow-therapeutic-index-drugs (last visited June 15, 2019).

[18] March 2015 Guidance at 2.

[19] *Id.* at 1.

Table 1: Comparison of Guidances

| | February 2008 Guidance | March 2015 Guidance |
|---|---|---|
| **Number of studies** | Two studies - Fasting & Fed | Two studies - Fasting & Fed |
| **Study design** | Single-dose, two-treatment, two-period crossover in-vivo (Strength – 400 mg) | Single-dose, **two-treatment, two-sequence**, **four-period, fully replicated crossover in vivo** (Strength – 400 mg)<br><br>**The applicant should use the reference-scaled average BE approach for carbamazepine** |
| **FDA's Explanation** | | FDA has concluded that Carbamazepine is a narrow therapeutic index (NTI) drug, based on the following evidence:<br>• The range between the effective carbamazepine concentrations and the concentrations associated with serious toxicity is narrow<br>• Sub-optimal doses or concentrations lead to therapeutic failure or severe toxicity<br>• Carbamazepine is subject to therapeutic monitoring based on pharmacokinetics measures<br>• Carbamazepine has low-to-moderate within-subject variability<br><br>The study should be a fully replicated crossover design in order to:<br>• **Scale BE limits to the variability of the reference product**<br>• **Compare test and reference products' within-subject variability** |

2. FDA's Review and Approval of Zydus's ANDA

Zydus developed a generic formulation of Tegretol-XR® adopting the technology platform similar to RLD. Zydus initially conducted a bioequivalence study that complied with the recommendations in the February 2008 Guidance, which Zydus submitted to FDA on March 28, 2013 as part of its ANDA No. 205571. Once FDA published the March 2015 Guidance, Zydus undertook to comply with the new recommendations for study design and submitted a passing bioequivalence study to FDA for its generic formulation. Zydus's study demonstrates that its product is bioequivalent to Tegretol-XR®. Accordingly, FDA determined that Zydus's ANDA

product was therapeutically equivalent (and A-rated) to the RLD, and FDA granted final approval to Zydus's ANDA No. 205571 on February 7, 2019.

D. Assessment of Approved Generic Carbamazepine Extended Release Tablets

Based on a review of available literature and documents in the public domain, Zydus believes that the Carbamazepine Extended Release Tablets approved in Taro's ANDA No. 078115 differ with respect to FDA's March 2015 Guidance.

Taro performed the bioequivalence studies used to support approval of its ANDA before FDA published the February 2008 Guidance according to the Summary Basis of Approval for Taro's application. Taro conducted a pivotal fed bioequivalence study using the 400 mg strength and a pivotal fasted study using 2x100 mg strengths, with each study designed as a "single-dose, randomized, two-treatment, two-sequence, crossover study in healthy adult subjects."[20] Therefore, the studies described in the approval package do not comply with the reference scaled bioequivalence approach set out in the March 2015 guidance. This suggests that FDA does not have sufficient information before it to confirm that Taro's drug product is therapeutically equivalent and substitutable for the RLD.

In addition, a comparison of the RLD Tegretol-XR® (NDA 020234) with Taro's Carbamazepine Extended Release Tablets (A078115) demonstrates that Taro's tablet size is significantly larger than the RLD for the 400 mg strength. The details of the comparison are provided below:

| | **Novartis (N020234)*** | **Taro Pharma (A078115)*** |
|---|---|---|
| |  |  |
| **Strength** | 400mg | 400mg |
| **Size** | 12mm | 17mm |
| **Shape** | Round | Capsule shape |

* Source: Dailymed

The differences observed in shape and larger tablet size of Taro's product (A078115) as compared to the RLD may present safety and compliance issues for the patient. These differences need attention especially for Carbamazepine, which is an NTI drug indicated for the chronic disease epilepsy, where optimum and regular dosing is critical.

E. Statutory and Regulatory Framework Governing ANDA Approval and TE Codes

An ANDA submitted under Section 505(j) of the FDCA is eligible for approval if it is a "duplicate of a listed drug," where the listed drug is typically the innovator product approved in a new drug application.[21] The ANDA must contain information demonstrating that the "active

[20] ANDA No. 078115 Summary Basis of Approval, at 2, *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/078115Orig1s000BioeqR.pdf.

[21] 21 C.F.R. § 314.101(d)(9).

ingredient" of the proposed generic drug product is "the same as that of the listed drug,"[22] meaning "identical in active ingredient(s)."[23]

An ANDA must also contain information to demonstrate that it is bioequivalent to the listed drug. [24] Two drugs are bioequivalent if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses."[25] Bioequivalence is "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety . . . becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."[26]

If the proposed generic product has the same active ingredient, strength, dosage form, and route of administration as the RLD, the products will be considered "pharmaceutically equivalent" to one another.[27] The proposed generic product must be both pharmaceutically equivalent and bioequivalent to the RLD to obtain ANDA approval. FDA considers two drug products to be "therapeutically equivalent" only if they are pharmaceutically equivalent, bioequivalent, and "can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling."[28]

Therapeutically equivalent products are listed in the Orange Book with an "A" rating, or an "AB" rating in the case of oral products for which bioequivalence has been demonstrated.[29] If, however, FDA believes that there is insufficient evidence to assure therapeutic equivalence of the generic product to the RLD, FDA will downgrade the product's therapeutic equivalence rating to "BX" until the Agency has adequate information before it to ensure equivalence. *Id.*

F. FDA Should Require All Pending and Approved ANDAs to Fully Comply With the March 2015 Guidance

As discussed above, older bioequivalence parameters have been deemed insufficient by FDA to demonstrate bioequivalence of NTI generic drugs, including carbamazepine extended release tablets. Therefore, older bioequivalence studies that do not comply with the updated parameters set out in the March 2015 Guidance will not be able to detect clinically significant differences in the pharmacokinetic profiles of the generic product and the RLD. Moreover, this could create risks for switching between generic products if one of those generic products is not therapeutically equivalent to the RLD. FDA's reliance on older studies to prove bioequivalence

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[22] 21 U.S.C. § 355(j)(2)(A)(ii)(I).

[23] 21 C.F.R. § 314.92(a)(1).

[24] 21 U.S.C. § 355(j)(2)(A)(iv).

[25] 21 U.S.C. § (j)(8)(B)(i).

[26] 21 C.F.R. § 320.1(e).

[27] 21 C.F.R. § 314.3.

[28] *Id.*

[29] *See* Preface to Orange Book, 39th ed. (2019), *available at* https://www.fda.gov/drugs/developmentapprovalprocess/ucm079068.htm.

– and therapeutic equivalence – of currently marketed carbamazepine extended release tablets is misplaced, and the risks of relying on older studies is significant for antiepileptic drugs.

In a previous example, FDA discovered that approved ANDAs for generic versions of the mood-stabilizer Wellbutrin XL, which had relied on older bioequivalence methodology, were not bioequivalent to the RLD. In that instance, FDA required the holders of all marketed ANDAs for the product to conduct bioequivalence studies using an updated methodology to confirm bioequivalence. Ultimately, some sponsors were unable to prove bioequivalence under the more sensitive parameters, and FDA sought withdrawal of ANDA products that could not confirm bioequivalence.[30]

FDA should ensure that pending and approved ANDAs comply with the study design requirements set out in the March 2015 Guidance. At a minimum, this includes a fully replicated crossover design that has scaled bioequivalence limits to the variability of the reference product and compare the within-subject variability of test and reference products. Absent such a showing, there is no assurance that the RLD and ANDA product are bioequivalent or that they share the same clinical profile. Moreover, FDA should apply the bioequivalence approval requirements consistently across all generic drug applications and require all ANDA holders to comply with the rigorous bioequivalence approval standards for NTI drugs that it applied to Zydus's ANDA. Any other result would contravene the statutory requirements for sameness, be at odds with FDA's prior actions, and be improper.[31]

### G. An Approved ANDA Cannot Maintain an "AB" TE Code Unless it Has Demonstrated Bioequivalence Per the March 2015 Guidance

FDA should downgrade the TE code for any approved ANDA product if the data before the Agency are insufficient to determine therapeutic equivalence.[32] Where data before FDA are insufficient to demonstrate therapeutic equivalence, "the drug products are presumed to be therapeutically inequivalent until the Agency has determined that there is adequate information to make a full evaluation of therapeutic equivalence."[33] Indeed, FDA has downgraded the rating of other approved generic products that it later deems have not sufficiently demonstrated therapeutic equivalence.[34] Likewise, FDA should downgrade the TE code to "BX" for any approved ANDA product to Tegretol-XR® until it has proven bioequivalence according to the March 2015 Guidance.

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[30] FDA, "Update: Bupropion Hydrochloride Extended-Release 300 mg Bioequivalence Studies," (Oct. 10, 2013), https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/update-bupropion-hydrochloride-extended-release-300-mg-bioequivalence-studies" (last visited June 18, 2019).

[31] *See Bracco Diagnostics. Inc. v. Shalala*, 963 F. Supp. 20, 27-28 (D.D.C. 1997) ("Government is at its most arbitrary when it treats similarly situated people differently") (internal citations omitted).

[32] *See* Preface to Orange Book, *supra* n. 29

[33] *Id.*

[34] Mallinckrodt Pharmaceuticals; Proposal to Withdraw Approval of an Abbreviated New Drug Application for Extended-Release Methylphenidate Tablets; Opportunity for a Hearing," 81 Fed. Reg. 71737-741 (Oct. 18, 2016); "Kremers Urban Pharmaceuticals Inc.; Proposal to Withdraw Approval of an Abbreviated New Drug Application for Extended-Release Methylphenidate Tablets; Opportunity for a Hearing," 81 Fed. Reg. 71741-745 (Oct. 18, 2016).

For all of the reasons described above, we respectfully request that FDA grant the actions requested in this citizen petition.

## III. ENVIRONMENTAL IMPACT

The actions requested herein are subject to categorical exclusion under 21 C.F.R. § 25.31(a).

## IV. ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), the Petitioner will submit economic impact information upon request by the Commissioner.

## V. CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: May 31, 2019. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Zydus Pharmaceuticals (USA) Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

Chad A. Landmon

Exhibits