



BLA 761385

**COMPLETE RESPONSE**

Teva Pharmaceuticals, Inc.  
Attention: David DeCicco  
Director, Global Biosimilar Regulatory Affairs  
145 Brandywine Parkway  
West Chester, PA 19380

Dear David DeCicco:

Please refer to your biologics license application (BLA) (b) (4)  
for TVB-009.

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

**FACILITY INSPECTIONS**

- (1) As part of the facility evaluation of (b) (4), a Remote Regulatory Assessment was performed. FDA identified deficiencies that were conveyed to the representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office that conducted the Remote Regulatory Assessment prior to your complete response to this letter. Your complete response should include the date(s) of the facility's correspondence(s) to address these deficiencies. FDA may need to perform an onsite pre-license inspection (PLI) before this application may be approved. Please be aware that we will not initiate the PLI until your complete response is received. Please work with the facility to resolve the related deficiencies and ensure the facility is ready for a PLI.

**PRESCRIBING INFORMATION**

Submit draft labeling that is responsive to our electronic communication dated (b) (4). Also incorporate relevant updates according to the most recently approved labeling for the reference product into your product labeling.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition,

submit updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.<sup>1</sup>

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the Prescription Drug Labeling Resources<sup>2</sup> and Pregnancy and Lactation Labeling Final Rule<sup>3</sup> websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.
- Additional resources for the PI, patient labeling, and carton/container labeling.

In addition, we encourage you to review the draft guidance for industry *Labeling for Biosimilar Products*.

## **CARTON AND CONTAINER LABELING**

Submit draft carton and container labeling based on our proposed revisions dated

(b) (4)

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<sup>1</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

<sup>2</sup> <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

<sup>3</sup> <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

## **MEDICATION GUIDE**

The following bolded statement or appropriate alternative must appear on the carton and container labeling per 21 CFR 208.24(d): **"ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide."**

## **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

We acknowledge receipt of your proposed REMS, included in your submission dated (b) (4), which contains a communication plan and a timetable for submission of assessments of the REMS. In accordance with section 505-1 of the FDCA, we agree that a REMS will be necessary for TVB-009, if it is approved, to ensure that the benefits of the drug outweigh the risk of severe hypocalcemia in patients with advanced chronic kidney disease (CKD) including dialysis-dependent patients associated with TVB-009.

The REMS, should it be approved, will create enforceable obligations. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

## **PROPRIETARY NAME**

Please refer to our correspondence dated (b) (4), which addresses the proposed proprietary name, (b) (4). This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

## **SAFETY UPDATE**

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the product under consideration regardless of indication, dosage form, or dose level.

- (1) Describe in detail any significant changes or findings in the safety profile and their relevance, if any, to whether there may be clinically meaningful differences between the proposed biosimilar product and the U.S.-licensed reference product.

- (2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
- Present new safety data from the clinical studies for the proposed indication using the same format as the original BLA submission.
  - Present tabulations of the new safety data combined with the original BLA data.
  - Include tables that compare frequencies of adverse events in the original BLA with the retabulated frequencies described in the bullet above.
- (3) Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
- (4) Provide case report forms and narrative summaries for each subject who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
- (5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original BLA data.
- (6) Provide updated exposure information for the clinical studies (e.g., number of subjects, person time).
- (7) Provide a summary of worldwide experience on the safety of this product, including adverse events known to be associated with the use of the product and immunogenicity. Include an updated estimate of use for this product marketed in other countries.
- (8) Provide English translations of current approved foreign labeling not previously submitted.

## **OTHER**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products*.

The product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact (b) (4)

Sincerely,

*{See appended electronic signature page}*

(b) (4)

Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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(b) (4)

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