

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761299Orig1s000**

**OTHER ACTION LETTERS**



BLA 761299

**COMPLETE RESPONSE**

Alvotech USA, Inc.  
c/o PharmaLex US Corporation  
c/o AmerisourceBergen  
1 West 1st Avenue  
Conshohocken, PA 19428

Attention: Sheela J. Mitta  
US Agent

Dear Ms. Mitta:<sup>1</sup>

Please refer to your biologics license application (BLA) dated and received December 20, 2021, and your amendments, submitted under section 351(k) of the Public Health Service Act for AVT02.

We acknowledge receipt of your amendment dated December 28, 2022, which constituted a complete response to our December 20, 2022, action letter.

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 INSPECTION**

Following inspection of the Alvotech hf, Reykjavik, Iceland (FEI: 3013702557) manufacturing facility listed in this application, the FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

**PRESCRIBING INFORMATION**

We reserve comment on the proposed labeling until the application is otherwise adequate. 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, including regulations and related guidance documents and the Selected

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<sup>1</sup> This Complete Response letter takes no position on whether this application would be eligible for or blocked by any exclusivity if it were otherwise eligible for approval.

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

Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances. In addition, we encourage you to review the FDA guidance for industry *Labeling for Biosimilar Products*.

## **CARTON AND CONTAINER LABELING**

We reserve comment on the proposed labeling until the application is otherwise adequate.

## **MEDICATION GUIDE**

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

## **PROPRIETARY NAME**

Please refer to correspondence dated, March 21, 2023, which addresses the proposed proprietary name, Simlandi. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

## **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.

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

- 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, call Saharat Patanavanich, Regulatory Project Manager, at (240) 402-0139.

Sincerely,

*{See appended electronic signature page}*

Nikolay P. Nikolov, MD  
Director  
Division of Rheumatology and Transplant Medicine  
Office of Immunology and Inflammation  
Office of New Drugs  
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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NIKOLAY P NIKOLOV  
06/28/2023 08:49:29 AM



BLA 761299

## COMPLETE RESPONSE

Alvotech USA, Inc.  
1201 Wilson Blvd. Ste. 2130  
Arlington, VA 22209

Attention: Brian DiPaolo  
Head of Global Regulatory, CMC

Dear Mr. DiPaolo:<sup>1</sup>

Please refer to your biologics license application (BLA) dated and received on December 20, 2021, and your amendments, submitted under section 351(k) of the Public Health Service Act for AVT02.

We also acknowledge receipt of your amendment dated November 29, 2022, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

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**

Following inspection of the Alvotech hf, Reykjavik, Iceland facility (FEI: 3013702557) listed in this application, FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

### **PRESCRIBING INFORMATION**

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### **PROPRIETARY NAME**

Please refer to correspondence dated, March 11, 2022, which addresses the proposed proprietary name, Simlandi. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

### **SAFETY UPDATE**

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- (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.
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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 Biosimilar Biological Product Sponsors or Applicants*.

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

If you have any questions, call Susan Rhee, Regulatory Project Manager, at 301-796-2402.

Sincerely,

*{See appended electronic signature page}*

Nikolay P. Nikolov, MD  
Director  
Division of Rheumatology and Transplant Medicine  
Office of Immunology and Inflammation  
Office of New Drugs  
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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NIKOLAY P NIKOLOV  
12/20/2022 08:30:45 PM