CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761343Orig1s000

OTHER ACTION LETTERS

BLA 761343

COMPLETE RESPONSE

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

Attention: Sheela J. Mitta
US Regulatory Agent for Alvotech

Dear Sheela Mitta,

Please refer to your biologics license application (BLA) dated and received October 11, 2022, submitted under section 351(k) of the Public Health Service Act for AVT04.

We have completed our review of this application 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 Alvotech hf, Reykjavik, Iceland (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

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[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected 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.

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

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, December 16, 2022, which addresses the proposed proprietary name, Selarsdi. 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.

ADDITIONAL COMMENTS

We have the following comments that are not approvability issues:

PRODUCT QUALITY

In your comparative analytical assessment (CAA), the evaluations of binding to FcγRIIIa 158F and FcγRIIIa 158V were performed using surface plasmon resonance (SPR). We note that the binding assay results for FcγRIIIa 158F and FcγRIIIa 158V show large variability for US-licensed Stelara (US-Stelara) with a range of 172 – 260% for FcγRIIIa 158F and a range of 153 – 259% for FcγRIIIa 158V. Similarly, the binding assay results show large variability for EU-approved Stelara (EU-Stelara) with a range of 171 – 282% for FcγRIIIa 158F and a range of 182 – 277% for FcγRIIIa 158V. Additionally, we note that the differences in the binding activity for both FcγRIIIa 158F and FcγRIIIa 158V between US-Stelara/EU-Stelara and AVT04 are very large. Provide a justification for the large data variability observed for your FcγRIIIa 158F and FcγRIIIa 158V binding assays and provide data and/or information to support that the methods developed for evaluation of binding to FcγRIIIa 158F and FcγRIIIa 158V are fit for their intended purpose.

MICROBIAL QUALITY

1) Microbial method qualification requires data from three independent in-process eluate lots. Update the submission with endotoxin and bioburden assay qualification data for in-process eluates (b) (4) with three independent process eluate lots.

2) To ensure that AVT04 drug product formulation does not mask the detectability of endotoxin in your endotoxin assay determine the effect of hold time on endotoxin

detection using endotoxin spiked samples. Refer to PDA Technical Report No. 82 for additional details.

3) Pressure monitoring is a critical process parameter that needs to be continuously monitored during sterile filtration. Provide data to demonstrate that you can routinely meet pressure acceptance criteria based on your microbial retention study during full scale routine production. Implement continuous in-line pressure monitoring upstream of the sterile filter during routine manufacturing.

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 Sascha Randolph, Regulatory Project Manager, at (301)796-8546.

Sincerely,

{See appended electronic signature page}

Shari L Targum, MD, MPH, FACP, FACC
Acting Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

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.

/s/

SHARI L TARGUM
10/11/2023 01:46:05 PM