DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research OND / OII / DRTM
10903 New Hampshire Ave. Silver Spring, MD 20993

MEMO TO FILE

Application.: BLA 761024 Supplement 11

Reviewer: Sabiha Khan, MD
Clinical Reviewer
Division of Rheumatology and Transplant Medicine

Submitted: December 8, 2022

Reviewed: April 4, 2023

Product: Amjevita (adalimumab-atto)

Indication: No new indications are sought with this supplement

Sponsor: Amgen

Submission: CMC Prior Approval Supplement for the addition of Amjevita 10 mg/0.2 mL strength

Synopsis

The current submission, sBLA 761024/11, is a CMC supplement for a 10 mg/0.2 mL strength in a pre-filled syringe (PFS) to be used for pediatric patients who weigh 10 kg to less than 15 kg to address PMR 3125-4, "Develop a presentation that can be used to accurately administer Amjevita (adalimumab-atto) to pediatric patients who weigh less than 15 kg."

To support the 10 mg/0.2 mL PFS presentation, the Applicant has referenced Module 3 content previously submitted under sBLA 761024/11 on September 29, 2021, and in the current submission, the Applicant has provided human factors (HF) data including a simulated use summative validation study and a carton differentiation summative validation study. No clinical studies were submitted, nor were required, for this supplement. Additionally, transportation qualification data were submitted to address previous Agency comments regarding the impact of plunger rod movement on sterility during shipment.

The Office of Biotechnology Products (OBP) and the Division of Medication Error Prevention and Analysis (DMEPA) Human Factors team recommend approval of this supplement. Further, the Office of Pharmaceutical Manufacturing Assessment (OPMA) has concluded the Applicant has addressed the plunger rod movement concerns that were previously identified and recommends approval of this supplement. Therefore, the Division recommends approval of sBLA 761024/11, with revisions to the labeling as agreed upon with the Applicant. The Division further considers that the information provided in sBLA 761024/11 is adequate to fulfill PMR 3125-4.

Background and Regulatory History:

Adalimumab-atto (Amjevita) is a recombinant human immunoglobulin (Ig) G1 monoclonal antibody (mAb) against tumor necrosis factor (TNF)-alpha. Adalimumab-atto was approved as a biosimilar to US-licensed Humira on September 23, 2016, for treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis (pJIA) (4 years of age and older), psoriatic arthritis, ankylosing spondylitis,

adult Crohn's disease, ulcerative colitis, and plaque psoriasis. The indications were subsequently expanded to include pJIA 2 years of age and older and Crohn's Disease 6 years of age and older on July 28, 2022. The approved strengths and presentations include a 40 mg/0.8 mL single-use PFS, a 20 mg/0.4 mL single-use PFS, and a 40 mg/0.8 mL single-use pre-filled pen.

At the time of original approval, the following PREA PMR (PMR 3125-4) was issued:

> Develop a presentation that can be used to accurately administer Amjevita (adalimumab-atto) to pediatric patients who weigh less than 15 kg
>
> Final Report Submission Date: September 2021

On September 29, 2021, the Applicant submitted a prior approval supplement (PAS), that included an assessment to fulfill PMR 3125-4. The assessment included the description and composition of a new 10 mg/0.2 mL PFS in addition to information on pharmaceutical development, manufacturing, control of drug product, the container closure system, stability information, and an analytical comparability assessment. Due to COVID-related delays, HF studies to support design validation were ongoing at the time of submission. The Applicant proposed to complete the combination product design validation prior to the commercial launch of the 10 mg/0.2 mL PFS and to provide the HF validation study results in a future annual report. The Division of Rheumatology and Transplant Medicine (DRTM), in consultation with DMEPA, determined that the absence of HF data constituted a filing issue and the Applicant's proposal to submit HF validation study results in a future annual report was not acceptable. On November 28, 2021, DRTM issued a refusal-to-file (RTF) letter stating that the Agency expected either data from a HF validation study, or a threshold (comparative) analysis with a use related risk analysis and a justification for not submitting data from a HF validation study would need to be submitting with the PAS to support the safe and effective use of the proposed product by the intended users, for intended uses, and in intended use environments. Additionally in the RTF letter, but unrelated to PMR 3125-4, the Agency asked the Applicant to provide plunger movement studies to address an issue with the Amjevita 10 mg/0.2 mL PFS plunger movement and potential breaches to the sterile boundary due to effects of varying air pressure during shipment.

On December 10, 2021, the Applicant submitted a deferral extension request for PMR 3125-4 to allow time to complete the HF studies. The Applicant proposed to provide the data in a future PAS supplement and requested an extension of final report submission date to December 2022. After discussion with the Pediatric Review Committee (PeRC), the Division granted the deferral extension request on February 28, 2022.

Review

The current supplement sBLA 761024/11, submitted on December 8, 2022, proposes an Amjevita 10 mg/0.2 mL PFS for pediatric patients who weigh 10 kg to less than 15 kg and is submitted to address PREA PMR 3125-4:

> Develop a presentation that can be used to accurately administer Amjevita (adalimumab-atto) to pediatric patients who weigh less than 15 kg
>
> Final Report Submission: December 2022

In addition to reference to Module 3 content submitted originally on September 29, 2021, which includes information on pharmaceutical development, manufacturing, control of drug product, the container closure system, stability information and an analytical comparability assessment, the Applicant has submitted HF data generated using the 10 mg/0.2mL PFS. The current submission also includes information on quality overall summary, container closure integrity, device design validation, device risk management, stability summary, and use-related risk analysis. Additionally, data has been submitted to address Agency comments provided in the RTF letter regarding plunger rod movement. The submitted information is reviewed below. No information from clinical studies was submitted, nor required for this supplement.

There is no change in drug substance, drug product composition or concentration, manufacturing facility,

materials, equipment, [redacted] purification process and in-process controls, and container closure system of the 10 mg/0.2 mL PFS compared to the currently approved 20 mg/0.4 mL and 40 mg/0.8 mL PFS presentations. The only change is [redacted]. The OBP review team found the process validation approach to validate the 10 mg/0.2 mL strength [redacted] acceptable.

The OBP review team has determined analytical comparability was demonstrated between the current approved strengths (Amjevita 20 mg/0.4 mL and Amjevita 40 mg/0.8 mL) and the proposed Amjevita 10 mg/0.2 mL using biochemical, biophysical, and biological analytical methods. Lot release, characterization, and forced degradation results demonstrated that Amjevita 10 mg/0.2 mL is comparable to Amjevita 20 mg/0.4 mL and Amjevita 40 mg/0.8 mL. OBP reviewed the submission and has concluded the comparability studies between Amjevita 10 mg/0.2 mL, and Amjevita 20 mg/0.4 mL and 40 mg/0.8 mL, the comparability between Amjevita 10 mg/0.2 mL process validation batch data and Amjevita 40 mg/0.8 mL batch data used to support the BLA, and the comparative analytical assessment results between the Amjevita 40 mg/0.8 mL drug product and US-licensed Humira lots at 40 mg/0.8 mL used in the original BLA submission, support the conclusion that Amjevita 10 mg/0.2 mL is highly similar to US-licensed Humira 10 mg/0.2 mL, and the strength of Amjevita 10 mg/0.2 mL is the same as that of US-licensed Humira 10 mg/0.2 mL notwithstanding minor differences in clinically inactive components. OBP has recommended approval of the supplement from the OBP perspective. See OBP review by You Zhuo, PhD, dated March 13, 2023.

The Applicant also submitted transportation qualification data, including details of a transportation simulation study which evaluated plunger movement during air transportation. The OPMA review team determined the Applicant adequately demonstrated that the PFS plunger movement does not breach the non-sterile boundary during air transport. From the sterility assurance perspective and based on the manufacturing facility assessment, OPMA has recommended an approval action (see OPMA review by Madushini Dharmasena, PhD dated March 29, 2023).

HF/usability engineering evaluations included a simulated use summative validation study and a carton differentiation summative validation study. DMEPA reviewed the submitted data and concluded the HF studies demonstrated use errors, close calls, and use difficulties associated with the critical and non-critical tasks. Based on DMEPA's review of the user interface, the available participant's subjective feedback, and the Applicant's mitigation strategies and root cause analysis, DMEPA did not identify additional risk mitigations to address the use errors. DMEPA has determined the risks have been mitigated to an acceptable level and no additional changes to the user interface are likely to further mitigate these risks. DMEPA recommends approval of the supplement from the DMEPA perspective. See DMEPA HF review by Murewa Oguntimein, PhD, MHS, CPH, MCHES, dated March 22, 2023.

Labeling

The Applicant's proposed changes to the PI included the following:

- Highlights
  - Dosage and Administration
    - Dosage table for Juvenile Idiopathic Arthritis has been updated to include pediatric age/weight group and recommended dosage
  - Dosage Forms and Strengths
    - New strength of 10 mg/0.2 mL added for single-dose PFS

- Section 2 Dosage and Administration
  - Under Section 2.2 Juvenile Idiopathic Arthritis, pediatric weight group of 10 kg to less than 15 kg has been included with recommended dosage of 10 mg every other week
  - Removal of text stating that there is no dosage information that allowed weight based dosing for pediatric patients below 15 kg

- Section 3 Dosage Forms and Strengths
  - Information about the Amjevita 10 mg/0.2 mL PFS was added

- Section 11 Description
  - Description of the Amjevita 10 mg/0.2 mL PFS including list of ingredients was added in alignment with the current description of the Amjevita 40 mg/0.8 mL PFS and autoinjector and 20 mg/0.4 mL PFS

- Section 16 How Supplied/Storage and Handling
  - Information about the Amjevita 10 mg/0.2 mL PFS including the number of units per carton, and NDC number was added

The IFU proposed for the 10 mg/0.2 mL PFS was informed by the HF validation study results and participant feedback to address observed use errors to include:

- Instructions to pinch skin and hold throughout the injection
- Instructions to insert the needle and inject medication into pinched skin, at a 45-degree angle
- An update to the title of the IFU to clarify that instructions are intended for HCPs and caregivers performing the injection

Labeling consultants, including OBP, OSE, OPDP and DMPP have reviewed the submitted labeling. OSE recommendations which pertain primarily to internal consistency and clarity of the labeling have been conveyed to the Applicant. All labeling changes were agreed upon with the Applicant.

Overall Conclusions

The OBP review team has determined the Applicant has provided adequate data and information to support a demonstration that Amjevita 10mg/0.2 mL is highly similar to US-Humira 10 mg/0.2 mL, notwithstanding minor differences in clinically inactive components. The Agency has further determined the data and information provided by the Applicant in this sBLA, including the data submitted from the clinical development program and the analytical similarity and comparability data, support a demonstration of no clinically meaningful differences between Amjevita 10 mg/0.2 mL and US-Humira 10 mg/0.2 mL. The conditions of use for Amjevita 10 mg/0.2 mL have been previously approved for US-Humira 10 mg/0.2 mL, and the strength, dosage form, and route of administration of Amjevita 10 mg/0.2 mL are the same as those of US-Humira 10 mg/0.2 mL.

The DMEPA review team has determined that the risks identified in the human factors studies have been mitigated to an acceptable level.

The totality of the data and information provided in the BLA, including this supplement, support licensure of Amjevita 10 mg/0.2 mL as a biosimilar to US-Humira 10 mg/0.2 mL. The labeling has been revised to include the 10 mg/0.2 mL PFS which will allow for dosing of patients 2 years of age and older with pJIA down to 10 kg.

The Applicant's submission was presented to PeRC on March 21, 2023, and PeRC agreed with the Division's recommendation that the submission adequately addresses PMR 3125-4. Therefore, the Division recommends approval of CMC supplement sBLA 761024/s11 for the Amjevita 10mg/0.2 mL PFS, and that PMR 3125-4 to "develop a presentation that can be used to accurately administer Amjevita (adalimumab-atto) to pediatric patients who weigh less than 15 kg" is fulfilled.

Action

The recommended action of this CMC supplement is Approval. In addition, with the approval of the 10 mg/0.2 mL strength, PMR 3125-4 is fulfilled.

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/

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04/04/2023 04:33:43 PM

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04/04/2023 04:35:59 PM