الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Saudi Public Assessment Report

(Summary Report)

Orladeyo®

Type of Application: New drug application.

Type of Product: New chemical entity.

Active Pharmaceutical Ingredient(s): Berotralstat dihydrochloride.

ATC code: B06A.

Dosage Form: Capsule.

Dosage Strength: 150 mg.

Pack Size: 28.

Shelf life: 36 months.

Storage Conditions: Do not store above 30°C.

Reference Product in SA (if applicable): NA.

Marketing Authorization Holder: BioCryst Pharmaceuticals, Inc.

Manufacturer: CATALENT.

Registration No.: 1608222499.

Date of Decision: Approved on 14/04/2022.

Proposed Indications: Orladeyo is indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 12 years of age and older.

Product Background

This product is considered as a new chemical entity, for Saudi regulatory purposes. Furthermore, this product is qualified to follow the SFDA's regulatory pathway for verification.

The SFDA approval for Orladeyo® (Berotralstat dihydrochloride 150 mg) is based on a review of the quality, safety and efficacy as summarised hereinafter:

Quality Aspects

Drug Substance

General Information:

Berotralstat Dihydrochloride is an off-white powder. It is soluble in methanol. It does have chirality. The structure has been fully elucidated using several spectroscopic techniques.

Manufacture, characterization and process controls:

Berotralstat Dihydrochloride is manufactured by Cambrex Karlskoga AB, Karlskoga, Sweden (Cambrex CK) and Cambrex Charles City, USA (Cambrex CC) through multiple steps chemical synthesis. A list of reagents and solvents used in the manufacturing process with identification of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) classification for solvents as well as the respective specifications has been submitted. The specifications for raw materials are acceptable. Potential and actual impurities were identified and assessed according to international guidelines and references on impurities.

Control of the drug substance:

The drug substance (DS) specification includes tests for assay, identification, impurities, water content, description, chloride content, residual solvents, residue on ignition, alkyl chlorides and chiral impurity. All methods and acceptance criteria included in the drug substance specifications have been described and justified and accepted. Batch analysis data and CoA have been presented by the drug substance manufacturer demonstrating compliance of three commercial scale batches with the drug substance specification. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the international guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing have been presented.

Container closure system:

The primary packaging is double Low-density polyethylene (LDPE) bags. The materials comply with pharmacopeia and regulatory requirements. The choice of the container closure system has been validated by stability data and it is adequate for the intended use of the product. The secondary packaging is an Open-top drum and lid constructed of polyethylene (PE).

Stability:

Stability data was provided on six commercial scale batches of the drug substance from the proposed manufacturer stored in the intended commercial package for 36 months under long term conditions 25°C/60%RH, and on six commercial scale batches for 6 months under accelerated conditions 40 ºC / 75% RH according to the SFDA Guidelines for Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products. The following parameters were tested: for assay, microbial, impurities, description, water content and chiral impurity. All batches remained stable at long-term conditions, and no significant changes or out-of-spec trends were observed. The stability results indicate that the drug substance manufactured by Cambrex CK and Cambrex CC is sufficiently stable. The stability results justify the proposed re-test period in the proposed container.

Drug Product

Description of the product and Pharmaceutical Development:

The drug products (DP) is presented as a Size 1 capsule, light blue opaque cap with black imprint "BCX" and white opaque body with black imprint "150" containing white or almost white or off-white powder. All excipients are well known pharmaceutical ingredients and their quality is compliant with international standards. "There are no novel excipients used in the drug products formulation". The list of excipients is included in section 6.1 of the Summary of Product Characteristics (SPC). The compatibility of the drug substance with the excipients has been adequately demonstrated. The development of the formulation composition including the formulation design, choices of product components (e.g., properties of the drug substance, excipients, container closure system), and manufacturing process has been adequately described.

Manufacture of the product:

The manufacturing process of the drug products consists of four main steps: intra-granular blending and lubrication, dry granulation, final blend and encapsulation. The process is considered to be a standard manufacturing process. The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Process controls with their control limits for the finished product manufacturing process have been provided and accepted.

Product control:

The drug products specifications (release and shelf life) include appropriate tests for this kind of dosage form: identification, description, assay, degradation products, content uniformity, dissolution, water content and microbial limits. All methods and acceptance criteria included in the drug products specifications have been described and justified and accepted. The analytical methods used have been adequately described and non-compendial methods appropriately

validated in accordance with the international guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis:

Batch analysis data and CoA have been presented by the drug products manufacturer demonstrating compliance of six pilot scale batches with the drug products specification.

Container Closure System:

The primary packaging is a Pentapharm® ACLAR® PA 200/02 rigid barrier polyvinylchloride (PVC) film and Amcor push-through blister lidding. The materials comply with pharmacopeia and regulatory requirements. The choice of the container closure system has been validated by stability data and it is adequate for the intended use of the product. The secondary packaging is a carton box.

Stability of the product:

Stability data was provided on six pilot scale batches of drug products from the proposed manufacturer stored in the intended commercial package for 24 and 36 months under long term conditions 25°C/60%RH and 30°C/65%RH, and on six pilot scale batches for 6 months under accelerated conditions 40 ºC / 75% RH according to the SFDA Guidelines for Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products. Photostability and stress testing have been performed. The following parameters were tested: identification, description, assay, degradation products, dissolution, water content and microbial limits. All batches remained stable at long-term, photostability, and stress conditions, and no significant changes or out-of-spec trends were observed. The stability results indicate that the drug products manufactured by Catalent, USA and Patheon, USA is sufficiently stable. The stability results justify the proposed shelf life of 36 months in the proposed container.

Clinical Aspects

The clinical development program for Orladeyo consisted of one pivotal phase 3 clinical studies: Study BCX7 353-302 for the efficacy and safety study and 2 supportive phase 2 studies for long-term safety and efficacy (BCX7 353-203 and BCX7 353-204).

Summary of the clinical studies presented hereafter:

- BCX7 353-302: a randomized, double blind, placebo controlled, parallel group, 3- part study in subjects with Type I or II HAE. To determine the efficacy of prophylactic berotralstat 110 and 150 mg administered once daily (QD) for 24 weeks compared to placebo and to assess the safety and tolerability. A total of 121 subjects were randomized and the rate of investigator-confirmed HAE attacks during entire 24-week treatment period was assessed as primary endpoint.

- BCX7 353-203: a randomized, double-blind, placebo-controlled, dose-ranging, parallel-group, multicenter study to evaluate the efficacy, safety, tolerability, PK, and PD of berotralstat as a preventative treatment to reduce the frequency of attacks in subjects with HAE over a 28-day period. 77 subjects were included. The primary endpoint was the number of confirmed HAE attacks.
- BCX7 353-204: an ongoing 2-arm, open-label, multicenter study to evaluate the long-term safety and effectiveness of daily oral 110 and 150 mg berotralstat in subjects with Type 1 or 2 HAE who either had participated in a previous berotralstat study or were berotralstat-naïve and expected to derive benefit from an oral treatment to prevent angioedema attacks. 227 subjects were enrolled through the data cutoff date for this application. The number and percentage of subjects with treatment-emergent adverse events were assessed as primary endpoint.

  The clinical pharmacology, efficacy and safety results from the aforementioned studies were assessed by the SFDA efficacy and safety department. Based on the review of the submitted evidence, the benefit/risk balance of Orladeyo is considered positive. Therefore, we recommend the approval of the marketing authorization of Orladeyo.

Product Information

The approved Summary of Product Characteristics (SPC) with the submission can be found in Saudi Drug Information System (SDI) at: https://sdi.sfda.gov.sa/

The date of revision of this text corresponds to that of the Saudi PAR. New information concerning the authorized medicinal product in question will not be incorporated into the Saudi PAR. New findings that could impair the medicinal product's quality, efficacy, or safety are recorded and published at (SDI or Summary Saudi-PAR report).

For inquiry and feedback regarding Saudi PAR, please contact us at Saudi.PAR@sdfa.gov.sa