الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Saudi Public Assessment Report

(Summary Report)

Takhzyro®

Type of Product: Monoclonal Antibody.

Active Pharmaceutical Ingredient(s): LANADELUMAB.

ATC code: QB06AC.

Dosage Form: Solution for injection.

Dosage Strength: 300 mg.

Pack Size: 2 ml.

Shelf life: 24 months.

Storage Conditions: Store in a refrigerator (2°c – 8°c).

Reference Product in SA (if applicable): NA.

Marketing Authorization Holder: Takeda Pharmaceuticals International AG.

Manufacturer: Catalent Indiana LLC formerly Cook Pharmica LLC.

Registration No.: 2406200100 – 2710222830.

Date of Decision: Approved on 13/12/2019.

Proposed Indications: Routine prophylaxis to prevent hereditary angioedema (HAE) attacks in patients 12 years and older.

Product Background

Takhzyro® (Lanadelumab) is considered as a new biologic orphan medicine for Saudi regulatory purposes (This means that it was developed for use against a rare disease), this product is qualified to follow the SFDA's regular regulatory pathway.

The SFDA approved Takhzyro® for marketing in Saudi Arabia based on a review of the quality, safety and efficacy as summarised hereinafter:

Quality Aspects

The proposed medicine quality assessment undertaken to meet the last version of SFDA's Data Requirements for Human Drugs Submission and relevant *ICH guideline*. The submission included a complete quality information about the drug substance and drug products that grante the sound quality of the entire shelf-life.

The drug substance (Lanadelumab) is a recombinant, fully human, IgG1, kappa light chain, monoclonal antibody expressed in Chinese hamster ovary (CHO) cells culture in a fed-batch mode and purified through a series of chromatographic, filtration and buffer exchange steps fully manufuctured and controlled by Rentschler Biopharma SE, Laupheim, Germany. The manufacturing process has a defined set of controls. The critical process parameters (CPPs) are considered with a proven acceptable ranges (PARs). The criticality of each process parameter and selection of in-process controls (IPCs) to assure process roubostness and reproducibility, process control was determined in accordance with *ICH Q8, Q9 and Q10 guidelines* using a risk-based approach based on process characterization data and platform knowledge. Detailed information on CPPs, IPCs and their corresponding acceptable ranges for the cell culture process, harvest steps and purification steps of the lanadelumab process has been provided.

The raw materials used in the lanadelumab manufacturing process are routinely tested or accepted based on the Certificate of Analysis from approved suppliers.

The biological activity of lanadelumab proved to be occurred through binding of complementarity determining regions (CDRs) with plasma kallikrein to occlude the active site and inhibit proteolysis of the endogenous substrate, high molecular weight kininogen (HMWK), thereby attenuating the generation of bradykinin, the potent vasodilator and mediator of hereditary angioedema pathology.

There are no issues pertaining to drug substance and drug product stability. There are no issues pertaining to drug substance and drug product specifications which found to be in compliance with the requirements of *ICH Q6B guidelines* and sufficiently justified with clarification of ommition of a number of test parameters from the routine specifications which has no effect on the product quality testing. All analytical procedures were validated in accordance with *ICH Q2 guidlines*.

The drug product is a sterile preservative-free solution for subcutaneous administration at a concentration of 150 mg/mL provided in one dosage strength: 300 mg. Each 300 mg vial is filled with a nominal volume of 2.0 mL of drug product. The composition of lanadelumab drug product (per 2.0 mL) is Sodium phosphate dibasic, Citric acid monohydrate, L-Histidine, Sodium chloride and Polysorbate 80 and Water for injections. Lanadelumab is stable in the current formulation under the specified manufacturing, shipping, and storage conditions. The drug product is manufactured by sterile filtration and aseptic filling of the drug substance into vials after thawing, pooling, and mixing, with no additional excipients added. The excipients and their functions in the drug product are provided. All the excipients comply with pharmacopeia monographs and they are commonly used in parenteral protein solutions. The drug product manufacturing process development has been fully described and controlled accordingly through identification of process parameters (PP) and (IPC) that have been established to ensure consistent process performance and product quality. Five full-scale batches of lanadelumab drug product were produced at the commercial manufacturing facility in accordance with a pre-approved process performance qualification (PPQ) protocol, which included prospective acceptance criteria for determining acceptable performance of the process validation runs.

The proposed commercial shelf life for lanadelumab drug product is 24 months at 5°C±3°C. All results from the primary stability lots submitted covered the entire shelf-life testing points and support the proposed shelf life, since the selected test parameters confirming the product quality and the provided results with no out of specification results.

Clinical Aspects

Efficacy and Safety

- The clinical development program for Takhzyro consisted of two efficacy and safety clinical studies: DX-2930-03 (Pivotal, HELP Study), DX-2930-04 (HELP Study Extension™)

Summary of the clinical studies presented hereafter:

- **1: DX-2930-03 (Pivotal, HELP Study):** This is a phase III, multicenter, randomized, double-blind, placebo-controlled efficacy and safety study. The primary objective was to evaluate DX-2930 for long-term prophylaxis against acute attacks of hereditary angioedema (HAE), while the secondary objective was to evaluate the safety of repeated subcutaneous (SC) administrations of lanadelumab. The study population were > 12 years of age with a confirmed diagnosis of HAE (Type I or II) and who experienced at least 1 investigator-confirmed attack per 4 weeks during the run-in period. The screened subjects were 159, of these subjects, 126 were randomized to 1:1:1 ratio to one of 3 dose regimens: 150 mg every 4 weeks (28 subjects), 300 mg every 4 weeks (29 subjects), or 300 mg every 2 weeks (27 subjects), and 41 subjects to the placebo arm. Out of the eligible subjects a 125 received at least 1 dose of the study treatment. The number of investigator-confirmed HAE attacks was a direct way to evaluate efficacy for the primary endpoint from the period (Day 0 through Day 182).

- **2: DX-2930-04 (HELP Study Extension™):** This is an open-label, long-term safety and efficacy extension study of Study DX-2930-03, to evaluate the investigational medicinal product, lanadelumab, in preventing acute angioedema attacks in patients with Type I and Type II HAE. Two types of subjects were enrolled into this study, the subjects who rolled over from Study DX-2930-03 and the subjects who were nonrollovers (ie, were not participants in Study DX-2930-03). Overall, 212 subjects were treated in this study, including 109 subjects who entered as rollover subjects from DX-2930-03 and 103 nonrollover subjects; all were included in the safety population. For the primary endpoint, the planned duration of this study significantly extended the total period of subjects exposure to study drug, thereby enabling an evaluation of the long-term safety of repeated SC administrations of lanadelumab in preventing HAE attacks.

- 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 Takhzyro is considered positive. Therefore, we recommend the approval of the marketing authorization of Takhzyro.

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