Saudi Public Assessment Report

(Summary Report)

Vistalvy®

Type of Application: New drug application.

Type of Product: New biosimilar.

Active Pharmaceutical Ingredient(s): Adalimumab.

ATC code: L04AB04.

Dosage Form: Solution for injection.

Dosage Strength: 40 mg/ 0.8 ml.

Pack Size: 1 ml.

Shelf life: 36 months.

Storage Conditions: Store at (2 – 8) °C, in the outer carton to protect from light. Do not freeze.

Reference Product in SA (if applicable): Humira®

Marketing Authorization Holder: Jamjoom Pharmaceuticals Company.

Manufacturer: Cadila Healthcare Limited, Ahmedabad-382213, Gujarat, India.

Registration No.: NA (rejected).

Decision and Decision Date: Rejected.

Proposed Indications: Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis and Crohn's disease.

Product Background

Vistalvy® is considered as a new biosimilar drug for SFDA purposes, it had been developed as a biosimilar product to Humira® (reference medicinal product containing adalimumab as an active substance).

The SFDA rejection for Vistalvy® (Adalimumab 40 mg/0.8ml) is based on the review of the quality, safety and efficacy which summarised hereinafter:

Quality Aspects

The quality assessment was undertaken to meet the last version of *GCC Data Requirements for Human Drugs Submission.* The submitted quality data included information pertaining to the quality of drug substance, drug product and comparability studies. The active ingredient is produced by cell culture using Chinese Hamster Ovary (CHO) cells in media with no human or animal-derived components. Expansion of the CHO cell culture from a single vial of the cell bank is propagated following typical monoclonal antibodies manufacturing process, the manufacturing activities of Adalimumab drug substance and drug product are carried out according to approved well control and validated processes as concluded by the SFDA quality reviewer team.
Multiple batches/lots of the candidate biosimilar drug product and reference product, HUMIRA® sourced from EU and US territories, characterized in a side-by-side manner for key quality attributes including physicochemical, structural and functional/biological properties of adalimumab using a comprehensive set of state-of-the-art analytical techniques to demonstrate analytical similarity all the provided comparability exercises well assessed and accepted. The real-time stability data demonstrates that the commercial scale batches of Adalimumab drug substance and drug product are stable till the proposed shelf life and storage conditions.
There are no issues pertaining to drug substance and drug product manufacturing process, comparability studies or stability. However, minor issues related to drug substance and drug product specifications and analytical procedures required more clarifications from the applicant.

Clinical Aspects

The clinical development program for Vistalvy consisted of two randomized, double-blinded, parallel-group trials: one phase I pharmacokinetic (BA1786163) study, and one phase III safety and efficacy (ADA.12.002.01. PROT) study.

Summary of the clinical studies presented hereafter:

- 1: Study (BA1786163), A phase1, randomized (1:1), double-blind, single dose, two-arm, parallel study to compare the pharmacokinetics (PK), immunogenicity and safety of Vistalvy and Humira. 154 healthy subjects were enrolled and randomized to either Vistalvy (n=77) or Humira (n=77). The primary endpoints were the area under the serum

concentration versus time curve from zero to the last quantifiable concentration (AUC_t), the area under the serum concentration-time curve from time 0 to infinity (AUC_i), and the maximum observed serum concentration over the specified time span (C_{max}).

- 2: Study (ADA.12.002.01. PROT.), A phase III, multicentric, prospective, randomized (1:1), double-blind, active-controlled parallel arm to evaluate the efficacy, tolerability and safety of Vistalvy and Humira in combination with methotrexate in patients with moderate to severe rheumatoid arthritis (n=120 subjects (60 per treatment group). The primary endpoint was the proportion of patients with an American College of Rheumatology (ACR) 20 response in both treatment groups at day 84 as compared to baseline.

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 Vistalvy is considered negative due to major design and statistical concerns in the phase III trial. The main flaws lays in its duration, sample size, and the statistical method. The study duration is considered short and the justification provided by the applicant was insufficient, A 12-week duration could be adequate to determine the similar reaching to efficacy plateau. However, the applicant needs to compare the long-term efficacy and anti-drug antibody (ADA) formation which is known to be accompanied by increased clearance and reduced exposure, as well as possible loss of efficacy. The study included only 120 patients with rheumatoid arthritis. This sample size is not enough to examine the clinical safety and efficacy. The reviewer believes that small sample size is due to the wide delta margin [28.5%]. The applicant's justification of the using this delta margin was unsatisfactory and not based on clinical judgement. In addition, the comparability was assessed using p-value only which is not a recommended approach to establish similarity in biosimilars, the applicant claimed the conventional method of testing equivalence hypotheses two, one-sided tests (TOST) was performed. However, this method was not pre-specified and described in the planned protocol and not provided in the clinical study report. Therefore, we recommend against the approval of the marketing authorization of Vistalvy.

Product Information

In light of the negative recommendation, the summary of product characteristics, labelling and package leaflet are not available at this stage.

The date of revision of this text corresponds to that of the Saudi PAR. The Saudi public assessment report (Saudi PAR): provides information for public about the evaluation of medicines submitted to have marketing authorization in Saudi Arabia and the considerations that led the SFDA to approve or not approve medicine authorization. For inquiry and feedback regarding Saudi PAR, please contact us at Saudi.PAR@sdfa.gov.sa