Saudi Public Assessment Report

(Summary Report)

Truvelog®

Type of Application: New Drug Application.

Type of Product: New Biosimilar Drug.

Active Pharmaceutical Ingredient(s): Insulin Aspart.

ATC code: A10AB05.

Dosage Form: Solution for injection in multiple use disposable pre-filled pen.

Dosage Strength: 100 U/ml.

Pack Size: 3 ml.

Shelf life: 24 Months.

Storage Conditions: Store in a refrigerator (2°C -8°C), protected from light.

Reference Product in SA (if applicable): NovoLog/ NovoRapid.

Marketing Authorization Holder: Sanofi Aventis group.

Manufacturer: Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany.

Registration No.: 2306222250.

Decision and Decision Date: Approved on 8/03/2022.

Proposed Indications: Truvelog is indicated for the treatment of diabetes mellitus (DM) in adults, adolescents and children aged 1 year and above.

Product Background

This product is considered as new biosimilar drug for Saudi regulatory purposes. Furthermore, this product is qualified to follow the SFDA's normal submission regulatory pathway.

The SFDA approval for Truvelog® (Insulin Aspart 100 mg/ml) is based on a review of the quality, safety and efficacy as summarized hereinafter:

Quality Aspects

Truvelog® quality assessment was undertaken to meet the last version of *GCC Data Requirements for Human Drugs Submission* . The submission included full information about the drug substance (DS). Insulin Aspart DS is a 2-chain peptide containing 51 amino acids which are connected via disulfide bonds; the primary structure is identical to human insulin except for the aspartic acid at position 28 of the B-chain instead of proline produced by recombinant DNA technology using Escherichia coli as a host cell for the expression plasmid. A detailed manufacturing process which consists of 14 steps is given to assure a reliable removal of related impurities/substances throughout the chromatographic steps of the downstream process, all ranges for operating parameters are provided accordingly through process control and process validation which demonstrates from the submitted results that process control within the narrative description to ensure consistent production. Detailed information on raw materials is provided showing that no materials of human or animal origin are used in the drug substance, and no antibiotics are added throughout the fermentation process. Structure confirmation of Insulin Aspart has been carried out on batches manufactured by Sanofi with well-known analytical techniques. Based on the quality target product profile, critical quality attributes (CQAs) were identified , which are by definition "a physical, chemical, biological or microbiological property or characteristic to ensure the desired product quality" in accordance with *ICH Q6B* guidelines are tested at release and shelf life. The analytical procedures applied to control the drug substance (testing of appearance, identification, assay, purity, related proteins, water,E. coli proteins, single-chain precursor, residual solvents - 1-propanol and microbial contamination) and drug product (appearance of the solution, identification, Assay, impurities, sterility, endotoxins, particulate matter, Assay zinc, container closure integrity , extractable volume and functionality of the injector) provided in details through acceptable method validation.

The manufacturing procedure is based on conventional dissolving, pH-adjusting, sterile filtration (validated according to Ph. Eur. "Insulin Preparations, Injectable"), aseptic filling (The aseptic procedures are validated by media fills) and packaging techniques. Each container is filled with a volume in slight excess of the labeled volume to ensure withdrawal and administration of the labeled volume. The complete filling of each cartridge is controlled during the step "inspection of the filled containers". The test for extractable volume is performed at the time of release. During development, only minor modifications were made in the manufacturing process to adapt the process to the batch sizes and to the state of the art equipment, based on the assessment of the

manufacturing process including process changes and process control. The control strategy built on input material controls, process controls, monitoring of process parameters, and the final DP specifications had been confirmed to ensure consistent drug product quality. All excipients used for the manufacture of Insulin Aspart solution for injection of 100 U/mL are well known for parenteral, are of compendial grade, and comply with the respective pharmacopoeial specifications at the time of release. The suitability of selecting Metacresol and phenol as preservatives for the multidose formulation has been illustrated. They are used in a concentration to pass the preservative efficacy requirements of the pharmacopeias (eg, "Efficacy of antimicrobial preservation", Ph. Eur. 5.1.3, "Antimicrobial effectiveness testing", USP <51>) described for multidose containers. Adequate preservation after manufacturing and storage has been demonstrated during stability studies and complies with USP and Ph. Eur. criterion A requirements. Concentrations of 1.55 up to 1.72 mg/mL meta cresol and 1.35 up to 1.50 mg/mL phenol meet the requirements of USP for the tested formulations and fulfill criterion A of Ph. Eur. There are no issues pertaining to drug substance and drug product stability. In general, there are no issues pertaining to drug substance and drug product specifications. All analytical procedures are validated the drug substance tested against official primary standards for insulin aspart.
Sanofi is taking a multi-step approach with data generated from a physicochemical similarity assessment that has been performed to demonstrate the in vitro similarity of Insulin Aspart solution for injection of 100 U/mL Truvelog® to the reference medicinal product NovoRapid®.

Clinical Aspects

The clinical development program for Truvelog consisted of four clinical studies: two pharmacokinetic (PK) and pharmacodynamics (PD) trials (PDY12695) and (PDY15287), and one safety trial (PDY15083). In addition, a one-phase III study (EFC15081) was performed to assess the efficacy, safety, and immunogenicity of SAR341402 Truvelog to NovoLog/NovoRapid in patients with Type 1 and 2 Diabetes Mellitus (T1DM or T2DM).

Summary of the clinical studies presented hereafter:

- PDY12695: a randomized, double-blind, controlled, single-dose, 3-treatment, 3-period, 6-sequence crossover study to compare exposure and activity of SAR341402 to Novorapid® and Novolog® using the euglycemic clamp technique, in 30 subjects with type 1 diabetes mellitus for ≥12 months, using a 10-hour euglycemic glucose clamp procedure.
  The primary PK endpoint used were:
  - INS-C_{max}: maximum observed concentration
  - INS-AUC_{last}: area under the concentration versus time curve calculated using the trapezoidal method from time zero to the real-time t_{last}.
  - INS-AUC: values with a percentage of extrapolation >20% will not be taken into account in the descriptive statistics.

  While the primary PD endpoints were:

- $GIR\text{-}AUC_{0\text{-}12h}$: the area under the body weight standardized glucose infusion rate (GIR) time curve from 0 to 12 hours post-administration.

- PDY15287: a phase I, single-center, randomized, double-blind, controlled, 2-treatment, 2-period, 2-sequence, single-dose crossover study to assess and compare PK and PD of SAR341402 to NovoRapid in 40 healthy Japanese male subjects, using a 12-hour euglycemic glucose clamp procedure.

  The primary PK endpoints used were:

  - $INS\text{-}C_{max}$: maximum observed concentration.
  - $INS\text{-}AUC_{last.}$: values with a percentage of extrapolation >20% will not be taken into account in the descriptive statistics

  While the primary PD endpoints were:

  - $GIR\text{-}AUC_{0\text{-}10h}$: the area under the body weight standardized GIR time curve from 0 to 10 hours post-administration.
  - GIR_{max}: maximum smoothed body weight standardized GIR.

- EFC15081: a phase 3, a 6-month, multicenter, multinational, randomized, open-label, active-controlled, 2-arm parallel-group study followed by a 6-month safety extension period to demonstrate non-inferiority of SAR341402 versus Novolog®/Novorapid in 597 randomized patients with T1DM or T2DM. The primary endpoint was the change in Glycohemoglobin (HbA1c) (%) from baseline to week 26.

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

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