الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Saudi Public Assessment Report

(Summary Report)

Grasustek®

Type of Product: Biosimilar.

Active Pharmaceutical Ingredient(s): PEGFILGRASTIM.

ATC code: L03AA13.

Dosage Form: Solution for injection.

Dosage Strength: 10 mg\ml.

Pack Size: 0.6 ml.

Shelf life: 36 months.

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

Reference Product in SA (if applicable): Neulastim®

Marketing Authorization Holder: Jazeera Pharmaceutical Industries (JPI).

Manufacturer: USV Private Limited Daman.

Registration No.: 1511222904.

Date of Decision: Approved on 31/10/2022.

Proposed Indications:

Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

Product Background

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

The SFDA approval for Grasustek® (pegfilgrastim 6mg/0.6 ml) marketing authorization is based on a review of the quality, safety and efficacy as summarised hereinafter:

Quality Aspects

The quality review of Grasustek® is performed in compliance with the last version of SFDA Data Requirements for Human Drugs Submission guideline and relevant International Council for Harmonisation (ICH) quality guidlines. Grasustek® drug product administered as a solution for injection being developed as a proposed biosimilar to the authorized reference product Neulastim® containing pegfilgrastim as an active drug substance formulated with sodium acetate, D-Sorbitol, and polysorbate 80.

Drug Substance qualifications:

Pegfilgrastim belongs to the family of medications known as Granulocyte Colony Stimulating Factors (G-CSF). Pegfilgrastim is produced by covalent attachment of an mPEG (Methoxy Polyethylene Glycopropionaldehyde) molecule to the amino terminal methionine residue of the Filgrastim protein.

The manufacturing process for Pegflastrim consists of two main stages, the first stage is manufacturing of Filgrastim (Recombinant human granulocyte colony-stimulating factor through upstream and downstream processes), and the second stage is PEGylation of Filgrastim with Polyethylene glycol (PEG) aldehyde to produce Pegflastrim drug substance. The manufacturing process consistency is controlled throughout a set of a regulatory accepted critical and non-critical process parameters and in-process controls, as a part of overall control strategy in alignment with the *ICH Q8, Q9 and Q11guidelines*. Manufacturing process validation is performed employed three consecutive batches showed consistency in manufacturing process. The control strategy for raw material is acceptable. Characterization of structural and functional properties of Pegflastrim is conducted throughout a set of analytical procedures and showed a batch to batch consistency.

The quality of drug substance is controlled through a set of specification parameters comply with the *ICH Q6B guidelines,* the specification parameters and acceptance limits are justified and based on statistical analysis and understanding of the product critical quality attributes. The analytical methods are described in sufficient details and validated in accordance to *ICH Q2 (R2).*

Drug Product qualifications:

Drug product is supplied as a sterile, preservative-free solution, packaged in 1 ml type l clear, colourless sterile tubular siliconized borosilicated glass barrel assembled with 27G ½ inch

stainless-steel needle having flexible, grey rigid needle shield. Each single use prefilled syringe is equipped with UltraSafe™ passive needle safety guard, in blisters made of plain foil medical grade paper and PVC film and suitable for administration by subcutaneous injection, the components of the drug product are fully described. The excipients used in the final formulation of drug product are of Pharmacopeial quality. The choice of formulation components and solution pH is scientifically disused.

Narrative description of the manufacturing process along with in-process controls (IPC) are provided in the required details. Validation of the drug product manufacturing process is provided and support consistency of manufacturing process. The quality of drug substance is controlled through a set of specification parameters, the specification parameters and limits are justified and based on statistical analysis and product understanding. The analytical methods are described in sufficient details and validated in accordance to *ICH Q2 (R2).*

Sufficient number of drug product batches are tested according to the release specification in place at the time of testing shows that the product met the pre-defined specifications and showing production consistency.

There are no issues pertaining to drug substance and drug product stability, since an appropriate stability data have been generated from bactches manufuctured following the current commercial process filled in the packaging material intended for commercial use and following relevant international guidelines. The data show good stability of the finished product and support the shelf life of 36 months.

The approval for the Grasustek® as a biosimilar for Neulastim® is based on the assessment of the comparability exercise that proves the similarity of the product quality.

Clinical Aspects

Efficacy and Safety

The clinical development program for Grasustek® consisted of three clinical studies: two phase I pharmacokinetics and pharmacodynamics studies (PEGF/USV/P1/001 and PEGF/USV/P1/003) and one phase III efficacy and safety study (PEGF/USV/P3/003).

Summary of the clinical studies presented hereafter:

- 1: PEGF/USV/P1/001, randomised, double-blind, two-treatment, two-period, two-sequence, crossover study to compare the pharmacodynamics and pharmacokinetics of a single subcutaneous injection of Pegfilgrastim (Grasustek®) and Neulasta® in total of 156 healthy male and female subjects.
- 2: PEGF/USV/P1/003, randomised, double-blind, two-treatment, two-period, two-sequence, crossover study to compare the pharmacodynamics and pharmacokinetics of a single

subcutaneous injection of 2 mg Pegfilgrastim (Grasustek®) and 2mg Neulasta® in total of 64 healthy male subjects.

3: PEGF/USV/P3/003, randomized, multicentre, double-blind, active controlled, parallel group, equivalence study comparing the safety and efficacy of Grasustek® and Neulasta® in 254 female patients with breast cancer undergoing myelosuppressive chemotherapy.

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

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