EDA Assessment Report for human medicinal product

(Scientific Discussion)

Koselugo 10 mg & 25mg Hard Capsule

(Selumetinib 10mg & 25mg (As hydrogen sulphate))

Date: October 2024

I. Introduction

-Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Koselugo 10mg & 25 mg Hard Capsule from Astrazeneca Scientific Office.

-The product is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 2 years and above.

II. Quality Aspect

Drug Substance

- Full details of the S part have been submitted for evaluation.
- The drug substance is white to yellow powder. It is practically insoluble in water, slightly soluble in ethanol and acetonitrile. The active substance does not exhibit stereoisomerism. Selumetinib hyd-sulfate is monomorphic and all batches produced using the proposed manufacturing process have exhibited consistent X-ray powder diffraction patterns (XRPD).
- The synthesis of drug substance 3 steps with the formation of 3 intermediates was revised and found to comply with ICH Q11 (Development and Manufacture of Drug Substances).
- The drug substance is elucidated via Infrared Spectroscopy (IR), Nuclear Magnetic Resonance (H^1 NMR, C^{13} NMR), Mass spectroscopy, elemental analysis and X-ray powder diffraction (XRPD).
- The drug substance specifications are Description, Identification (IR & XRPD), Assay, Organic impurities, Residual solvents, Water content, Residue on ignition/sulfated ash and Particle size.
- Analytical methods were adequately described and validated. They were revised and found to be suitable for the required testing.
- The applicant provided batch analysis results of 10 batches. The results of all tests were well within the specification limits and batch data was found acceptable.
- Container closure system is Double Low-density polyethylene (LDPE) bags-food grade in foil-lined fibreboard drum. The specifications of the primary packaging component are provided including appropriate identification test for the primary packaging in contact with the drug substance. All these specifications are revised and found to be satisfactory.

- Stability of API is is submitted in accelerated 40°C±2°C /75% ± 5% RH and long-term storage conditions 25°C ±2°C /60% ± 5% RH and conclude the conformity of specifications during the shelf life and storage conditions. The retest period of the API is 84 months when stored below 30°C in the proposed container.

Medicinal Product

- **Product Description**

-The 10 mg capsule is presented as a white to off-white, banded capsule marked with 'SEL 10' printed in black ink.

-The 25 mg capsule is presented as a blue, banded capsule marked with 'SEL 25' printed in black ink.

- The excipients are: Vitamin E polyethylene glycol succinate, Hard hypromellose capsule shell, Imprinting ink
- Composition of capsule sealing band: Hypromellose, Purified water and Ethanol anhydrous (evaporated).
- Composition of white hypromellose capsule shell: Carrageenan, Potassium chloride, Titanium dioxide, Hypromellose
- Composition of Ink for white capsule shell: Shellac glaze, Iron oxide black, Propylene glycol and Ammonium hydroxide.
- Composition of blue hypromellose capsule shell: Carrageenan, Potassium chloride, FD&C Blue 2, Ferric oxide yellow, Titanium dioxide, Hypromellose,
- Composition of ink for blue capsule shell Ferric oxide red, Ferric oxide yellow, FD&C Blue 2 Aluminium lake, Carnauba wax, White shellac and Glyceryl monooleate
- The drug is packed in white, high-density polyethylene (HDPE) bottle with a child-resistant screw closure made of polypropylene (PP). The blue closure for the 25 mg and the white closure for the 10 mg are made of the same material and are equivalent. Inside the bottle is desiccant, enclosed within HDPE. An induction seal membrane provides tamper evidence.

- **Pharmaceutical development**, the development of the product has been described, the choice of excipients is justified and their functions explained. The formulation design focused on the development of a formulation which would preserve the chemical and physical stability of selumetinib hyd-sulfate during manufacture and for the shelf-life of the product while maintaining

the kinetic solubility advantage imparted during dissolution which is essential to achieve the desired in vivo bioavailability.

- Overall, the choices of the packaging, manufacturing process, compatibility, overage physicochemical properties and microbiological attributes are justified.
- Manufacturing process, the manufacturing process consists of melting, charging, mixing, encapsulation, capsule banding and packaging.
- The manufacturing process has been adequately validated on three full production scale batches per strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.
- Control of excipients, all excipients comply with USP, Ph Eur and European standard for coloring agents.
- Product specification includes Description, Identification, Assay, Degradation products, Dissolution and Uniformity of dosage units.
- The Analytical methods used in testing the finished pharmaceutical product were presented in the dossier. They were reviewed and found to be suitable for the required testing.
- Batch Analysis from the proposed production site were provided for clinical, primary stability and process validation batches of both strengths. The results of all tests were well within specification limits and batch data was found acceptable.
- Stability of finished pharmaceutical product is submitted in accelerated (40°C/75% RH) and long-term (25°C/60% RH & 30°C/75% RH) storage conditions. Detailed review was carried out for all stability indicating parameters and all found in line with their acceptance criteria throughout all time intervals. The provided stability study supports the proposed shelf life of 36 months when stored in white, high density polyethylene (HDPE) with a child-resistant (CR) cap made of polypropylene (PP) below 30°C.

- Additionally, the manufacturer submitted stability study to support the holding time of 24 months applied to selumetinib capsules 10 and 25 mg in the bulk pack (Double low-density polyethylene bags, twist tied. Desiccant containing silica gel is placed in between the first and the second bag then placed inside a container/drum) when stored below 25°C.

- Moreover, the manufacturer submitted an in-use stability study to simulate patient use. The data support an in-use period of at least 4 weeks at 25°C/60% RH and 30°C/75% RH when stored in the original bottle.

- Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies, a declaration/certificate of TSE/BSE free is submitted for shellac glaze, which is derived from an insect, used in the printing ink.

Summary basis of opinion:
From Chemistry, Manufacture and Control perspective, the main concerns found during the evaluation process were as follow:

For the Drug substance

-Brief description of the manufacturing process clarifying the reagents, solvents and catalysts used in the manufacturing process of selumetinib hyd sulfate should be presented.

-Elemental analysis to confirm the % of elements comprising the structure of selumetinib should be submitted.

For the Drug product:

-TSE/BSE Certificate of shellac glaze derived from an insect and used in the printing ink should be submitted.

The Quality of the drug product has been found satisfactory after:

-The drug substance manufacturer updated the description of the manufacturing process to include narrative description of the synthetic process (raw materials, solvents, catalysts and reagents) which was revised and found to be consistent with the submitted flow diagram.

-The drug substance manufacturer submitted elemental analysis, the actual% results were revised and found complying with the theoretical % results.

-The applicant provided a statement concerning shellac glaze that there is no BSE/TSE risk which is acceptable.

Recommendation:

Based on the review of CTD quality module and other supplementary documents; from the quality point, the product is approved.

III. Non-Clinical& Clinical Aspects

Introduction

- Selumetinib is a well-known active substance with established efficacy and tolerability.

- The product Koselugo, containing the active substance selumetinib, is used to treat pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) and symptomatic inoperable plexiform neurofibromas (PN).

- Neurofibromatosis type 1 (NF1) is a rare genetic disorder. It is caused by mutations in the so-called NF1 tumour suppressor gene, which codes for the tumour suppressor protein neurofibromin 1.

-Early signs of NF1 include café au lait spots and general hyperpigmentation of the skin that develop in the first two years of life. Plexiform (having the form of a network) neurofibromas (PN) occur in one third of patients with NF1.

- Superficial neurofibromas are benign and do not need to be removed unless they are causing problems. Surgical removal is the standard therapy for patients with PN. However, it is often not an option because of nerve involvement and the associated risk of nerve damage or severe bleeding.

- Since this is a rare, life-threatening disease, Koselugo has been authorised as an orphan drug. The term "orphan drug" is used to refer to important medicines for rare diseases.

Summary of the clinical studies submitted to EDA:

- **Efficacy & Safety Study**: Sprint Phase II, Stratum I: open-label single arm multi-center study on pediatric patients with NF1 & inoperable PN with PN-related morbidity at enrolment.

- **Safety, PK &Efficacy:** Sprint Phase I, open-label single arm, dose escalation, multi-center study on pediatric patients with NF1 & inoperable PN.

- **PK & Safety:** This was a phase 1, open label, single dose study to determine the rates and routes of elimination of a single dose of [14C]-selumetinib and its metabolites by assessment of concentrations of total [14C] radioactivity in blood and plasma, concentrations of selumetinib and N-desmethyl selumetinib in plasma and percent recovery of the radioactive dose in urine and faeces, A total of 6 healthy male volunteers, aged 50 to 65 years (inclusive), were recruited at 1 study center.

-Based on the clinical study of Koselugo Hard Capsule submitted to EDA, found to recommend the approval of the marketing authorization of product.