EDA Assessment Report for human medicinal product

(Scientific Discussion)

Litfulo 50 mg Hard Capsule

Ritlecitinib 50 mg (as Tosylate)

Date: July, 2025.

I. Introduction

-Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Litfulo Hard Capsule from Pfizer Biopharmaceuticals Egypt LLC.

-The product is indicated for the treatment of severe alopecia areata in adults and adolescents 12 years of age and older

II. Quality Aspect

Drug Substance

- Full details of the S part have been submitted for evaluation.
- The drug substance is white to off white to pale pink solid. Ritlecitinib tosylate is classified as a BCS class III active substance (high solubility and low permeability). Ritlecitinib tosylate is non-hygroscopic. Ritlecitinib tosylate exists as a single crystal form (Form 1) and no other polymorphs have been observed. Ritlecitinib tosylate has two asymmetric centers, giving four possible stereoisomers. The chiral pure (2S,5R) isomer is used in the finished product
- The synthesis of drug substance, which includes 4 synthetic steps with the formation of two intermediates, was revised and found to comply with ICH Q11 (Development and Manufacture of Drug Substances). The choice of the starting materials is adequately justified. A list of raw materials was provided with specifications. The proposed specifications for both intermediates were found acceptable.
- The drug substance is elucidated via IR Spectroscopy, Mass Spectrometry (MS), Nuclear Magnetic Resonance Spectroscopy (^{1}H NMR & ^{13}C NMR), Ultraviolet/Visible (UV/Vis) Spectrum and X-Ray Diffraction.
- The drug substance specifications are Identification by IR, Chiral Identification by LC, Assay (LC), Impurities (LC), Water Content, Residual Solvents (GC), Counter ion and Particle Size Distribution (Laser Diffraction).
- 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 4 commercial batches. The results of all tests were well within the specification limits and batch data was found acceptable
- The API is packed in two sealed, low density polyethylene (e.g. LDPE) anti-static liners then inserted into a high-density polyethylene (HDPE) drum.
- Stability of API 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 36 months when stored in the proposed container.

Medicinal Product

- **Product Description**

-Immediate release (IR) hypromellose (HPMC) opaque hard capsule containing 50 mg of ritlecitinib (as tosylate. Capsules are size #3 with yellow body and blue cap, the body is printed with “RCB 50” and the cap is printed with “Pfizer” in black.

-The product is packed in aluminum foil blisters with aluminum foil lidding.

-The excipients are Microcrystalline cellulose, Lactose Monohydrate, Crospovidone (Type A) and Glycerol Dibehenate.

-Composition of hard capsule shell: Hypromellose, Titanium Dioxide, Yellow Iron Oxide and Brilliant blue FCF – FD&C Blue 1.

- Composition of printing ink: Shellac, Propylene Glycol, Ammonia Solution concentrated, Black Iron Oxide and Potassium Hydroxide.

- **Pharmaceutical development**

-The development of the product has been described, the choice of excipients is justified and their functions explained. It was aimed to develop an immediate release dosage form containing ritlecitinib that meet the established Quality Target Product Profile (QTPP).

-Overall, the choices of the packaging, manufacturing process, compatibility, overage physicochemical properties and microbiological attributes are justified.

- **Manufacturing process**

-The manufacturing process consists of blending, screening, blending, encapsulation and packaging.

- **Control of excipients**

-All excipients comply with USP, Ph Eur and European standard for coloring agents.

- **Control of Drug Product**

-Product specification includes Appearance, Identification (LC & UV), Assay (LC), Degradation Products (LC), Dissolution (UV), Uniformity of Dosage Units by weight variation and Microbial Limits.

-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 and primary stability batches. The results of all tests were well within specification limits and batch data was found acceptable.

- **Container closure system**

-The drug product is packed in aluminum foil blisters with aluminum foil lidding then further placed in carton box. The aluminum foil blisters are composed of Oriented Polyamide/Aluminum Foil/Polyvinyl chloride (OPA/Al/PVC).

- **Stability**

-Stability of finished pharmaceutical product is submitted in accelerated (40°C/75% RH) and long-term (25°C/60% RH, 30°C/65% 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 30 months when stored in in the original package in order to protect from light.

- **Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies**

-A declaration/certificate of TSE/BSE free is submitted for lactose monohydrate used in the manufacture of Litfulo Hard Capsules.

- **Summary basis of opinion:**

From Chemistry, Manufacture and Control perspective, the main concern found during the evaluation process was as follow:
-Justification for the discrepancy in the control limit of some organic impurities in the drug substance between the two subsections 3.2.S.3.2 (impurities) and 3.2.S.4.1 (specifications).

The Quality of the drug product has been found satisfactory after:
-The drug substance manufacturer has updated the impurities subsection (3.2.S.3.2) to include the more restricted control limit of organic impurities thereby the control limits match with those in the specification subsection (3.2.S.4.1).

III. Non-Clinical& Clinical Aspects

Introduction

-Ritlecitinib is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature.

-Ritlecitinib is indicated for the treatment of severe alopecia areata in adults and adolescents 12 years and older. It is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, cyclosporine or other potent immunosuppressants.

*Summary of Listing of Clinical Studies:

- Study Title:

***Bioavailability (BA) Study Reports:**

-A Phase 1, Open-Label, Single-Dose 3-Way Crossover Study to Evaluate the Relative Bioavailability of a Solid Dose Formulation of Ritlecitinib Under Fasting Conditions and the Effect of a High Fat Meal on the Bioavailability of The Solid Dosage Formulation of Ritlecitinib in Healthy Participants.

***Comparative BA and Bioequivalence (BE) Study Reports:**

1-A Phase 1, Randomized, Open-Label, Cross-Over, Single Dose Study to Estimate the Relative Bioavailability of Candidate Capsule Formulations of Ritlecitinib Relative to Tablets in Healthy Participant.

2- A Phase 1, Randomized, Open-Label, Cross-Over, Single-Dose Study to Evaluate the Bioequivalence of Candidate Capsule Formulations of Ritlecitinib to Tablets and Estimate the Effect of High-Fat Meal on Bioavailability in Healthy Participants.

3- A Phase 1, Randomized, Open-Label, Cross-Over, Single Dose Study to Estimate the Relative Bioavailability of Pediatric Ritlecitinib Capsules and Spray Congealed Beads Relative to Adult Capsules in Healthy Adult Participants.

4- An Open Label, Phase 1, Two-Arm Study to Assess Target Occupancy and Functional Inhibition of JAK3 and TEC Kinases by Single Doses of Ritlecitinib in Healthy Adult Participants

***Based on the clinical study Litfulo 50 mg Hard Capsule submitted to EDA, found to recommend the approval of the marketing authorization of product.**