الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Saudi Public Assessment Report

(Summary Report)

Atectura®

Type of Application: New drug application.

Type of Product: New chemical entity.

Active Pharmaceutical Ingredient(s): Mometasone Furoate (indacaterol as acetate).

ATC code: R03AK.

Dosage Form: Inhalation powder, hard capsule.

Dosage Strength: 80,150 – 160,150 – 320,150 µg.

Pack Size: 30.

Shelf life: 24 Months.

Storage Conditions: Do not store above 30°C.

Reference Product in SA (if applicable): NA.

Marketing Authorization Holder: Novartis Europharm Limited.

Manufacturer: NOVARTIS Pharma Stein AG.

Registration No.: 2104221968 – 2104221969 – 2104221967.

Date of Decision: Approved on 29/03/2022.

Proposed Indications: Maintenance treatment of asthma in adults and adolescents 12 years of age and older not adequately controlled with inhaled corticosteroids and inhaled short-acting beta2-agonists.

Product Background

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

The SFDA approval for Atectura® (Mometasone Furoate 320,150 160,150 80,150 µg) is based on a review of the quality, safety and efficacy as summarised hereinafter:

Quality Aspects

Drug Substance

General Information:

Indacaterol acetate is a slightly hygroscopic, white to yellow or beige powder. it does have chirality. Polymorphism has been observed. The structure has been fully elucidated using several spectroscopic techniques.

Manufacture, characterization and process controls:

Indacaterol acetate is manufactured by Novartis Pharma Schweizerhalle AG, Switzerland and Novartis Integrated Services Limited-International Service Laboratory, Ireland through multiple steps chemical synthesis. A list of the catalysts, reagents and solvents used in the manufacturing process with identification of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) classification for solvents as well as the respective specifications has been submitted. The specifications for raw materials are acceptable. Potential and actual impurities were identified and assessed according to international guidelines and references on impurities.

Control of the drug substance:

The drug substance (DS) specification includes tests for assay, appearance, identification, related substances, water content, enantiomer by High Performance Liquid Chromatography (HPLC), residual solvents, sulphated ash, amorphous content, clarity of solution, colour of solution, assay of salt forming agent, particle size and microbial test. All methods and acceptance criteria included in the the drug substance specifications have been described, justified and accepted. Batch analysis data and CoA have been presented by the drug substance manufacturer demonstrating compliance of three commercial scale batches with the drug substance specification. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the international guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Container closure system:

The primary packaging is a polyethylene (PE) bag. The materials comply with pharmacopeia and regulatory requirements. The choice of the container closure system has been validated by stability data and it is adequate for the intended use of the product. The Secondary packaging is a PE/PETP/ALU/PETP bag.

Stability:

Stability data was provided on three pilot scale batches of the drug substance from the proposed manufacturer stored in the intended commercial package for 18 months under long term conditions 25ºC ±2 ºC/60% RH and 30ºC ±2 ºC/75% RH, and on three pilot scale batches for 6 months under accelerated conditions (40 ºC / 75% RH) according to the SFDA Guidelines for Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products. The following parameters were tested: assay, appearance, identification, related substances, enantiomer by HPLC, loss on drying, clarity of solution, colour of solution, specific surface area, amorphous content, particle size and microbial test. All batches remained stable at long-term conditions, and no significant changes or out-of-spec trends were observed. The stability results indicate that the drug substance manufactured by Novartis Pharma Schweizerhalle AG, Switzerland and Novartis Integrated Services Limited-International Service Laboratory, Ireland is sufficiently stable. The stability results justify the proposed re-test period in the proposed container.

Mometasone furoate:

Mometasone furoate is a white powder. Its solubility is low in water and high in polar organic solvents. It does have chirality. Polymorphism has been observed. The structure has been fully elucidated using several spectroscopic techniques.

Manufacture, characterization and process controls:

Mometasone furoate is manufactured by MSD International GmbH, Singapore through multiple-steps chemical synthesis. A list of the reagents and solvents used in the manufacturing process with identification of ICH classification for solvents as well as the respective specifications has been submitted. The specifications for raw materials are acceptable. Potential and actual impurities were identified and assessed according to international guidelines and references on impurities.

Control of the drug substance:

The drug substance specification includes tests for assay, appearance, identification, impurities, residual solvents, microbial test, loss on drying and specific optical rotation. All methods and acceptance criteria included in the drug substance specifications have been described, justified and accepted. Batch analysis data and CoA have been presented by the drug substance manufacturer demonstrating compliance of four commercial scale batches with the drug substance specification. The analytical methods used have been adequately described and non-compendial

methods appropriately validated in accordance with the international guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Container closure system:

The primary packaging is triple layer polyethylene bags with silica gel packaged and stored in plastic container. The materials comply with pharmacopeia and regulatory requirements. The choice of the container closure system has been validated by stability data and it is adequate for the intended use of the product.

Stability:

Stability data was provided on six batches of the drug substance from the proposed manufacturer stored in the intended commercial package for (36 months) under long term conditions (30ºC ±2 ºC/65% RH), and on six batches for 6 months under accelerated conditions (40 ºC / 75% RH) according to the SFDA Guidelines for Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products. The following parameters were tested: assay, appearance, impurities and moisture. All batches remained stable at long-term conditions, and no significant changes or out-of-spec trends were observed. The stability results indicate that the drug substance manufactured by MSD International Gmbh, Singapore is sufficiently stable. The stability results justify the proposed re-test period in the proposed container.

Drug Product

Description of the product and Pharmaceutical Development:

The drug product (DP) is presented as a Inhalation powder, hard capsule. All excipients are well known pharmaceutical ingredients and their quality is compliant with international standards “There are no novel excipients used in the drug product formulation”. The list of excipients is included in section 6.1 of the SPC. The compatibility of the drug substance with the excipients has been adequately demonstrated. The development of the formulation composition including the formulation design, choices of product components (e.g., properties of the drug substance, excipients, container closure system), and manufacturing process has been adequately described.

Manufacture of the product:

The manufacturing process of the drug product consists of five main steps: screening and blending, final blending, encapsulation, equilibration and packaging. The process is considered to be a standard manufacturing process.

The manufacturing process has been validated and It has been demonstrated and it is capable of producing the finished product of intended quality in a reproducible manner. Process controls with

their control limits for the finished product manufacturing process have been provided and accepted.

Product control:

The drug product specifications (release and shelf life) include appropriate tests for this kind of dosage form: assay, appearance of contents, appearance of shell, fine particle mass, degradation products, enantiomer, loss on drying, uniformity of delivered dose, uniformity of dosage units by content and microbial tests. All methods and acceptance criteria included in the drug product specifications have been described, justified and accepted. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the international guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis:

Batch analysis data and CoA have been presented by the drug product manufacturer demonstrating compliance of three commercial scale batches for each strength with the drug product specification.

Container closure system:

The primary packaging is a PA/AL/PVC (ALU/ALU) blister. The materials comply with pharmacopeia and regulatory requirements. The choice of the container closure system has been validated by stability data and it is adequate for the intended use of the product. The Secondary packaging is a carton box.

Stability of the product:

Stability data was provided on three commercial scale batches of drug product for each strength from the proposed manufacturer stored in the intended commercial package for 24 months under long term conditions (30°C/75% RH), and on three commercial scale batches for 6 months under accelerated conditions (40 ºCs / 75% RH) according to the SFDA Guidelines for Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products. Photostability has been performed on a one batche. The following parameters were tested: assay, appearance of contents, appearance of shell, fine particle mass, degradation products, enantiomer, loss on drying, uniformity of delivered dose and microbial tests.

All batches remained stable at long-term and Photostability conditions, and no significant changes or out-of-spec trends were observed. The stability results indicate that the DP manufactured by (Novartis Pharma Stein AG, Switzerland) is sufficiently stable. The stability results justify the proposed shelf life of 24 months in the proposed container.

Clinical Aspects

Efficacy and Safety

The clinical development program for Atectura consisted of four phase III safety and efficacy clinical studies: CQVM149B2301, CQVM149B2303, CQVM149B2302, and CQMF149A2210 in addtion to several PK/PD studies.

Summary of the clinical studies presented hereafter:

- CQVM149B2301: A multi-center, randomized, 52 weeks treatment, double blind, triple-dummy, parallel-group study to assess the efficacy and safety of QMF149 compared with mometasone furoate in patients with asthma including a total of 2216 subjects as of 21-Nov-2018 data cutoff date, subjects aged 12-75 with a primary endpoint analysis of trough FEV1 (forced expiratory volume in 1 second) at Week 26.
- CQVM149B2303: A multi-center, randomized, 12 weeks treatment, double blind study to assess the efficacy and safety of QMF149 (150/80 µg) compared with mometasone furoate (MF) Twisthaler® (200 µg) in adult and adolescent patients with asthma, included a total of 802 subjects aged 12-75 with a primary endpoint analysis of trough FEV1.
- CQVM149B2302: A multicenter, randomized, 52-week, double blind, parallel group, active-controlled study to compare the efficacy and safety of QVM149 with QMF149 in patients with asthma, included a total of 3092 subjects aged 17-78 with a primary endpoint analysis of trough FEV1 at Week 26.
- CQMF149A2210: A randomized, multi-center, parallel group, double blind, study to assess the safety of QMF Twisthaler® (500/400 µg) and mometasone furoate Twisthaler® (400 µg) in adolescent and adult patients with persistent asthma, included a total of 1508 subjects aged 12-70 with a primary endpoint of safety analysis of QMF149 500/400 µg o.d. Twisthaler compared to MF 400 µg o.d. Twisthaler.

The clinical pharmacology, efficacy and safety results from the aformentioned studies were assessed by the SFDA efficacy and safety department. The evaluation did not identefy major safety concerns and efficacy was demonestrated across the clinical development program. Based on the review of the submitted evidence, the benefit/risk balance of Atectura® is considered positive. Therefore, we recommend the approval of the marketing authorization of Atectura®.

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