Refusal Public Assessment Report for Human Medicinal Products

Glycopyrronium 12.5 mcg (as Glycopyrronium Bromide 15.6 mcg) Powder for Inhalation

1. Overview:

Based on the review of safety & efficacy data
The Egyptian Drug Authority (EDA) refused granting the marketing authorization for the medicinal products containing Glycopyrronium 12.5 mcg (as Glycopyrronium Bromide 15.6 mcg) as powder for Inhalation.

- The application for Glycopyrronium 12.5 mcg (as Glycopyrronium Bromide 15.6 mcg) powder for Inhalation is refused, as the submitted data does not meet the requirements for marketing authorization for submitted product with the submitted concentration.

2. Legal basis for application:

The application was submitted to the **Scientific Evaluation Unit for Pharmaceutical Products and Drug Development** in accordance to **EDA Chairman decision 450/2023 (Case 1)**.

3. Applied Scientific Information

3.1 Pharmacotherapeutic group

An anticholinergic

3.2 Therapeutic indication

The applicant has proposed the following therapeutic indications for Glycopyrronium 12.5 mcg (as Glycopyrronium Bromide 15.6 mcg) as powder for Inhalation in Hard Capsule:

For the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

3.3 Therapeutic dose:

- **The Proposed dosage regimen is:**
  Use 1 capsule inhaled through the NEOHALER inhaler 2 times each day
  (1 capsule in the morning and 1 capsule in the evening).

3.4 Mechanism of action:

Glycopyrronium is a long-acting muscarinic antagonist which is often referred to as an anticholinergic.
It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, glycopyrrolate exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation.
The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations.
In preclinical in vitro as well as in vivo studies, prevention of methacholine-induced broncho constrictive effects was dose-dependent and lasted longer than 24 hours.
The clinical relevance of these findings is unknown. The bronchodilation following inhalation of glycopyrronium is predominantly a site-specific effect.

3.5 Warnings associated with the drug:

- The applicant provided a list of warnings for the use of submitted product, which include:

1 Deterioration of Disease and Acute Episodes
2 Paradoxical Bronchospasm
3 Immediate Hypersensitivity Reactions
4 Worsening of Narrow-Angle Glaucoma
5 Worsening of Urinary Retention

4. Scientific Assessment:

* The applicant provided data about safety and efficacy of Glycopyrronium 12.5 mcg based on published literature

Based on the review of available applied data for the submitted product, the following has been found:

- The applicant did not submit sufficient recent clinical data or scientific evidence supporting the efficacy of Glycopyrronium for treatment of COPD with the applied concentration (12.5 mcg) as monotherapy &with the applied dosage regimen submitted by company (twice daily) .
- The applicant failed to provide a scientific justification for the applied low sub-therapeutic concentration of Glycopyrronium 12.5 mcg compared to the reference concentration 50 mcg which will lead to Misuse where the therapeutic dose is below the therapeutic level (sub-therapeutic)
- The applicant failed to submit any therapeutic advantage for Glycopyrronium in the submitted concentration over existing alternatives with standard dose (Glycopyrronium 50mcg/ once daily)

5. By Searching in Reference countries approved by Technical committee of drug control it was found that:

The International regulatory status in the reference countries & scientific reference at the time of submission is as the following:

*Glycopyrronium 12.5 mcg (as Glycopyrronium Bromide 15.6 mcg) is not available alone or in combination in reference countries & scientific reference

****Glycopyrronium is available alone in different concentartions as follows:**

- **In TGA, MHRA, Austria, Switzerland, Japan, Singapore, Newzealand, Canada, France, Sweden & Netherlands:**

Trade Name: Seebri Breezhaler
Generic Name: 63 mcg Glycopyrronium Bromide eq. to 50 mcg Glycopyrronium.
(each capsule contains 63 mcg glycopyrronium bromide equivalent to 50 mcg glycopyrronium. The delivered dose (the dose that leaves the mouthpiece of the SEEBRI BREEZHALER inhaler) is equivalent to 44 mcg glycopyrronium)
Dosage Form: Powder for inhalation in capsule
Company: Novartis

- **In BNF 85:**

Trade Name: Seebri Breezhaler
Generic Name: Glycopyrronium bromide 55 microgram
(each capsule delivers 55 micrograms of glycopyrronium bromide (equivalent to 44 micrograms of glycopyrronium)
Dosage Form: Inhalation powder capsules with device.
Company: Novartis

****Glycopyrronium is available in different concentration as combination as follows:**

In EMA:
Trade Name: Trydonis 87 micrograms/5 micrograms/9 micrograms
Generic Name: Each delivered dose (the dose leaving the mouthpiece) contains :
87 micrograms of beclometasone dipropionate + 5 micrograms of formoterol fumarate dihydrate + 9 micrograms of glycopyrronium (as 11 micrograms glycopyrronium bromide).
Dosage Form: Pressurised inhalation, solution
Dose: The recommended dose is two inhalations twice daily.
Company: Chiesi Farmaceutici S.p.A.

In FDA as:
Trade name: Bevespi Aerosphere
Generic name: Glycopyrronium Bromide 9 mcg + Formetrol Fumarate 4.8 mcg
Dosage form: Inhalation aerosol.
Dose: Two inhalations equal one dose.
Company: Astrazeneca Pharmaceuticals LP, Wilmington

****N.B.: Glycopyrronium 12.5mcg (Glycopyrrolate 15.6 mcg) was available in FDA but discontinued as follow** :
Trade Name::Seebri™ Neohaler® (glycopyrrolate) inhalation powder, for oral inhalation
Generic Name: contain 15.6 mcg of glycopyrrolate (equivalent to 12.5 mcg of glycopyrronium) inhalation powder for use with the Neohaler
Company :Novartis
Indication : for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)
Dose:For oral inhalation only. with the NEOHALER device. The inhalation of the powder contents of one SEEBRI capsule (15.6 mcg) twice-daily

5.1 Indication & dose :
Acc. To TGA:
Once-daily maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD).

6. Conclusion:

Based on Scientific assessment of the applied medicinal product and submitted data by the applicant the following conclusions were established as follow:

- **Insufficient Clinical Data:**

There is no sufficient recent scientific or clinical data supporting the efficacy for this specific concentration as Monotherapy in treatment of COPD.

More research &studies are needed for submitted products in applied concentrations to be clinically tested for efficacy in relieving symptoms of patients with chronic obstructive pulmonary disease (COPD)

- **Sub-therapeutic concentration**

The applied concentration (12.5mcg) as twice daily dose regimen is sub-therapeutic compared to reference product with Glycopyrronim 50mcg which lead to increasing the risk of uncontrolled and progressive disease

- **Less patient compliance & dosing error :**

The applied dose regimen (twice daily) in submitted concentration (12.5mcg) is associated with less patient adherence & a high risk of dose omission (forgetting to take a dose) compared to standard dose regimen for Glycopyrronium 50mcg (once daily)

- **No Therapeutic advantage :**

Absence scientific data demonstrate that Glycopyrronium in the submitted concentration & dosage regimen has any therapeutic advantage over existing alternatives with standard dose (Glycopyrronium 50mcg)

6.1 Scientific Evaluation Committee has adopted a **negative opinion**, recommending refusal of marketing authorization for the medicinal product containing **Glycopyrronium 12.5 mcg (as glycopyrronium Bromide 15.6 mcg) Powder for Inhalation**

6.2 Technical Committee of Drug Control: refused granting the marketing authorization for the medicinal products containing **Glycopyrronium 12.5 mcg (as glycopyrronium Bromide 15.6 mcg) Powder for Inhalation in Hard Capsule**

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