Refusal Public Assessment Report for Human Medicinal Products

Chlorpheniramine maleate 2mg/ml + Dexamethasone 0.5mg/ml as Oral dosage form

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 Chlorpheniramine maleate 2mg/ml + Dexamethasone 0.5mg/ml as Oral dosage form

- The application for Chlorpheniramine maleate 2mg/ml + Dexamethasone 0.5mg/ml is refused, as the submitted data does not meet the requirements for marketing authorization for submitted product with the submitted concentrations.

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 3)**.

3. Applied Scientific Information

3.1 Pharmacotherapeutic group

Corticosteroid & Potent antihistamine (H1-antagonist)

3.2 Therapeutic indication

The applicant has proposed the following therapeutic indications for Chlorpheniramine maleate and Dexamethasone Syrup:

- The combination of chlorpheniramine maleate and dexamethasone is indicated for the treatment of the following conditions:
- **Allergic Conditions**: Effective in reducing symptoms associated with allergies such as itching, hives, and allergic rhinitis.
- **Respiratory Diseases**: Provides relief in conditions like asthma and chronic obstructive pulmonary disease (COPD), where inflammation and allergic reactions are present.
- **Common Cold:** Helps alleviate symptoms such as runny nose, sneezing, nasal congestion, and itchy throat, providing comprehensive relief from cold-related discomfort.
- **Arthritis and Rheumatic Disorders**: Reduces inflammation and pain in musculoskeletal conditions such as rheumatoid arthritis and osteoarthritis.
- **Rhinitis (Allergic and Non-Allergic)**: Alleviates symptoms of nasal congestion, sneezing, and postnasal drip.
- **Allergen-Induced Reactions**: Controls acute allergic responses triggered by exposure to environmental allergens like pollen, dust, and animal dander.
- **Itchy Throat/Skin**: Reduces symptoms of itching and discomfort associated with various allergic and dermatologic conditions.

3.3 Therapeutic dose:

*** Chlorpheniramine Maleate**

Usual adult dose: 4 mg every 4-6 hours (maximum daily dose: 24 mg).

*** Dexamethasone**

Typical doses vary widely based on indication: 0.5 to 9 mg/day.

- **The Proposed dosage regimen is:**
  * 2-4mL, 2-4 times a day, based on tolerability and effectiveness.
  * Do not exceed 12 mL/day due to the chlorpheniramine limit.

3.4 Mechanism of action:

This dual mechanism allows for both symptomatic relief and control of the inflammatory cascade, providing comprehensive management of allergic and inflammatory conditions.

4. Scientific Assessment:

* The applicant provided data about safety and efficacy of Chlorpheniramine maleate and Dexamethasone based on published literature as Monotherapy with referenced concentrations in different dosage forms (oral solution or tablets).

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

- The applicant did not submit clinical data or scientific evidence supporting the safety & efficacy of the fixed-dose combination (FDC) of Chlorpheniramine maleate and Dexamethasone in the applied concentrations.
- The applicant failed to provide a scientific justification for the applied high concentrations of Chlorpheniramine maleate and Dexamethasone which lead to exposure of adverse effects of each active ingredient. So, the safety profile for the applied combination is not confirmed.
- The applicant failed to submit additive Therapeutic advantage for fixed dose combination of Chlorpheniramine maleate 2mg/ml + Dexamethasone 0.5mg/ml over existing alternatives.

**** The Scientific rational applied by the company was as follows:**

- Mechanistic Synergy
- Clinical Advantages of the Combination
  - Comprehensive Symptom Relief
  - Faster Onset with Sustained Effect
- Reduction in Dosage and Side Effects
- Broader Spectrum of Action
- Combined Dosing Flexibility including Therapeutic Balance & Ease of Use
- Safety Considerations

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:

**** The fixed-dose combination of Chlorpheniramine and Dexamethasone is not available in any reference country.**

- So, there is no reliable data about safety and efficacy for the applied medicinal product with these concentrations " Chlorpheniramine maleate 2mg/ml + Dexamethasone 0.5mg/ml". as oral dosage form

**** Each active Ingredient available as:**

5.1 Dexamethasone as Oral Elixir, Solution:

0.5mg/5ml, 2mg/5ml in:
FDA, Canada, Austria, Singapore

*** According to Canada:**

5.1.1 Indication:

is used orally in the management of disorders responsive to adrenocortical hormone therapy such as:

- Allergic States: Control of severe or incapacitating allergic conditions not responsive to adequate trials of conventional treatment
- Rheumatic Disorders: As adjunctive therapy for short term administration during an acute episode or exacerbation of psoriatic arthritis, rheumatoid arthritis
- Dermatologic Diseases: Pemphigus, bullous dermatitis herpetiformis, severe erythema multiform (Stevens-Johnson syndrome), exfoliative dermatitis, mycosis fungoides, severe psoriasis, severe seborrheic dermatitis.
- Ophthalmic Diseases: Severe acute and chronic allergic and inflammatory processes.
- Endocrine Disorders: Primary or secondary adrenocortical insufficiency.
- Respiratory Diseases: Symptomatic sarcoidosis, Loeffler's syndrome, berylliosis, fulminating or disseminated pulmonary tuberculosis, aspiration pneumonitis.
- Hematologic Disorders: Idiopathic and secondary thrombocytopenia in adults, acquired (autoimmune) hemolytic anemia, erythroblastopenia (RBC anemia), congenital (erythroid) hypoplastic anemia.
- Neoplastic Diseases: For palliative management of leukemias and lymphomas in adults
- Edematous States: To induce a diuresis or emission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.
- Cerebral Edema: treat patients with cerebral edema from various causes.
- Gastrointestinal Diseases: During a critical period of the disease in ulcerative colitis, regional enteritis.
- Miscellaneous: Tuberculous meningitis with subarachnoid block or impending block.
- Diagnostic testing: Dexamethasone is used in the diagnostic testing of adrenocortical hyperfunction.
- Antiemetic effect: High-dose dexamethasone regimens have been used effectively for the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy.

5.1.2 Dose:

The initial dosage varies from 0.75 mg to 9 mg a day depending on the disease being treated. Individualize dosage according to the severity of the disease and the patient's response. The severity, prognosis, expected duration of the disease and the patient's reaction to medication are primary factors in determining dosage

5.1.3 Warning:

- Use the lowest possible dose of corticosteroid to control the condition under treatment, and when dosage reduction is possible, the reduction should be gradual.
- During treatment with dexamethasone for specific physical stress conditions (trauma, surgery, childbirth, etc.), a temporary increase in dose may be required.
- Since complications of treatment with corticosteroids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

- Use corticosteroid with caution in renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.
- Regular checkups with doctors (including vision checkups in three-month intervals) are advised during long-term treatment.
- Even in cases of prolonged adrenocortical insufficiency after discontinuation of treatment, the administration of glucocorticoids can be necessary in physically stressful situations. An acute therapy-induced adrenocortical insufficiency can be minimized by slow dose reduction until a planned discontinuation time.

5.1.4 Serious side effects from using Dexamethasone:

Allergic reaction, Cushing's syndrome, Diabetes, Edema, Gastrointestinal perforation
Mental health problems, High blood pressure, Thromboembolism, Glaucoma, Cataract

5.2 Clorpheniramine maleate as Oral Solution, Dry syrup, Drops, Liquid, Syrup:

2mg/5ml, 2mg/1gm in:
MHRA, Japan, Singapore

According to MHRA:

5.2.1 Indication:

For the symptomatic relief of hay fever, vasomotor rhinitis, urticaria, angioneurotic oedema, reactions to food or medicines, serum reactions and insect bites.

5.2.2 Dose:

Adults and children over 12 years: Two 5ml doses every four to six hours up to a maximum of six doses in 24 hours as required.

5.2.3 Warning:

- given with caution to patients with epilepsy, severe cardiovascular disorders, liver disorders, renal impairment, glaucoma, urinary retention, prostatic enlargement, pyloroduodenal obstruction, asthma, bronchitis, bronchiectasis, thyrotoxicosis and severe hypertension.
- Special care should be taken when using chlorpheniramine maleate in children and the elderly as they are more likely to experience the neurological anticholinergic effects and paradoxical excitation (e.g. Increased energy, restlessness, nervousness).
- Avoid use in elderly patients with confusion.
- The anticholinergic properties of chlorphenamine may cause drowsiness, dizziness, blurred vision and psychomotor impairment in some patients which may seriously affect ability to drive and use machinery.
- The effects of alcohol may be increased and therefore concurrent use should be avoided.
- If symptoms do not go away within 5 days talk to your pharmacist or doctor.

5.2.4 Adverse effects From using chlorpheniramine:

Sedation, dizziness, abnormal coordination, headache, Nausea, vomiting, dyspepsia, allergic reaction, urticaria, muscle weakness, haemolytic anemia, tachycardia, palpitation, arrythmias, hypotension, fatigue, urinary retention

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:**
The absence of scientific or clinical data or published literature supporting the efficacy or safety of Chlorpheniramine and Dexamethasone as a fixed-dose combination for the proposed concentrations.

- **Inappropriate dosing:**
This formulation has an extremely high concentration of both active ingredients which lead to dosing error & increasing the risk of overdosing toxicity.

- **Risk of increased corticosteroid serious adverse effects:**
The use of fixed dose combination in proposed applied concentration may lead to unnecessary administration of powerful corticosteroid that increase the patient exposure to serious side effects of corticosteroids such as adrenal suppression & metabolic disturbance.
- **Synergistic effect for adverse effects:**
Co-administration of dexamethasone (potent corticosteroid) and chlorpheniramine (Sedative antihistamine) as a fixed dose combination in applied concentration create a complex adverse effect profile & may exacerbate intensity of corticosteroid- and antihistamine-related side effects.

- **No Additive Therapeutic Advantage:**
There is no Scientific data demonstrated the fixed dose concentrations of Chlorpheniramine maleate 2mg/ml and Dexamethasone 0.5mg/ml offer any added therapeutic benefit over alternatives and may instead increase the risk of medication errors.

- **More research & studies are needed**:
a fixed dose combination in applied concentrations is needed to be clinically tested for safety & efficacy & ensuring the drugs work together as intended without increasing side effect.

6.1 Scientific Evaluation Committee has adopted a **negative opinion**, recommending refusal of marketing authorization for the medicinal product **Chlorpheniramine maleate 2mg/ml + Dexamethasone 0.5mg/ml as oral dosage form.**

6.2 Technical Committee of Drug Control: refused granting the marketing authorization for the medicinal products containing **Chlorpheniramine maleate 2mg/ml + Dexamethasone 0.5mg/ml as oral dosage form**

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