Refusal Public Assessment Report for Human Medicinal Products

(Diphenhydramine Hydrochloride +Oxeladine Citrate + Guaiphenesin)

as Oral Dosage Form

1. Introduction:

Based on the review of safety & efficacy data

The Egyptian Drug Authority (EDA) refused granting the marketing authorization for the medicinal products containing the following formula**:**

(Diphenhydramine Hydrochloride + Oxeladine Citrate + Guaifenesin) as Oral Dosage Form

The application for Diphenhydramine Hydrochloride +Oxeladine Citrate + Guaiphenesin is refused as the submitted data fails to establish a compliant safety and efficacy profile.

2. Legal basis for application:

The application is submitted to the Scientific Evaluation Unit for Pharmaceutical Products and Drug Development according to EDA Chairman decision 150/2022

3. Scientific Overview:

3.1. Applied Scientific Information for

(Diphenhydramine Hydrochloride + Oxeladine Citrate + Guaifenesin) as Syrup

3.1.1. Pharmacotherapeutic class

Diphenhydramine hydrochloride is a sedating antihistamine Oxeladine is a centrally acting cough suppressant. Guaiphenesin increases production of respiratory tract fluids to help liquefy and reduce viscosity of tenacious sputum

3.1.2. Therapeutic indication

Acute and chronic bronchitis, asthmatic bronchitis, and common cold associated with cough.

3.1.3. Therapeutic dose:

The proposed dosage Regimen (according to product Leaflet):

- Adults: 1 tablespoonful 3-4 times daily.
- Children over 6 years: ½ - 1 teaspoonful 3-4 times daily.

3.1.4. Warnings associated with the drug:

Precautions:

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

• Due to its diphenhydramine content, it may cause some drowsiness; so affected patients should not drive or operate machinery.

• It should be used with care in cases of closed-angle glaucoma, urinary retention, prostatic hypertrophy, or epilepsy.

Contraindications:

• Hypersensitivity to any of the components of the drug.
• Patients with acute porphyria.
• Premature infants or neonates.
• It is contraindicated in children less than 2 years, and not to be taken with children less than 6 years without medical supervision

Pregnancy and Lactation:

• It is better not to recommend this combination in cases of pregnancy especially in the first trimester and lactation.

Side Effects:

• It may cause gastrointestinal discomfort.
• It may cause some CNS depression.
• It may give some antimuscarinic effects such as blurred vision and urinary difficulty or retention.

3.1.5. Scientific Rational:

1-Multimodal Target Engagement

• Peripheral clearance of secretions: Guaifenesin improves mucus transport and reduces mechanical triggers for cough.
• Central suppression of cough reflex: Oxeladine citrate inhibits coughing at the medullary cough center, reducing reflex sensitivity.

• Modulation of allergic or sensory irritation: Diphenhydramine attenuates histamine-mediated irritation and may contribute to central sensory dampening.

These mechanisms operate at different levels of the cough pathway—peripheral secretion dynamics, central neural processing, and sensory hypersensitivity—creating a therapeutic synergy that may provide broader symptomatic relief compared with monotherapy.

2- Clinical Advantages :

In a clinical setting, cough often comprises both productive and non-productive components due to:
mixed pathophysiologic drivers such as mucus retention, sensory irritation, and reflex sensitization. A combination product that directly enhances mucus mobilization while concurrently reducing both reflex cough triggers and underlying allergic irritation addresses this complexity more comprehensively than single-agent therapies.

3- Safety

Each component has been used in cough products for decades and possesses an established safety profile when used within recommended doses. Guaifenesin is generally well tolerated. Oxeladine citrate, as a centrally acting non-opioid antitussive,lacks the respiratory depressive and addictive risks of opioid cough suppressants. Diphenhydramine's safety profile is well characterized, with predictable anticholinergic effects that are manageable with appropriate dosing and patient education

3.2. Scientific Concerns:

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

- The applicant failed to submit any Scientific evidence or published literature to support the efficacy and the safety of this combination which poses an elevated risk of side effects due to the unnecessary exposure to multiple active ingredients
- The applicant failed to submit additive Therapeutic advantage for the use of this combination rather than the use of the individual components administered separately

4. Regulatory Status

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:
*No scientific references or reference countries are available for the same combination

***The closest combination is available in TGA as follows:**

- Lotussin Oral liquid

(Dextromethorphan HBr Monohydrate 1.25mg + Diphenhydramine HCL 1mg +Ephedrine HCL 1.5mg + Guaifenesin 10mg) ml
Co.: Proqualix Pty Ltd - in Administration Status: Active (Export only)

***Oxeladine Citrate 2mg/ml is available in ANSM as follows:**

• Paxeladine 0.2%, syrup
Oxeladine Citrate 0.2g/100ml
Co.: Mayoly Pharma France Status**:** Valid, Marketed

5. Overall Conclusion & Recommendation:

Based on the scientific assessment of the submitted data, the following conclusions were drawn.

Lack of Therapeutic Justification & Existence of Pharmacological Antagonism

- **Opposing Mechanisms of Action**:The combination includes an antihistamine (Diphenhydramine), an antitussive (Oxeladine Citrate), and an expectorant (Guaifenesin), which possess different and, in some cases, possess conflicting therapeutic goals.
- **Inhibition of Mucus Clearance**: Guaifenesin promotes mucus clearance by increasing airway secretions, whereas Oxeladine suppresses the protective cough reflex required to expel these secretions. Concurrent administration lacks clinical rationale and risks mucus retention and bronchial plugging.
- **Anticholinergic Interference:** Diphenhydramine exerts significant anticholinergic effects, leading to mucosal drying and increased sputum viscosity. This directly neutralizes the intended expectorant action of Guaifenesin.

Insufficient Evidence of Safety Clinical Benefit :

- No published robust clinical evidence or literature has been provided demonstrating that the fixed-dose combination offers superior efficacy or safety compared with the individual components administered separately or with established therapeutic alternatives.
- Combining three active ingredients with overlapping CNS-depressant and anticholinergic profiles exposes patients to unnecessary safety risks (e.g., excessive sedation, dry mouth, urinary retention) without proven additive therapeutic gain.

More research & studies are needed
To support the safety and efficacy of the proposed Fixed-Dose Combination

Scientific Evaluation committee adopted a negative opinion, recommending the refusal of the marketing authorization of the products containing (Diphenhydramine Hydrochloride +Oxeladine Citrate + Guaiphenesin) as Oral Dosage Form

Technical Committee of Drug Control:

refused granting the marketing authorization for the medicinal products containing

(Diphenhydramine Hydrochloride +Oxeladine Citrate + Guaiphenesin) as Oral Dosage Form

6. Final Decision:

Following a comprehensive evaluation of safety and efficacy, the Scientific Evaluation Committee and the Technical Committee for Drug Control have determined that the application for the medicinal product (Diphenhydramine Hydrochloride +Oxeladine Citrate + Guaiphenesin) as Oral Dosage Form lacks the necessary scientific justification and clinical validation to ensure a safe risk-benefit profile.
Accordingly, the Egyptian Drug Authority (EDA) issues a final rejection regarding marketing authorization for all products containing this fixed dose combination (Diphenhydramine Hydrochloride + Oxeladine Citrate + Guaifenesin) as Oral Dosage form.