Refusal Public Assessment Report for Human Medicinal Products

(Azithromycin Dihydrate + Loteprednol Etabonate Ophthalmic Suspension)

Overview:

Based on the review of safety & efficacy data
The Egyptian Drug Authority (EDA) refused granting the marketing authorization for the medicinal products containing Azithromycin Dihydrate + Loteprednol Etabonate as eye drops.
The application for Azithromycin Dihydrate + Loteprednol Etabonate eye drops is refused, as the submitted data does not meet the requirements for marketing authorization for submitted product as Fixed Dose Combination.

Legal basis for application:

The application is submitted to Scientific Evaluation unit for pharmaceutical products and Drug Development according to EDA Chairman decision **450/2023 (First Case)**

Applied Scientific Information

- Pharmacotherapeutic group

- **Loteprednol Etabonate:** Corticosteroid
- **Azithromycin:** Macrolide Antibiotic

- Therapeutic indication

The applicant has proposed the following therapeutic indications for Azithromycin Dihydrate + Loteprednol Etabonate as Ophthalmic Suspension as follows:

- **Blepharitis and Blepharoconjunctivitis** (inflammatory conditions with bacterial involvement)
- **Trachoma** (a chronic infectious eye disease)
- **Treatment of infections associated with inflammation** (e.g., bacterial conjunctivitis with coexistent ocular inflammation)

- Therapeutic dose:

The proposed dosage regimen for **Azithromycin + Loteprednol Ophthalmic Suspension**:
1 drop, 3 times daily in the affected eye(s).

- Warnings associated with the drug:

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

- **Loteprednol Etabonate:**
  - **Intraocular Pressure (IOP) Elevation and Glaucoma Risk:** Prolonged use of corticosteroids, including Loteprednol, may lead to elevated intraocular pressure (IOP) and potential glaucoma, which can cause optic nerve damage and defects in visual acuity.
  - **Cataract Formation:** Chronic use of corticosteroids may contribute to posterior subcapsular cataract formation.

- **Secondary Infections:** Extended use may suppress the ocular immune response, increasing the risk of secondary infections, including fungal infections.
- **Use in Susceptible Populations:** Caution is advised in patients with a history of glaucoma, ocular infections, or corneal thinning, as the risk of complications may be exacerbated.
- **Discontinuation:** If no improvement is observed after 2 days of treatment, reevaluation by an ophthalmologist is recommended.

- **Azithromycin:**

- **Local Adverse Reactions:** The most frequently reported adverse reactions include eye irritation, stinging, and burning at the site of application. Less common reactions include contact dermatitis, corneal erosion, and dry eye.
- **Antibiotic Resistance:** Prolonged use may result in the development of resistant bacterial strains. Azithromycin should be used only for the duration indicated in the treatment regimen to minimize this risk.
- **Hypersensitivity Reactions:** Anaphylactic reactions have been reported with systemic use of azithromycin, and although rare, may occur with topical application.

Scientific Assessment:

-The applicant provided data about safety and efficacy of Azithromycin Dihydrate + Loteprednol Etabonate Ophthalmic Suspension) 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 clinical data or scientific evidence supporting the use of Loteprednol and Azithromycin as fixed dose combination for applied therapeutic purpose.

- The applicant failed to submit data about Pharmacodynamics and pharmacokinetics of the two ingredients in fixed dose combination.

-The applicant did not submit scientific evidence about a unique therapeutic advantages for fixed dose combination over existing such as improved efficacy, safety or patient adherence .

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

The applicant proposed that a fixed dose combination of Azithromycin Dihydrate + Loteprednol Etabonate as Ophthalmic Suspension could offer benefits in treatment of conditions such as blepharitis that involve both bacterial infection and inflammation. Blepharitis, which affects tens of millions of people worldwide, causes symptoms such as redness, irritation, and scaly skin at the edges of the eyelids. Azithromycin plays an important role in blepharitis (drug of choice) particularly no other choices (as sulfacetamide) is available.

It could also be used in treatment of ocular inflammations in which the ophthalmologists need an effective and save steroid does not affect IOP.

Azithromycin+loteprednol combination eye drop is the best in treating conditions (blepharitis, conjunctivitis, and trachoma) due to the effectiveness of azithromycin in treating these special cases.

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

- This combination is not available in reference countries at the time of submission
- There is no reliable data about safety and efficacy for the applied medicinal product.

Each active Ingredient is available alone as:

-Loteprednol 0.5 % Eye Drops available in MHRA as 0.5 % Eye Drops, Suspension

Indication: Treatment of post-operative inflammation following ocular surgery.

Dose: One to two drops four times daily beginning 24 hours after surgery and continuing throughout the post-operative period. The duration of treatment should not exceed 2 weeks.

-Azithromycin 1% Eye drops available in FDA as 1% sterile topical ophthalmic drops

Indication: Treatment of bacterial conjunctivitis caused by susceptible isolates of the following microorganisms: CDC coryneform group G, Haemophilus influenzae, Staphylococcus aureus, Streptococcus mitis group, and Streptococcus pneumoniae.

Dose: Instill 1 drop in the affected eye (s) twice daily, eight to twelve hours apart for the first two days and then instill 1 drop in the affected eye (s) once daily for the next five days.

Conclusion:

Based on Scientific assessment of the applied medicinal product and submitted data by the applicant.

-Insufficient Clinical Data: The applicant has not provided robust clinical data or published literature supporting the efficacy or safety of Azithromycin and Loteprednol as a fixed-dose combination for the proposed indications, including blepharitis, blepharoconjunctivitis, and trachoma.

-Uncertainty Regarding Pharmacokinetics and Pharmacodynamics: There is a lack of information regarding the pharmacokinetic and pharmacodynamic interactions between Azithromycin and Loteprednol when used together. These two agents have different pharmacological profiles, including different dosing regimens and durations, which may complicate their co-administration in a single formulation.

-Safety profile issues: The combination of Azithromycin and Loteprednol as fixed dose combination form raises concerns about potential side effects, such as the development of resistant bacterial strains and the masking of bacterial infections by corticosteroids. The long-term use of corticosteroids may also exacerbate the risk of ocular hypertension, cataract formation, and secondary infections.

-Insufficient therapeutic Justification: This fixed-dose combination did not offer a unique therapeutic advantages over existing such as improved efficacy, safety or patient adherence .

-More research & studies are needed : Both active ingredients (Azithromycin & Loteprednol) have different dosage regimen, so a fixed dose combination is needed to be clinically tested for safety & efficacy & ensuring the drugs work together as intended without increasing side effect or reducing efficacy.

- The Scientific Evaluation committee adopted a negative opinion, recommending the refusal of the marketing authorization for the medicinal product. **Azithromycin Dihydrate + Loteprednol Etabonate Ophthalmic Suspension**

- The Technical committee of drug control: refused granting the marketing authorization for the medicinal products containing containing Azithromycin Dihydrate + Loteprednol Etabonate as eye drops.

……