Arab Republic of Egypt
Egyptian Drug Authority
CAPP

جمهورية مصر العربية
هيئة الدواء المصرية
الإدارة المركزية للمستحضرات الصيدلية

EDA Assessment Report for human medicinal product

(Scientific Discussion)

Qulaperafen 708mg/100mL Oral Suspension

(Levocloperastine Fendizoate)

Date: February, 2024

I. Introduction

Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for "Qulaperafen 708mg/100mL Oral Suspension" from Utopia Pharmaceuticals.

The product is indicated as cough suppressant.

II. Quality Aspect

Drug Substance

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.
- The drug substance is an almost white to white crystalline powder. It is soluble in dimethyl formamide, insoluble in water and it is non-hygroscopic. It has one chiral center and it is synthesized as S-enantiomer with (S)- configuration. It also exhibits polymorphism.
- The synthesis of drug substance consists of five stages, with the formation of four intermediates. All starting materials, reagents, solvents are well controlled.
- The drug substance is elucidated via Elemental analysis, Mass spectroscopy, IR, UV Spectroscopy, Nuclear Magnetic Resonance (^{1}H and ^{13}C) and the structure is well characterized. Levocloperastine Fendizoate shows polymorphism, polymorphic evaluation report (by P-XRD) is submitted to prove crystalline form of drug substance.
- The drug substance specifications include the following tests description, solubility, identification (IR and melting point), loss on drying, specific optical rotation, sulfated ash, particle size distribution, heavy metal related substances (by HPLC), assay (by HPLC), residual solvents (by GC), and chiral purity. All limits are acceptable.
- Analytical methods were adequately described and validated.
- The applicant provided batch analysis results of 3 drug substance batches demonstrating compliance with the current drug substance specification.
- Levocloperastine Fendizoate is packed in single white transparent LDPE (food grade bag) and sealed with plastic strip seal. The sealed bag is kept into black LDPE bag and sealed with plastic strip seal. Finally, the bags are packed in HDPE drums.
- Container closure system is suitable to store drug substance and comply with food grade packaging material and the specifications are acceptable.
- Stability of drug substance is submitted as (accelerated at 40°C ± 2°C, RH 75% ± 5%) and (long term at 30°C ± 2°C, RH 75% ±5%), and conclude the conformity of specifications during the retest period and storage conditions. The storage conditions for Levocloperastine Fendizoate are "store at temperature not exceeding 30°C. Keep away from direct sunlight, heat and water.".

Medicinal Product

- **Product Description**

- White to off White viscous homogenous suspension with banana odor.

  The product is packed in amber glass bottle (Type III) contains 100mL suspension with (HDPE) plastic closure with compressible (LDPE) plastic foam linear + red tamper evident ring.

- The excipients are; Xanthan Gum, Polysorbate 20, Simethicone emulsion 30%, Xylitol, Methyl p-hydroxybenzoate, Propyl p-hydroxybenzoate, Propylene glycol, Banana flavor liquid, Purified water.

- **Pharmaceutical development**, the development of the product has been described, the choice of excipients is justified and their functions explained. It was aimed to develop a product equivalent to the reference product.

- Overall, the choices of the packaging, manufacturing process, compatibility, overage physicochemical properties and microbiological attributes are justified.

- **Manufacturing process**, the manufacturing process consists of dissolution, emulsification and filling steps.

- Control of excipients, all excipients comply with USP and Eur.ph except for banana flavor liquid, is in-house and the specifications of the excipients are acceptable.

- Product specification includes the four universal tests as description, identification, assay, impurities and additional tests as pH, specific gravity, deliverable volume, resuspendability, dissolution, identification of methylparaben, propylparaben and assay of methylparaben, propylparaben and microbiological examination. All limits are acceptable.

- Analytical methods were adequately described and validated.

- Batch Analysis from the proposed production site were provided for three primary batches, demonstrating compliance with the release specification

- Container closure system is suitable to store finished pharmaceutical product and comply with food grade packaging material and the specifications are acceptable.

- Stability of Finished Pharmaceutical Product is submitted (accelerated at 40°C ± 2°C/75% RH ± 5% RH) and long-term at 30°C ± 2°C/65% RH ± 5% RH) and conclude the conformity of specifications during the shelf-life and storage conditions".

- There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

Summary basis of opinion:

From Chemistry, Manufacture and Control perspective, the main concerns found during the evaluation process were as follow:

- The supplier of drug substance was asked to confirm the absence of risk of conversion of the polymorphic from produced throughout the shelf-life.

- The applicant was asked to discuss the selection of dissolution medium parameters.

The Quality of the drug product has been found satisfactory after:

- The applicant has replied with the confirmatory stability studies over 33 months at the proposed storage conditions, and there is no significant change in XRPD and DSC submitted data between batches.

- The applicant has discussed the selection of dissolution medium parameters, for example, dissolution medium, apparatus and speed and how selected conditions resulted in satisfactory release condition for the dosage from.

III. Non-Clinical

No new preclinical data have been submitted with this application. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application. An Environmental Risk Assessment has not been performed as this product is intended for generic substitution and therefore will not result in an increase of risk to the environment during use, storage and disposal.

IV. Clinical Aspects

Introduction

Cloperastine HCl is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature.

Cloperastine HCl is indicated for:

1-Asthma

-indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older.

2-Exercise-Induced Bronchoconstriction (EIB)

- indicated for prevention of exercise-induced bronchoconstriction (EIB) in patients 6 years of age and older.

3-Allergic Rhinitis

- indicated for the relief of symptoms of seasonal allergic rhinitis in patients 2 years of age and older and perennial allergic rhinitis in patients 6 months of age and older. Because the benefits may not outweigh the risk of neuropsychiatric symptoms in patients with allergic rhinitis, reserve use for patients who have an inadequate response or intolerance to alternative therapies.

Pharmacokinetics

Bioequivalence Study

The bioequivalence study of Qulaperafen 400 mg/ 100 ml Oral Suspension (Utopia Pharmaceuticals, Egypt) relative to Privituss 400mg/ 100ml Oral Suspension administered to healthy participants.

Design

This study was an open label, randomized, fasting, single oral dose, two treatments, two sequences and two periods, crossover study with a washout interval of two weeks between dosing in healthy participants.

Biological Samples Collection;

Before dosing (pre-dose) and at 0.00, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 12.00, 24.00, 48.00 & 72.00 hours post dosing.

Analytical Methods

All procedures used to perform the bio-analyses of Cloperastine HCl in subject samples were executed according to international guidelines and official publications.

CRO developed an adequately validated method to ensure data integrity, Accuracy and Precision of data generated during sampling, sample treatment and bioanalyses. The bioequivalence study accordance with acceptable standards of Good Clinical Practice (GCP) and Good Laboratory Practice (GLP).

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of Cloperastine HCl under fasting conditions.

Treatment N=27	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	88.19	101.98	5.01	4.63± 1.46	16.71± 7.07
Reference	81.28	93.54	4.61	4.81± 1.58	19.30± 5.71
***Ratio (90%) CI**	107.47 (94.91-121.69)	106.73 (94.81-120.15)	106.79 (97.16-117.38)	------	------
CV (%)	---	-------	------	------	------

*ln-transformed values

Conclusion

The 90% confidence intervals calculated for AUC $_{0\text{-}t_n}$, AUC$_{0\text{-}\infty}$, and C $_{max}$ are within the bioequivalence acceptance range of 80-125%

Based on this study demonstrated that the Active Pharmaceutical Ingredient Cloperastine HCl in Qulaperafen 708mg/100ml oral suspension (Utopia Pharmaceuticals, Egypt) & Privituss 400 mg/ 100 ml Oral Suspension are Bioequivalent after a single oral dose of test and reference administration under fasting conditions on 27 participants.