Public Assessment Report
Scientific discussion

Levocetirizine Substipharm 5 mg orodispersible tablet
Evianzin 5 mg orodispersible tablet
Loritozin 5 mg orodispersible tablet

(Levocetirizine dihydrochloride)

ES/H/0398/001/DC
ES/H/0399/001/DC
ES/H/0400/001/DC

Applicant: Substipharm Developpement

This module reflects the scientific discussion for the approval of **Levocetirizine Substipharm 5 mg, Evianzin 5 mg and Loritozin 5 mg orodispersible tablet**. The procedure was finalised on April 2017.

INTRODUCTION

This decentralised procedure concerns a generic application of levocetirizine dihydrochloride, under Levocetirizine Substipharm 5 mg, Evianzin 5 mg and Loritozin 5 mg orodispersible tablets, claiming essential similarity with the innovator product Xazal 5 mg film-coated tablets (UCB Pharma, S.A.). Xazal 5 mg film-coated tablets has been registered in Germany since January 01st, 2001.

The legal basis of the application is Article 10(1) of Directive 2001/83/EC.

With Spain as the Reference Member State in this decentralised procedure, Substipharm Developpement is applying for the Marketing Authorisations of Levocetirizine Substipharm 5 mg, Evianzin 5 mg and Loritozin 5 mg orodispersible tablets in:

- ES/H/0398/001/DC: FR
- ES/H/0399/001/DC: IT
- ES/H/0400/001/DC: UK

Levocetirizine is the active enantiomer of cetirizine. It is a selective, second generation histamine H_1 receptor antagonist licensed for the symptomatic treatment of allergic rhinitis (AR), including perennial allergic rhinitis (PAR) and chronic idiopathic urticaria (CIU). The pharmacological profile includes a rapid onset and long duration of antihistaminic effect; rapid absorption and high bioavailability; a low potential for drug interactions; a low volume of distribution; and a lack of effect on cognition, psychomotor function and the cardiovascular system

Levocetirizine is indicated for the symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) and urticaria in adults and children aged 6 years and above.

The daily recommended dose is 5 mg (1 orodispersible tablet).

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation for Levocetirizine Substipharm 5 mg, Evianzin 5 mg and Loritozin 5 mg orodispersible tablets for Substipharm Developpement.

I. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

DRUG SUBSTANCE

Levocetirizine dihydrochloride is not described in the Ph. Eur. The Active Substance Master File (ASMF) procedure is used for Levocetirizine dihydrochloride.

Levocetirizine dihydrochloride is a white to off white crystalline powder. Levocetirizine dihydrochloride is a chiral molecule; the ASMF-holder synthesises the R-enantiomer. It does not show polymorphism. It is BSC class I substance.

A brief description of the manufacturing process along with the synthetic scheme are given in the Applicant's Part of the ASMF. The synthesis covers several synthetic steps. Starting materials are fully justified. Detailed information of the manufacturing process is in the Restricted Part of the ASMF submitted.

Active substance specifications are justified adequately.

In general sufficient information about analytical methods are provided and the batch analysis

data shows that all three of the batches conform to the specification criteria.

The re-test period has been claimed and stability results support this retest period.

DRUG PRODUCT

Description of the product

Levocetirizine 5 mg Orodispersible Tablets are round, white to off-white, flat, and bevelled edged tablets plain on both sides. Each orodispersible tablet contains 5 mg of levocetirizine dihydrochloride.

The qualitative composition is as follows:

- Levocetirizine dihydrochloride
- Polacrilin potassium
- Lactose monohydrate
- Aspartame (E951)
- Silica, colloidal anhydrous
- Magnesium stearate
- Blackcurrant flavour (contains flavouring substances, flavouring preparations, natural flavouring substances, Maize maltodextrin, E1518 Glyceryl triacetate, E1505 Triethyl citrate, E150d Sulphite ammonia caramel and moisture)
- Pharmaburst B2 (contains Mannitol (E421), Polyplasdone, Sorbitol (E420) and Syloid)

Levocetirizine 5 mg Orodispersible Tablets are in packed in Aluminium/Aluminium blister.

Pharmaceutical development

The pharmaceutical development has been properly described. Justification about the formulation proposed is included. The function of the excipientes has been discussed. The excipients are suitable for the pharmaceutical form selected.

Manufacture of the product and process controls

The manufacturing process is described in detail; in-process controls are adequate.

The validation studies show that the manufacturing process for the product is suitable for routine production of the medicinal product.

Excipients

The information provided is adequate. These excipients, except flavour excipient and Pharmaburst B2, are described in European Pharmacopoeia or USP, and they are analysed according to the corresponding monographs. The composition of the flavour Blackcurrant and Pharmaburst B2 are properly described.

Product specification

Specifications proposed are adequate. The product specifications cover appropriate parameters for this dosage form. The limits proposed for the different parameters have been adequately justified.

All analytical methods have been correctly described and validated following the ICH Q2 (R1) Guideline.

Container closure system

Information about container closure system is correct. Levocetirizine 5 mg Orodispersible Tablets are in packed in Aluminium/aluminium blister.

Stability

Stability studies have been performed following the ICH guidelines. The stability data support the proposed shelf-life of *36 months with no special storage conditions.*

II-2 Non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology of the active substance has been provided, which is based on up-to-date and adequate scientific literature.

The submitted application concerns orodispersible tablets with the active substances in the same form as the reference product.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate and the Member States agreed that no further non-clinical studies are required.

Environmental Risk Assessment (ERA)

A completed ERA has not been submitted.

The lack of ERA is justified by consumption data of levocetirizine from the IMS database which reveal that consumption of levocetirizine has decreased during the last 3 years (2014 - 2016) in the CMS and RMS. Thus, no increase of released amounts of levocetirizine in the following years has to be expected.

II.3 Clinical aspects

Introduction

Levocetirizine dihydrochloride is a well-known drug with established efficacy and safety.

No new clinical efficacy or safety studies were conducted, which is acceptable for this abridged application. A clinical overview has been provided, which is based on scientific literature. The Member States agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

Biowaiver

Not applicable. The Applicant only applies for the 5 mg strength and this strenght is tested *in vivo*.

Bioequivalence

To support the application, the Applicant has submitted one bioequivalence study "an open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study in healthy, adult, human subjects under fasting condition".

The application concerns an immediate release orodispersible tablet formulation, the pharmacokinetic parameters of levocetirizine are linear with dose and the reference product may be taken without regard to meals as indicated in the innovator SmPC. Therefore, a single dose study under fasting conditions is considered acceptable to demonstrate bioequivalence with the innovator product.

The study was carried-out at Lambda Therapeutic Research Ltd., Plot No. 38, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-380 061, Gujarat, India and the principal investigator was Dr. Ketul Modi, M.B.B.S.

The final protocol dated April 08th, 2015 and Informed Consent Documents were reviewed by the Independent Ethics Committee (IBIOME) and approved on April 13th, 2015.

The study was carried out from April 20th, 2015 to April 30th, 2015 and the study periods are described below:

- Period-I: April 20th, 2015 to April 23rd, 2015 (dosing day April 21st, 2015)

– Period-II: April 27th, 2015 to April 30th, 2015 (dosing day April 28th, 2015)

The analytical portion was conducted at Lambda Therapeutic Research Ltd., Plot No. 38, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-380 061, Gujarat, India from May 29th, 2015 to June 09th, 2015.

The trial has been conducted in compliance with GCP requirements. Monitoring reports have been submitted. QA statement of audits assuring compliance to GCP was issued by Head-QA. The clinical, the analytical, the pharmacokinetic and the statistical sites have been inspected by Regulatory Authorities of the European Union without critical findings.

Design

This bioequivalence study was an open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study in healthy human subjects under fasting condition with a washout of 7 days.

The wash-out period of at least 7 days is considered adequate since the drug has a half-life of approximately 7.9 ± 1.9 hours and this washout exceeds 5 elimination half-lives.

Considering the elimination half-life of levocetirizine, the sampling schedule and the sampling time period of 48 hours seems long enough to estimate PK parameters.

Considering the expected time to peak concentration (0.9 hours), sampling is reasonably frequent over the first 2 hours and should be sufficient to allow an accurate measurement of t_{max} and C_{max}.

Test product: Levocetirizine Athena 5 mg ODT manufactured by Athena Drug Delivery Solutions Pvt. Ltd., India. Batch number: RD/GMP/14044. Batch size: 125,000 tablets. Expiry date (Re-test): May 2016. Assay (content): 98.9% of label claim.

Reference product:

Xyzall® 5 mg tablet manufactured by Aesica Pharmaceuticals s.r.l. Via Praglia 15 10044 Pianezza (TO), Italie for UCB Pharma S.A., from the French market. Batch number: 134254. Expiry date: April 2018. Assay (content): 99.2% of label claim.

After an overnight fasting of at least 10 hours, a single oral dose of either the test or the reference product was administered to the subjects in sitting posture.

The test product was administered without water. The subjects were instructed to wet their mouth by swallowing 20 ± 02 mL of drinking water directly before placing the investigational medicinal product on the tongue. The reference product was administered with 240 mL of drinking water at ambient temperature.

No water was allowed from 01 hour before to 01 hour after dose administration (excluding the 20 ± 2 mL immediately before dosing of Test Product-T or 240 mL of water administered concomitantly with the Reference Product-R).

The reference product is adequate with regards to expiry date, content and it was obtained from the French market.

According to the Guideline on the investigation of bioequivalence, since the reference product is taken with water and the ODT can be taken with or without water, if bioequivalence between ODT taken without water and reference formulation with water is demonstrated, bioequivalence of ODT taken with water can be assumed. The ODT was administered after wetting with 20 mL of water (without the intake of a glass of water to investigate the worst case scenario).

A total of 25 subjects including one additional subject were enrolled and checked in for the study. The additional subject was checked out of the facility as none of the subject discontinued or was withdrawn from the study prior to dosing in Period-I.

Hence, as per the protocol, 24 subjects (Subject Nos. 1001-1024) were dosed in Period-I of the study and all the dosed subjects completed the clinical phase.

Out of 24 subjects 23 were included in the statistical analysis. Subject No. 1017 had pre-dose concentration greater than 5% of C_{max} for levocetirizine. Hence he was excluded from pharmacokinetic and statistical analysis in accordance with the Guideline on investigation of bioequivalence.

The study population is considered acceptable with regards to demographic characteristics. The inclusion and exclusion criteria are also considered acceptable.

There were some protocol deviations that do not seem to impact on study validity since the actual time-points of the sample collection were used for the calculation of pharmacokinetic parameters.

There was no concomitant medication.

Analytical methods

The analytical method has been adequately validated before the conduct of the study and during the analysis of the subject samples. Therefore, the analytical method is considered acceptable for analysis of the plasma samples.

Pharmacokinetic data analysis

The selected primary pharmacokinetics variables (i.e., AUC_{0-t} and C_{max}) are appropriate for a single dose bioequivalence study.

Pharmacokinetic parameters were calculated using a non-compartmental method with acceptable software. AUC was calculated by the linear trapezoidal rule. The methods used in this study for the pharmacokinetic calculations are considered acceptable.

Statistical analysis

The statistical analyses using the GLM procedure were performed on ln-transformed AUC_{0-t} and C_{max}. The ANOVA factors are correct for a 2x2 design.

The results are summarized in the table below.

PK Parameter	90% Confidence Intervals			
	Point estimate%	Lowe limit %	Upper Limit %	Intra-subject CV%
C_{max}	90.9%	86.84%	95.14%	9.0%
AUC_{0-t}	98.5%	94.76%	102.42%	7.7%

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference with respect to the extent and rate of absorption/exposure as the 90% confidence intervals for the ratio test/reference of the ln-transformed C_{max} and AUC_{0-t} of levocetirizine are within the acceptance range of 80-125%.

Risk Management Plan

A risk management plan in accordance with the requirements of Directive 2001/83/EC as amended has been submitted.

No additional risk minimization activities were required beyond those included in the product information.

Discussion on the clinical aspects

Efficacy and safety of the active substance levocetirizine dihydrochloride are well documented for the reference medicinal product. The design of the submitted bioequivalence study is adequate and the results conclude bioequivalence with the reference product.

III OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bioequivalence has been shown in compliance with the requirements of European Union guidance documents.

The SmPC, PIL and labelling are considered satisfactory and consistent with the information for the reference medicinal product. The user testing of the Package Information Leaflet has been tested in accordance with Article 59(3) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

The benefit/risk balance was considered to be positive.

Agreement between Member States was reached during the procedure. The decentralised procedure was finalised with a positive outcome in April 2017.