Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Levocetirizine dihydrochloride 5 mg film-coated tablets

levocetirizine dihydrochloride

PL 43542/0070

Euro-Link Pharma Limited

LAY SUMMARY

Levocetirizine dihydrochloride 5 mg film-coated tablets
levocetirizine dihydrochloride

This is a summary of the Public Assessment Report (PAR) for Levocetirizine dihydrochloride 5 mg film-coated tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Levocetirizine 5 mg tablets in this lay summary for ease of reading.

For practical information about using Levocetirizine 5 mg tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Levocetirizine 5 mg tablets and what is it used for?
This product is a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Xyzal 5 mg film coated tablets.

Levocetirizine 5 mg tablets is used for the treatment of signs of illness (symptoms) associated with:

- allergic rhinitis (including persistent allergic rhinitis)
- nettle rash (urticaria)

How does Levocetirizine 5 mg tablets work?
Levocetirizine 5 mg tablets contain the active substance levocetirizine dihydrochloride. Levocetirizine dihydrochloride is an antiallergic medication, which acts by blocking receptors in the body that are responsible for an allergic reaction.

How is Levocetirizine 5 mg tablets used?
The pharmaceutical form of this medicine is a film-coated tablet, and the route of administration is oral (by mouth).

The recommended dose for adults and children aged 6 years and over is one tablet daily.

Levocetirizine 5 mg tablets should be swallowed whole with water and may be taken with or without food.

The duration of use depends on the type, duration and course of the patient's complaints and is determined by their physician.

Special dosage instructions for specific populations:

Renal and hepatic impairment
Patients with impaired kidney function may be given a lower dose according to the severity of their kidney disease, and in children the dose will also be chosen on the basis of body weight; the dose will be determined by the patient's doctor.

Patients who have severe impairment of kidney function must *no*t take Levocetirizine 5 mg tablets.

Patients who only have impaired liver function should take the usual prescribed dose.

Patients who have both impaired liver and kidney function may be given a lower dose depending on the severity of the kidney disease, and in children the dose will also be chosen on the basis of body weight; the dose will be determined by the patient's doctor.

Elderly patients aged 65 years and above
No adaptation of the dose is necessary in elderly patients, provided their renal function is normal.

Use in children
Levocetirizine 5 mg tablets is *not* recommended for children under 6 years of age.

For further information on how Levocetirizine 5 mg tablets is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Levocetirizine 5 mg tablets have been shown in studies?
Because Levocetirizine 5 mg tablets is a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Levocetirizine 5 mg tablets?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Levocetirizine 5 mg tablets is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are considered to be the same as the reference medicine.

Why was Levocetirizine 5 mg tablets approved?
It was concluded that, Levocetirizine 5 mg tablets has been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Levocetirizine 5 mg tablets?

As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Levocetirizine 5 mg tablets. The RMP details the important risks of Levocetirizine 5 mg tablets, how these risks can be minimised, any uncertainties about Levocetirizine 5 mg tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

There are no safety concerns associated with use of Levocetirizine 5 mg tablets.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Levocetirizine 5 mg tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Levocetirizine 5 mg tablets

A marketing authorisation for Levocetirizine 5 mg tablets was granted in the United Kingdom (UK) on 19 February 2024.

The full PAR for Levocetirizine 5 mg tablets follows this summary.

This summary was last updated in March 2024.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Levocetirizine dihydrochloride 5 mg film-coated tablets (PL 43542/0070) could be approved.

The product is approved for the following indications:

- symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis), and
- urticaria in adults and children aged 6 years and above.

Levocetirizine, the (R) enantiomer of cetirizine, is a potent and selective antagonist of peripheral H1-receptors.

Binding studies revealed that levocetirizine has high affinity for human H1-receptors (Ki = 3.2 nmol/l). Levocetirizine has an affinity 2-fold higher than that of cetirizine (Ki = 6.3 nmol/l).

Levocetirizine dissociates from H1-receptors with a half-life of 115 ± 38 min. After single administration, levocetirizine shows a receptor occupancy of 90% at 4 hours and 57% at 24 hours.

Pharmacodynamic studies in healthy volunteers demonstrate that, at half the dose, levocetirizine has comparable activity to cetirizine, both in the skin and in the nose.

This application was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Xyzal 5 mg film coated tablets that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation for Levocetirizine dihydrochloride 5 mg film-coated tablets was granted in the United Kingdom (UK) on 19 February 2024.

II QUALITY ASPECTS

II.1 Introduction

Each Levocetirizine dihydrochloride 5 mg film-coated tablet contains 5 mg levocetirizine dihydrochloride, corresponding to 4.2 mg of levocetirizine.

In addition to levocetirizine dihydrochloride, this product also contains the excipients:
Tablet Core
Croscarmellose sodium, microcrystalline cellulose (MCC 102), colloidal silicon dioxide and magnesium stearate.

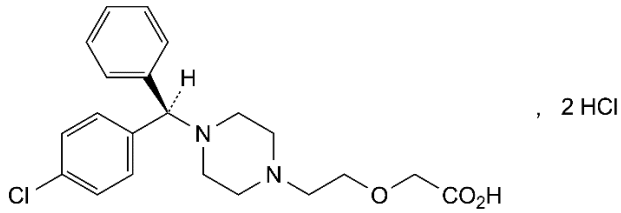
Film coating
Opadry white (03K58884)

The finished product is packaged in aluminium (Alu) – polyvinylchloride (PVC) blister and are available in pack sizes of 30 (3×10's count) tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: levocetirizine dihydrochloride
Chemical Name: [2-[4-[(*R*)-(4-Chlorophenyl)(phenyl)methyl]piperazin-1-yl]ethoxy]acetic acid dihydrochloride.
Molecular Formula: $C_{21}H_{27}Cl_3N_2O_3$
Chemical Structure:



Molecular Weight: 461.8
Appearance: White or almost white powder
Solubility: Freely soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

The information related to the active substance was provided in an ASMF. The Active substance is the subject of a Ph.Eur. monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant

specification. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution profile was provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

No excipients of animal or human origin are used in the final products.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months, with the storage conditions ‘Store at temperature below 25°C’, is acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of levocetirizine dihydrochloride are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology

No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics

No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology

No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment

A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the application is for generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the marketing authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisation was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of levocetirizine dihydrochloride is well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the application, the applicant submitted the following:

Study 1

This study was an open label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover oral bioequivalence study comparing Levocetirizine dihydrochloride 5 mg film-coated tablets (test product) and Xyzal 5 mg film coated tablets (reference product) in healthy, adult, human subjects under fasting conditions.

After an overnight fast of at least 10 hours, subjects were administered a single oral dose of either test or reference product, with approximately 240 ml of water. Blood samples were taken pre-dose and up to 48 hours post dose, with a washout period of 7 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Table 1: Bioequivalence Results (Geometric Least Squares Mean Ratios and 90% CIs for Levocetirizine (n=28)

Parameter (Unit)	(Ln-transformed) Geometric Least Square Mean			90% Confidence Interval T vs R
	Test Product (T)	Reference Product (R)	Ratio (T/R)%	
C_{max} (ng/mL)	157.201	159.221	98.73	94.45-103.21
AUC_{0-t} (hr.ng/mL)	1579.529	1591.075	99.27	95.62-103.07

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted for this application and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with this application, and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation was recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with levocetirizine dihydrochloride is

considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved UK version of the SmPC and PIL for this product are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**