Public Assessment Report

Decentralised Procedure

Levocetirizine Dihydrochloride 5 mg film-coated tablets

Procedure No: UK/H/5647/001/DC

UK Licence No: PL 36390/0176

Cipla (EU) 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 (PL 36390/0176; UK/H/5647/001/DC). Levocetirizine Dihydrochloride 5 mg film-coated tablets will be referred to as Levocetirizine 5 mg tablets throughout this report, for ease of reading. It explains how Levocetirizine 5 mg tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Levocetirizine 5 mg tablets.

For practical information about using Levocetirizine 5 mg tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Levocetirizine 5 mg tablets and what are they used for?
Levocetirizine 5 mg tablets are a ‘generic medicine’. This means that they are similar to a ‘reference medicine’, already authorised in the European Union (EU) called Xyzal 5 mg film-coated tablets.

Levocetirizine 5 mg tablets are used for the treatment of signs of illness associated with allergic rhinitis (including persistent allergic rhinitis) and nettle rash (urticarial).

How do 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 are Levocetirizine 5 mg tablets used?
Levocetirizine 5 mg tablets should be swallowed whole with water, and may be taken with or without food.

Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

The recommended dose for adults and children aged 6 years and over is one tablet daily. Levocetirizine 5 mg tablets are not recommended for children under 6 years of age.

Patients with impaired kidney function may be given a lower dose according to the severity of their kidney disease, and in children (aged 6 years and over) the dose will also be chosen on the basis of body weight. The dose for these two categories of patients will be determined by the doctor.

This medicine can only be obtained with a prescription.

What benefits of Levocetirizine 5 mg tablets have been shown in studies?
Because Levocetirizine 5 mg tablets are a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Xyzal 5 mg film-coated tablets. 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?
Because Levocetirizine 5 mg tablets are a generic medicine, their benefits and possible side effects are taken as being the same as those of the reference medicine, Xyzal 5 mg film-coated tablets.

For further information, please see the package leaflet.

Why are Levocetirizine 5 mg tablets approved?
It was concluded that, in accordance with EU requirements, Levocetirizine 5 mg tablets have been shown to have comparable quality and be bioequivalent to Xyzal 5 mg film-coated tablets. Therefore, the view was that, as for Xyzal 5 mg film-coated tablets, the benefits outweigh the identified risks and Levocetirizine 5 mg tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Levocetirizine 5 mg tablets?
A risk management plan has been developed to ensure that Levocetirizine 5 mg tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Levocetirizine 5 mg tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Levocetirizine 5 mg tablets
Bulgaria, Croatia, the Czech Republic, France, Greece, Hungary, Ireland, Italy, Malta, Poland, Portugal, Romania, Slovakia, Spain and the UK agreed to grant a marketing authorisation for Levocetirizine 5 mg tablets on 20 January 2015. The marketing authorisation in the UK was granted to the Marketing Authorisation holder, Cipla (EU) Limited, on 24 February 2015.

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

For more information about treatment with Levocetirizine 5 mg tablets, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in April 2015.
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I Introduction

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation (MA) for the medicinal product Levocetirizine 5 mg tablets.

This product is a prescription-only medicine (POM), indicated for the Symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) and urticaria.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Bulgaria, Croatia, the Czech Republic, France, Greece, Hungary, Ireland, Italy, Malta, Poland, Portugal, Romania, Slovakia and Spain as Concerned Member States (CMSs).

This application was made under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product. The reference medicinal product, which has been authorised in accordance with Community provisions in force for not less than 10 years in the European Economic Area (EEA), is Xyzal 5 mg film-coated tablets; this product was authorised to UCB Watford Limited in the UK on 24 September 2009. The licence for Xyzal 5 mg film-coated tablets subsequently underwent a change of ownership procedure to the current MA holder, UCB Pharma Limited, on 05 September 2005 (PL 00039/0539). Xyzal 5 mg tablet was licensed on a full dossier within the EU through a Mutual Recognition Procedure (MRP) in 2001 (DE/H/0299/01/MR); it was first approved in Germany as Xusal Tablets 5mg on 4 January 2001.

Levocetirizine 5 mg tablets contain the active ingredient levocetirizine dihydrochloride. Levocetirizine dihydrochloride is a selective antagonist of peripheral H1-receptors and is the R-enantiomer of the racemic compound cetirizine dihydrochloride. It was developed as an improvement on cetirizine (the S-enantiomer does not contribute to the antihistaminic effects of the racemate), at half the daily dose of cetirizine, with the same indications.

The anti-allergic and anti-inflammatory activities of H1-antihistamines occur through a variety of mechanisms. Anti-allergic activities such as the inhibition of the release of mediators from mast cells and basophils probably involve a direct inhibitory effect on calcium-ion channels that reduces the inward calcium current activated by the depletion of the intracellular store of calcium. Anti-inflammatory effects such as the inhibition of the expression of cell adhesion molecules and the chemotaxis of eosinophils and other cells may involve down-regulation of the H1-receptor-activated nuclear factor-kB, a commonly found transcription factor that binds to the promoter and enhancer regions of many genes that regulate the production of pro-inflammatory cytokines and adhesion protein.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

Since Levocetirizine 5 mg tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary.

With the exception of one bioequivalence study, no new clinical data were provided with this application. A bioequivalence study was performed, which compared the pharmacokinetics...
of the applicant’s Levocetirizine 5 mg tablets with those of the reference product, Xyzal 5 mg film-coated tablets, in healthy subjects under fasting conditions. The bioequivalence study was conducted in line with current Good Clinical Practice (GCP).

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

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports issued by the inspection services of the MHRA as certification that acceptable standards of GMP are in place at those non-Community sites.

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

The RMS and CMSs considered that the application could be approved at the end of procedure (Day 210) on 20 January 2015. After a subsequent national phase, a licence was granted in the UK to Cipla (EU) Limited on 24 February 2015.
II  Quality aspects

II.1  Introduction
The application is submitted according to Article 10(1) of Directive 2001/83/EC, as amended. The applicant has specified Xyzal 5 mg film-coated tablets (PL 00039/0539) as the EU reference medicinal product (MA Holder: UCB Pharma Limited).

Levocetirizine 5 mg tablets are formulated as white, oval-shaped, biconvex, film-coated tablets, debossed with ‘C5’ on one side and plain on the other.

Each film-coated tablet contains 5 mg of the active ingredient levocetirizine dihydrochloride. The excipients present in the tablet core are: anhydrous lactose, lactose monohydrate, microcrystalline cellulose, crospovidone (Type A) and magnesium stearate. The excipients in the Opadry white 04F58804 film-coating are: hypromellose (E464), titanium dioxide (E171), macrogol 6000.

The tablets are packed in aluminium - oriented polyamide/aluminium/polyvinylchloride (aluminium - OPA/aluminium/PVC) blisters, which are further packed into cartons in pack sizes of 7, 10, 14, 20, 28, 30, 50, 56, 84 and 100 tablets.

II.2  Drug Substance
Levocetirizine dihydrochloride
INN: levocetirizine dihydrochloride
Chemical Name: (-)-2-[2-[4-[(4-Chlorophenyl)phenylmethyl]-piperazinyl]ethoxy]acetic acid dihydrochloride

Structure:

![Structure of Levocetirizine Dihydrochloride](image)

Molecular formula: C_{21}H_{25}ClN_{2}O_{3}.2HCl
Molecular weight: 461.8
Appearance: white to almost white powder.
Solubility: freely soluble in water, methanol.

Levocetirizine dihydrochloride is not described in the European, British or United States Pharmacopoeia 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 specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis. No materials of animal or human origin are used in the production of the active substance.

Appropriate proof-of-structure data have been supplied for the active substance. All potential impurities have been identified and monitored appropriately.
An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. 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 has been shown to comply with current guidelines concerning contact with food.

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

II.3 Medicinal Product
Pharmaceutical development
The aim of the pharmaceutical development was to develop a generic product essentially similar to the reference medicinal product, Xyzal 5 mg film-coated tablets.

The development of the product has been adequately described. Comparative dissolution and impurity profiles have been demonstrated between Levocetirizine 5 mg tablets and the reference medicinal product.

In order to show Levocetirizine 5 mg tablets are equivalent to the reference medicinal product, Xyzal 5 mg film-coated tablets, with regard to bioavailability, a bioequivalence study was performed. This is discussed in Section IV – Clinical aspects.

All the excipients used in the manufacture of the proposed formulation, other than the film-coating excipient, Opadry white, comply with their respective European Pharmacopoeia monographs. Opadry white complies with a satisfactory in-house specification.

Satisfactory certificates of analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients are sourced from animal or human origin, except for lactose monohydrate and anhydrous lactose. A declaration has been provided by the suppliers of anhydrous lactose and lactose monohydrate stating that the lactose used in the manufacture of lactose monohydrate and anhydrous lactose is of animal origin and is derived from milk that has been collected from healthy animals in the same way as milk for human consumption. This satisfies the requirements of the Note for Guidance (NfG) on the reduction of transmission of spongiform encephalopathy (EMA/410/01 rev.3), which is acceptable.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the finished product, together with an appropriate account of the manufacturing process. The manufacturing process has been validated for three pilot scale batches and a commitment has been provided to validate the first three consecutive production scale batches of finished product successfully before market launch.
Product Specifications
The finished product specification is satisfactory. Satisfactory batch analysis was performed on three pilot scale batches of the finished product. Certificates of analysis have been provided for all working standards used.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. The data from these studies support a shelf-life for the finished product of 2 years when stored in the original package in order to protect from moisture. There are no special storage temperature conditions for this product.

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III Non-clinical aspects
The pharmacodynamic, pharmacokinetic and toxicological properties of levocetirizine dihydrochloride are well-known. As this active substance is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. The non-clinical overview based on a literature review is, thus, appropriate.

The non-clinical overview has been written by an appropriately qualified person. The non-clinical overview on the pharmacology, pharmacokinetics and toxicology is adequate.

Since Levocetirizine 5 mg tablets are intended for generic substitution, they will not lead to an increased exposure to the environment. An environmental risk assessment is, therefore, not deemed necessary.

IV Clinical aspects
IV.1 Introduction
With the exception of bioequivalence data, no new clinical data have been submitted and none are required for an application of this type. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
In support of this application the marketing authorisation holder has submitted results from the following bioequivalence study:

A randomized, balanced, open label, two-treatment, two-period, two-sequence, single dose, crossover study in healthy subjects under fasting conditions to determine whether the test product, Levocetirizine 5 mg tablets, and the reference product, Xyzal 5 mg film-coated tablets, are bioequivalent.

Subjects received the test or reference treatment after an overnight fast of at least 10 hours. Subjects were not allowed to drink water from 1 hour before dosing until 2 hours post-dose, except for the 240ml of drinking water given at the time of dosing. No food was permitted
until 4 hours after dosing. Blood samples were taken for the measurement of pharmacokinetic parameters pre-dose and up to 72 hours post-dose. The two treatment periods were separated by an 8-day washout period.

The Primary Efficacy variables were $C_{\text{max}}$, $\text{AUC}_{0-t}$ and $\text{AUC}_{0-\infty}$. The secondary efficacy variables were $T_{\text{max}}$, $t\text{-half}$ and terminal elimination rate constant.

The geometric mean and 90% confidence intervals for levocetirizine based on least square means obtained from ANOVA and ratio of test and reference products for the log-transformed parameters $C_{\text{max}}$, $\text{AUC}_{0-t}$ and $\text{AUC}_{0-\infty}$, as ascertained from this study are summarized below:

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Geometric mean</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test (T)</td>
<td>Reference (R)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>284.31</td>
<td>280.55</td>
</tr>
<tr>
<td>$\text{AUC}_{0-t}$ (hr ng/ml)</td>
<td>2434.39</td>
<td>2455.34</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$ (hr ng/ml)</td>
<td>2609.06</td>
<td>2639.72</td>
</tr>
</tbody>
</table>

The 90% confidence intervals were within the acceptance criteria of 80.00% to 125.00%. Based on these results, the proposed product, Levocetirizine 5 mg tablets, can be considered to be bioequivalent with the reference product Xyzal 5 mg film-coated tablets.

**IV.3 Pharmacodynamics**

No new pharmacodynamics data are required for this application and none have been submitted.

**IV.4 Clinical efficacy**

No new clinical efficacy data are required for this application and none have been submitted.

**IV.5 Clinical safety**

With the exception of the data collected during the bioequivalence study, no new data have been provided and none are required. The bioequivalence study appears to have been conducted safely with no adverse or serious adverse events reported. No clinically significant changes were noted in post-study laboratory data or results of physical examination.

**IV.6 Risk Management Plan (RMP)**

The marketing authorisation holder has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Levocetirizine 5 mg tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
Summary table of safety concerns

| Important identified risks                                                                 | • Use in patients with renal impairment |
|                                                                                           | • Hepatitis                              |
|                                                                                           | • Suicidal ideation                      |
|                                                                                           | • Urinary retention in patients with predisposing factors e.g. prostatic hyperplasia |

| Important potential risks                                                                 | • The administration of levocetirizine to infants and toddlers aged less than 2 years |
|                                                                                           | • CNS depression and sedation with concomitant use of other CNS depressants, including alcohol |
|                                                                                           | • Potential Misuse                        |

| Missing information                                                                    | • Use in pregnant and lactating women |
|                                                                                           | • Use in children with renal impairment |

Planned risk minimisation activities

<table>
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<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use in patients with renal impairment</td>
<td>Levocetirizine is excreted mainly via kidneys. The use of levocetirizine is contraindicated in patients with severe renal impairment at less than 10 ml/min creatinine clearance. This safety concern has been mentioned in Section 4.3., “Contraindications” of the SPC and Section 2; “What you need to know before you take Levocetirizine dihydrochloride 5 mg film-coated tablets” of PIL.</td>
<td>None</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Very rare cases of hepatitis have been reported in post-marketing experience. This safety concern has been mentioned in Section 4.8 “Undesirable effects” of the SPC and Section 4 “Possible side effects” of PIL.</td>
<td>None</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>This safety concern has been mentioned in Section 4.8 “Undesirable effects” of the SPC and section 4.4 “Possible side effects” of the PIL states the patient could have recurring thoughts of or preoccupation with suicide, however its frequency is not known.</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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<td>-----------------------------------------------------------------------------</td>
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<tr>
<td>Urinary retention in patients with predisposing factors e.g. prostatic hyperplasia</td>
<td>This safety concern has been mentioned in Section 4.4 “special warnings and precautions for use” of the SPC and Section 2 “what you need to know before you take levocetirizine tablets” of PIL. Caution should be taken in patients with predisposing factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as levocetirizine may increase the risk of urinary retention.</td>
<td>None</td>
</tr>
<tr>
<td>Use in infants and toddlers aged less than 2 years</td>
<td>This risk is mentioned in section 4.2 (Posology and method of administration) of SPC and section 2 (What you need to know before you take Levocetirizine tablets) of PIL. Due to the lack of data in this population, the administration of levocetirizine to infants and toddlers aged less than 2 years is not recommended.</td>
<td>None</td>
</tr>
<tr>
<td>CNS depression and sedation with concomitant use of other CNS depressants, including alcohol</td>
<td>This risk is mentioned in section 4.5 (Interaction with other medicinal products and other forms of interaction) of SPC and section 2 (What you need to know before you take Levocetirizine tablets) of PIL. In sensitive patients the simultaneous administration of cetirizine or levocetirizine and alcohol or other CNS depressants may have effects on the central nervous system, although it has been shown that the racemate cetirizine does not potentiate the effect of alcohol.</td>
<td>None</td>
</tr>
</tbody>
</table>
Safety concern | Routine risk minimisation measures | Additional risk minimisation measures
---|---|---
Use in pregnant and lactating women | As per section 4.6 (Fertility, pregnancy and lactation) of SPC and, there are no or limited amount of data from the use of levocetirizine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of levocetirizine during pregnancy. In sensitive patients the simultaneous administration of cetirizine or levocetirizine and alcohol or other CNS depressants may have effects on the central nervous system, although it has been shown that the racemate cetirizine does not potentiate the effect of alcohol. If the patient is pregnant or breast-feeding, thinks she may be pregnant or is planning to have a baby, a doctor or pharmacist should be consulted before taking this medicine. Levocetirizine is expected to be excreted to be into the milk and due to lack of data levocetirizine use is not recommended during breast-feeding, especially for a long term treatment. | None
Use in children with renal impairment | As per section 4.6 (Fertility, pregnancy and lactation) of SPC, Due to the lack of data in this population, the administration of levocetirizine to infants and toddlers aged less than 2 years is not recommended. | None

V.7 Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for this application.

V User consultation
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the package leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.
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. Conclusive bioequivalence data demonstrates that the test product Levocetirizine 5 mg tablets can be considered bioequivalent with the reference product Xyzal 5 mg film-coated tablets. Therefore, the well-established positive benefit/risk analysis of the reference Xyzal 5 mg film-coated tablets is applicable for this generic product as well.

The application contains an adequate review of published clinical data. There are no major objections to approval of this generic product on clinical grounds.

The benefit/risk balance of this product is considered favourable.

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 Directive 2012/84/EU, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

The currently approved labelling is listed below:
Levocetirizine Dihydrochloride 5 mg film-coated tablets

Each film-coated tablet contains 5 mg Levocetirizine dihydrochloride.

Also contains:
- Lactose Monohydrate & Anhydrous Lactose
- See leaflet for further information

Read the package leaflet before use.
Keep out of the sight and reach of children.

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.

MA Holder:
Cipla (EU) Limited
Hillbrow House, Hillbrow Road,
Esher, Surrey, KT10 9NW, United Kingdom

PL 36390/0176
PA 1809/009/001
MA 886/00001

BARCODE
Table of content of the PAR update for MRP and DCP
Steps taken after the initial procedure with an influence on the Public Assessment Report
(Type II variations, PSURs, commitments)

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<th>Product information affected</th>
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<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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