Public Assessment Report

Decentralised Procedure

Levocetirizine Dihydrochloride 5 mg film-coated tablets

UK/H/3483/001/DC
UK licence number: PL 25298/0014

Brown & Burk UK Limited
On 21 September 2012, the MHRA granted Brown & Burk UK Limited a Marketing Authorisation (licence) for the medicinal product, Levocetirizine Dihydrochloride 5 mg film-coated tablets (PL 25298/0014). This is a prescription-only medicine (POM).

These tablets contain the active ingredient, levocetirizine dihydrochloride, which is an antiallergic medicine. Levocetirizine Dihydrochloride 5 mg film-coated tablets are used for the treatment of symptoms associated with allergic rhinitis (including persistent allergic rhinitis) and nettle rash (urticaria).

Based on the data submitted by Brown & Burk UK Limited, Levocetirizine Dihydrochloride 5 mg film-coated tablets were considered to be a generic version of the UK reference product, Xyzal 5 mg film coated Tablets (PL 00039/0539, UCB Pharma Ltd).

No new or unexpected safety concerns arose from this application. It was judged that the benefits of Levocetirizine Dihydrochloride 5 mg film-coated tablets outweigh the risks; hence a Marketing Authorisation has been granted.
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Module 1

Information about Initial Procedure

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Levocetirizine Dihydrochloride 5 mg film-coated tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10(1)</td>
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<tr>
<td>Active Substance</td>
<td>Levocetirizine dihydrochloride</td>
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<tr>
<td>Form</td>
<td>Film-coated tablets</td>
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<tr>
<td>Strength</td>
<td>5 mg</td>
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<td>MA Holder</td>
<td>Brown &amp; Burk UK Limited 5 Marryat Close, Hounslow West, Middlesex, TW4 5DQ, UK</td>
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<tr>
<td>Reference Member State (RMS)</td>
<td>UK</td>
</tr>
<tr>
<td>Concerned Member States (CMS)</td>
<td>Germany</td>
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<td>Procedure Number</td>
<td>UK/H/3483/001/DC</td>
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<tr>
<td>Timetable</td>
<td>End of Procedure: Day 210 – 04 July 2012</td>
</tr>
</tbody>
</table>
Module 2

Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3

Patient Information Leaflet

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4

Labelling

Levocetirizine Dihydrochloride 5 mg film-coated tablets

Contains lactose
See package leaflet for further information
Read the package leaflet before use.
Oral use.
Keep out of the sight and reach of children.

Levocetirizine Dihydrochloride 5 mg film-coated tablets

Levocetirizine dihydrochloride #5 mg film-coated Tablets
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Brown & Burk UK Limited a Marketing Authorisation (MA) for the medicinal product, Levocetirizine Dihydrochloride 5 mg film-coated tablets (PL 25298/0014; UK/H/3483/001/DC) on 21 September 2012. The product is a prescription-only medicine.

This is a generic application for Levocetirizine Dihydrochloride 5 mg film-coated tablets, submitted under Article 10(1) of Directive 2001/83 EC, as amended. The application refers to the UK product, Xyzal 5 mg film coated Tablets (PL 00039/0539), licensed to UCB Pharma Ltd. The cross-referenced product was originally authorised as PL 08972/0036 on 24 September 2001 and underwent a Change of Ownership (CoA) procedure to the current UCB Pharma Ltd licence on 08 November 2005. The UK reference product has been authorised in the EU for more than 10 years, thus the period of data exclusivity has expired.

With the UK as the Reference Member State (RMS) in this Decentralised procedure, Brown & Burk UK Limited applied for a Marketing Authorisation for Levocetirizine Dihydrochloride 5 mg film-coated tablets in Germany.

Levocetirizine Dihydrochloride 5 mg film-coated tablets are indicated for the symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) and urticaria.

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.

No new non-clinical or clinical efficacy studies were conducted for this application, which is acceptable given that the application was for a generic version of a product that has been licensed for over 10 years.

The application is supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Levocetirizine Dihydrochloride 5 mg film-coated tablets, to that of the clinical reference product, Xyzal 5 mg film coated Tablets (UCB Pharma Ltd). The bioequivalence study was carried out in accordance with 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 and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. 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 or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well-established.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Levocetirizine Dihydrochloride 5 mg film-coated tablets</th>
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<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Levocetirizine dihydrochloride</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Antihistamine for systemic use, piperazine derivatives (R06AE09)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Film-coated tablets</td>
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<tr>
<td></td>
<td>5 mg</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/3483/001/DC</td>
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<tr>
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<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>DE</td>
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<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 25298/0014</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Brown &amp; Burk UK Limited 5 Marryat Close, Hounslow West, Middlesex, TW4 5DQ, UK</td>
</tr>
</tbody>
</table>
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

Levocetirizine dihydrochloride

Nomenclature:
INN: Levocetirizine dihydrochloride
Chemical names: 2-[2-[4-[(R)-(4-chlorophenyl) -phenyl-methyl]piperazine-1-yl]ethoxy] acetic acid dihydrochloride

Structure:

![Molecule structure](image)

Molecular formula: \( \text{C}_{21}\text{H}_{27}\text{Cl}_{3}\text{N}_{2}\text{O}_{3} \cdot 2\text{HCl} \)
Molecular weight: 461.8 g/mol
CAS No: 130018-87-0
Physical form: White to off-white crystalline powder
Solubility: Soluble in methanol and water

The active substance, levocetirizine dihydrochloride, is not the subject of a European Pharmacopeia (Ph. Eur) or British Pharmacopeia (BP) 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. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

Appropriate specifications have been 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 specifications. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturers during validation studies.

The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging in direct contact with the active substance complies with relevant Ph. Eur requirements and satisfies Directive 2002/72/EC (as amended); it is suitable for contact with foodstuffs.

Appropriate stability data have been generated for active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and an appropriate retest period has been applied.
MEDICINAL PRODUCT

Description and Composition

Levocetirizine Dihydrochloride 5 mg film-coated tablets are presented as white, biconvex, oval-shaped, film-coated tablets debossed with ‘I’ and ‘12’ on one side and a scoreline on the other side. The scoreline is not to facilitate dosing. Each tablet contains 5 mg of the active ingredient, levocetirizine dihydrochloride.

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, microcrystalline cellulose (E460), colloidal anhydrous silica (E551) and magnesium stearate (E572) making up the tablet cores; and hypromellose (E464), titanium dioxide (E 171) and macrogol 400 constituting the film-coating. Appropriate justification for the inclusion of each excipient has been provided.

All excipients of the tablet cores comply with their respective Ph. Eur monographs. The film-coating formulation complies with satisfactory in-house specifications and its constituents comply with their respective Ph. Eur monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

Magnesium stearate has been confirmed as being of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. None of the excipients are sourced from genetically modified organisms. There were no novel excipients used.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The objective was to develop a stable, generic, immediate-release film-coated tablet formulation containing 5 mg levocetirizine dihydrochloride, bioequivalent to the reference product, Xyzal 5 mg film coated Tablets (UCB Pharma Ltd).

Comparative dissolution data were provided for batches of the test products and appropriate reference products. The dissolution profiles were satisfactory.

 Manufacture

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies were conducted and the results were satisfactory. The validation data demonstrated consistency of the manufacturing process.

Finished product specification

Finished product specifications are provided for release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.
Container Closure System

Levocetirizine Dihydrochloride 5 mg film-coated tablets are licensed for marketing in aluminium-aluminium blister strips, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in a pack size of 1, 2, 4, 5, 7, 10, 14, 15, 20, 21, 28, 30, 40, 50, 60, 70, 90, 100 and 120. The MAH has stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. These data support the applied shelf-life of 36 months. This medicinal product does not require any special storage conditions.

Quality Overall Summary

A satisfactory quality overall summary is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information

The approved Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The PIL user-testing report has been evaluated and is accepted. It supports the readability of the package leaflet. The labelling fulfils the statutory requirements for Braille.

The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

Conclusion

The quality grounds for this application are considered adequate. There are no objections to approval of Levocetirizine Dihydrochloride 5 mg film-coated tablets from a pharmaceutical point of view.
III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable considering that this is an application for a generic version of a product that has been licensed for more than 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of levocetirizine dihydrochloride, a widely used and well-known active substance. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the UK product, Xyzal 5 mg film coated Tablets (UCB Pharma Ltd).

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This was an application for a generic product and there is no reason to conclude that marketing of this product will change the overall use pattern of the existing market. There are no environmental concerns associated with the method of manufacture or formulation of the product.

There are no objections to approval of Levocetirizine Dihydrochloride 5 mg film-coated tablets from a non-clinical point of view.

III.3 CLINICAL ASPECTS

BACKGROUND

Levocetirizine is a selective, potent, oral second generation histamine H1 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.

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.

The pharmacokinetics of levocetirizine are linear with dose- and time-independent with low inter-subject variability. The pharmacokinetic profile is the same when given as the single enantiomer or when given as cetirizine. No chiral inversion occurs during the process of absorption and elimination.

Levocetirizine is rapidly and extensively absorbed following oral administration. Peak plasma concentrations are achieved 0.9 h after dosing. Steady state is achieved after two days. Peak concentrations are typically 270 ng/ml and 308 ng/ml following a single and a repeated 5 mg o.d. dose, respectively. The extent of absorption is dose-independent and is not altered by food, but the peak concentration is reduced and delayed.
INDICATIONS
Levocetirizine Dihydrochloride 5 mg film-coated tablets are indicated for the symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) and urticaria.

The indications are consistent with those for the reference product and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION
The recommended daily dose is 5 mg (one film-coated tablet).

The posology is consistent with that for the reference product and is satisfactory.

CLINICAL PHARMACOLOGY
The clinical pharmacology of levocetirizine dihydrochloride is well-known. With the exception of the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for this application.

Pharmacokinetics - bioequivalence study
The application is supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Levocetirizine Dihydrochloride 5 mg film-coated tablets, to that of the reference product, Xyzal 5 mg film coated Tablets (UCB Pharma Ltd). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis were provided for the test and reference products.

This was an open-label, randomised, two-treatment, two-sequence, two-period, single dose crossover bioequivalence study conducted in healthy adult human subjects under fasting conditions. Following an overnight fast, a single 5 mg dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 4 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose and at specified time points up to 48.0 hours after administration of test or reference product. Plasma levels of levocetirizine were detected by a validated LC-MS/MS method.

The primary pharmacokinetic parameters for the study were $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) of the ratio of the test and reference products fell within the acceptance range, 0.80-1.25 (80.00%-125.00%), for log-transformed $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ for levocetirizine.

Results:
An appropriate number of subjects completed the study and were included in the pharmacokinetic evaluation and statistical analysis.

Safety - There were no deaths or serious or significant adverse events.

The summary of the results of the bioequivalence study are tabulated below:
Summary pharmacokinetic data for levocetirizine for a randomised, 2-way, single-dose crossover study; healthy subjects, dosed fasted; t=48 hours. Wash-out period: 4 days.

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>(In-transformed) Geometric Least Squares Mean</th>
<th>Ratio (B / A)%</th>
<th>90% Confidence Interval (Parametric)</th>
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</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>Test Product-B: 225.173</td>
<td>Reference Product-A: 217.684</td>
<td>103.4 %</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (ng.h/mL)</td>
<td>Test Product-B: 2343.419</td>
<td>Reference Product-A: 2431.402</td>
<td>96.4 %</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (ng.h/mL)</td>
<td>Test Product-B: 2448.854</td>
<td>Reference Product-A: 2543.803</td>
<td>96.3 %</td>
</tr>
</tbody>
</table>

$C_{\text{max}}$  maximum plasma concentration  
$AUC_{0-t}$  area under the plasma concentration-time curve from time zero to t hours  
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity

**Discussion on Bioequivalence**

The results of the bioequivalence study show that the test and reference products are bioequivalent, under fasting conditions, as the confidence intervals for $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ fall within the acceptance criteria ranges of 80.00-125.00% in line with current guidelines.

**Clinical efficacy**

No new data have been submitted and none are required. The reference product is established and the application is supported by the demonstration of bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of levocetirizine dihydrochloride is well-established from its extensive use in clinical practice.

**Clinical safety**

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of levocetirizine dihydrochloride is well-known.

**CLINICAL OVERVIEW**

A satisfactory clinical overview is provided and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

**PRODUCT INFORMATION:**

**Summary of Product Characteristics (SmPC)**

The approved SmPC is consistent with that for the reference product and is acceptable.

**Patient Information Leaflet**

The PIL is in line with the approved SmPC and is satisfactory.

**Labelling**

The labelling is satisfactory.

**CONCLUSIONS**

Sufficient clinical information has been submitted to support this application. The risk-benefit of the product is considered favourable from a clinical perspective. The grant of a Marketing Authorisation was, therefore, recommended.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Levocetirizine Dihydrochloride 5 mg film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Levocetirizine Dihydrochloride 5 mg film-coated tablets and the reference product, Xyzal 5 mg film coated Tablets (UCB Pharma Ltd).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The approved SmPC is consistent with that for the UK reference product and is satisfactory.

A mock-up PIL has been provided. The package leaflet is in line with the SmPC and is satisfactory. It 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. 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.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label. The MAH has stated that not all licensed pack sizes may be marketed. They have committed to submitting mock-ups for unmarketed pack sizes to the relevant regulatory authorities for approval before those packs are commercially marketed.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant’s Levocetirizine Dihydrochloride 5 mg film-coated tablets is a generic version of the reference product, Xyzal 5 mg film coated Tablets (UCB Pharma Ltd). Extensive clinical experience with levocetirizine dihydrochloride is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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