Public Assessment Report

Scientific discussion

Desloracell 5 mg, film-coated tablet
(desloratadine)

NL License RVG: 112807

Date: 6 July 2015

This module reflects the scientific discussion for the approval of Desloracell 5 mg, film-coated tablet. The marketing authorisation was granted on 12 May 2014. For information on changes after this date please refer to the ‘steps taken after finalisation’ at the end of this PAR.
I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Desloracell 5 mg, film-coated tablet from Medcell Pharma B.V.

The product is indicated for the relief of symptoms associated with:
- allergic rhinitis
- urticaria.

A comprehensive description of the indications and posology is given in the SmPC.

Desloratadine is a non-sedating, long-acting histamine antagonist with selective peripheral H1-receptor antagonist activity. After oral administration, desloratadine selectively blocks peripheral histamine H1-receptors because the substance is excluded from entry to the central nervous system.

This national procedure concerns a generic application claiming essential similarity with the innovator product Aerius 5 mg film-coated tablets which is registered in the EEA by Merck Sharp & Dohme Ltd. The marketing authorisation was first registered on 15 January 2001 through a centralized procedure (EU/1/00/160/001-013).

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Desloracell 5 mg is a blue, round, biconvex film-coated tablet with “LT” debossed on one side and plain on the other side.

The film-coated tablets are packed in OPA/Aluminium/PVC blisters.

The excipients are:
- Tablet core - microcrystalline cellulose, pregelatinised maize sarch, mannitol, talc, magnesium stearate
- Tablet coating - hypromellose 6cP, titanium dioxide (E171), macrogol 6000 and indigo carmine aluminium lake.

II.2 Drug Substance

The active substance is desloratadine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white to off-white crystalline powder, which is freely soluble in methanol, soluble in ethanol, very slightly soluble in acetone and insoluble in water.

The desloratadine molecule does not contain any chiral centres, but exhibits structural isomerism. Desloratadine exists in two different polymorphic forms, Forms I and II. Both forms are stable and bioequivalent.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
There is only one synthetic step from loratadine to desloratadine. Loratadine is accepted as the starting material as its synthesis and control are supported by a valid CEP. The manufacturing process of the active substance has been described in sufficient detail.

Quality control of drug substance
The drug substance specification is has been established in-house by the MAH, based on the primary specification of the DMF holder, with no additional requirements. The specifications are acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided by the DMF holder. This is acceptable as no additional requirements are applied by the MAH. The specification of the DMF-holder has been updated to be in line with the Ph.Eur. monograph. The MAH committed to update the specification accordingly by means of variation after registration.

Stability of drug substance
The results of the accelerated (25°C/60% RH) and long term (5±3°C) stability studies on 3 consecutive batches indicate that the drug substance is relatively stable and justify the proposed retest period of 4 years under refrigeration.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Dissolution profiles for the bioequivalence study test and reference batches were generated at three different pH levels: pH 1.2, pH 4.5 and pH 6.8.
For the profiles at pH 1.2 and 6.8 more than 85% was dissolved within 15 minutes. The dissolution profile at pH 4.5 also demonstrated similar dissolution for both test and reference batch.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of direct compression followed by coating and packaging and can be considered a standard process. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot-scale batches. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with their respective Ph.Eur monographs. The Opadry coating specifications are set according to the manufacturer. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, uniformity of dosage units, average tablet mass, assay, related substances and microbiological tests. The release and shelf-life requirements are identical. The specifications are acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided for 3 pilot-scale batches and 3 production-scale batches stored at 30°C/65% RH (36 months and 18 months respectively) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Alu-Alu blister packs.
At accelerated and long-term conditions some trends were observed. However, all results remain within the specification limits. A photostability study in compliance with ICH Q1b demonstrated that the tablets are photostable.
Based on the stability data provided, the proposed shelf-life of 36 months without special storage conditions packed in Al-Al blisters can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
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. Magnesium stearate is of vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Desloracell 5 mg, film-coated tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH committed to update the dossier in line with the Ph. Eur. monograph on desloradine and submit a variation to notify this update.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Desloracell is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Aerius, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Desloradine is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the MEB agrees that no further clinical studies are required.

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

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Desloracell 5 mg (Medcell Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Aerius 5 mg tablets (SP Europe, Belgium).

The choice of the reference product in the bioequivalence study is acceptable, as the innovator product has been registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects. Each subject received a single dose (5 mg) of one of the 2 desloratadine formulations. The tablet was orally administered under fasted conditions. There were 2 dosing periods, separated by a washout period of 17 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 24, 36, 48 and 72 hours after administration of the products.

Desloratadine can be taken without regard to meals. Therefore, a single dose, cross-over study under fasted conditions is the correct design to establish bioequivalence between two formulations. Desloratadine has a terminal elimination half-life of approximately 27 hours. Instead of AUC_{0-t}, a truncated AUC (AUC_{0-72h}) was estimated. This is in accordance with the guidance on investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1, “A sampling period longer than 72 hours is not considered necessary for any immediate release formulation. Hence for drugs with a long half-life, comparison of extent of exposure using truncated AUCs at 72 hours is acceptable.”. The wash-out period of 17 days is long enough for subjects with normal metabolism of desloratadine.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Three subjects failed to report for period 2. The remaining 21 subjects completed the study were eligible for pharmacokinetic analysis.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=21</th>
<th>(\text{AUC}_{0-72}) pg/ml/h</th>
<th>(\text{C}_{\text{max}}) pg/ml</th>
<th>(\text{t}_{\text{max}}) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>47538 ± 14268</td>
<td>2749 ± 629</td>
<td>4.50 (1.50-6.00)</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>50258 ± 15865</td>
<td>2872 ± 779</td>
<td>4.50 (1.00-5.50)</td>
<td></td>
</tr>
</tbody>
</table>

*Ratio (90% CI)

0.95 (0.89-1.02) 0.96 (0.89-1.04)

CV (%) 12 14

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours

\(\text{C}_{\text{max}}\) maximum plasma concentration
\(\text{t}_{\text{max}}\) time for maximum concentration
\(\text{t}_{1/2}\) half-life

*ln-transformed values

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-72} and \(\text{C}_{\text{max}}\) are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Desloracell 5 mg is considered bioequivalent with Aerius 5 mg tablets.

There was one adverse event during the conduct of the study. The laboratory abnormality (documented as adverse event) detected during the end of the study safety analysis was raised liver enzymes (serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase). This adverse event was detected during the end of study safety analysis and hence could not be attributed to either the test or the reference product. No serious adverse events were reported during the conduct of this study.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).
IV.3 Risk Management Plan

The MAH has submitted a risk management plan, 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 Desloracell.

- Summary table of safety concerns as approved in RMP

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important potential risk</td>
<td>Hypospadias</td>
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<tr>
<td>Missing information</td>
<td>Exposure during breastfeeding</td>
</tr>
<tr>
<td></td>
<td>Exposure during pregnancy</td>
</tr>
<tr>
<td></td>
<td>Exposure in children younger than 12 years old</td>
</tr>
</tbody>
</table>

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Aerius. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

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. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. In both rounds 90% of the test participants were able to find the information requested within the package leaflet of which 90% showed that they understand it.

In conclusion, 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

Desloracell 5 mg, film-coated tablet has a proven chemical-pharmaceutical quality and is a generic form of Aerius 5 mg film-coated tablets. Aerius is a well-known medicinal product with an established favourable efficacy and safety profile.

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

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Desloracell with the reference product, and has therefore granted a marketing authorisation. Desloracell 5 mg, film-coated tablet was authorised in the Netherlands on 12 May 2014.
<table>
<thead>
<tr>
<th>Scope</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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<td>Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites), the activities for which the manufacturer importer is responsible do not include batch release.</td>
<td>IA/G</td>
<td>26-6-2014</td>
<td>11-8-2014</td>
<td>Non-approval</td>
<td>No</td>
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<td>Change to importer, batch release arrangements and quality control testing of the finished product: Replacement or addition of a manufacturer responsible for importation and/or batch release, not including batch control/testing</td>
<td>IA/G</td>
<td>18-3-2015</td>
<td>14-4-2015</td>
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