# Decentralised Procedure

# Public Assessment Report

# Desloratadin axcount 5 mg Filmtabletten

# Desloratadine

# DE/H/5934/003/DC

# (formerly UK/H/5815/003/DC)

# Applicant: Axcount Generika GmbH

# Date: 11.02.2020

**This module reflects the scientific discussion for the approval of "Desloratadin axcount 5 mg Filmtabletten". The procedure was finalised on 7th March 2016.**

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# ADMINISTRATIVE INFORMATION

| | |
|---|---|
| **Name of the medicinal product in the RMS:** | Desloratadin axcount 5 mg Filmtabletten |
| **Name of the drug substance (INN name):** | Desloratadine |
| **Pharmaco-therapeutic group (ATC Code):** | R06AX27 |
| **Pharmaceutical form(s) and strength(s):** | Film-coated tablets; 5 mg |
| **Reference Number(s) for the Decentralised Procedure:** | DE/H/5934/003/DC (formerly UK/H/5815/003/DC) |
| **Reference Member State:** | DE (formerly UK) |
| **Concerned Member States:** | ES |
| **Applicant (name and address):** | Axcount Generika GmbH<br>Max-Planck-Straße 36 d<br>61381 Friedrichsdorf<br>Germany |

# I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Health care products Regulatory Agency (MHRA) granted Bristol Laboratories Ltd, a marketing authorisation for the medicinal product Desloratadine tablets (PL 17907/10501; UK/H/5815/003/DC) The product is a prescription-only medicine (POM) indicated in adults and adolescents aged 12 years and older for the relief of symptoms associated with:

- allergic rhinitis (see section 5.1 of the SmPC)
- urticaria (see section 5.1 of the SmPC)

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Spain and Germany as Concerned Member State (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Aerius 5 mg film-coated tablets, which was centrally authorised to Schering Plough Europe on 15 January 2001 and subsequently unde1went a change of ownership procedure to the current marketing authorisation holder (MAH) Merck Sharp & Dohme Ltd.

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. Desloratadine has demonstrated antiallergic properties from in vitro studies. These include inhibiting the release of proinflammatory cytokines such as IL-4, IL-6, IL-8, and IL-13 from human mast cells/basophils, as well as inhibition of the expression of the adhesion molecule P-selectin on endothelial cells. The clinical relevance of these observations remains to be confirmed.

The applicant submitted one bioequivalence study with their original submission. However, following recent regulatory action, the bioequivalence study that was performed to support this application was not considered suitable. The applicant therefore submitted a new bioequivalence study to support these applications. The applicant has stated that the new bioequivalence study was conducted in accordance with the current EMA guidance documents, Good Clinical Practice (GCP), as established by the International Conference on Harmonization (ICH), the basic principles defined in Division 5 of the Canadian Food and Drug Regulations, the Belmont Report, the European Directive EC/2001, and the principles enunciated in the World Medical Association Declaration of Helsinki (Fortaleza, Brazil, October 2013).

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that these applications were based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

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 these products.

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, '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 and CMS considered that the applications. could be approved at the end of procedure on 07 March 2016. After a subsequent national phase, licences were granted in the UK on 05 April 2016.

After changing the RMS, Germany is the new RMS. The former procedure number was UK/H/5815/003/DC.

# II. QUALITY ASPECTS

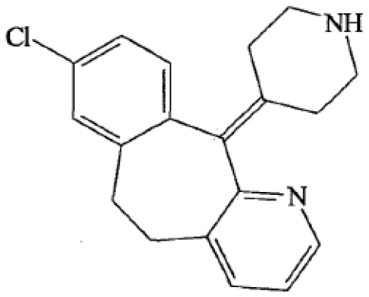
## II.1 Introduction

Each film-coated tablet contains 5 mg desloratadine, as the active ingredient. Other ingredients consist of the pharmaceutical excipients:

Tablet core:
Cellulose microcrystalline, partially pregelatinised maize starch, magnesium stearate and colloidal anhydrous silica

Tablet coating (Opadry blue):
Hypromellose 6cp, titanium dioxide (E171), microcrystalline cellulose, stearic acid and Indigo carmine (E132).
The finished product is packed into transparent polychlorotrifluoroethylene (PCTFE)/ polyvinyl chloride (PVC) or PVC/polyethylene (PE)/polyvinylidene chloride (PVDC) aluminium blister packs of 1, 2, 3, 5, 7, 10, 14, 15, 20, 21, 30, 50, 90 or 100 tablets. Not all pack sizes may be marketed.
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

## II.2 Drug substance

| | |
|---|---|
| INN name: | Desloratadine |
| Other name: | Descarboyethoxyloratadine |
| Chemical name: | 8-Chloro-11-(piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta [1,2-b]pyridine. |
| Molecular formula: | $C_{19}H_{19}ClN_2$ |
| Structure: |   |
| Molecular weight: | 310.8 g/mol |
| Description: | White to off-white powder with pink cast. |
| Solubility: | Very slightly soluble or practically insoluble in water, freely soluble in ethanol (96 per cent), slightly soluble or very slightly soluble in heptane. |

Desloratadine was not the subject of a European Pharmacopoeia monograph at the time of assessment.

All aspects of the manufacture and control of the active substance, desloratadine, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

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.

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.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.

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 objective of the development programme was to formulate safe, efficacious film-coated tablets containing 5 mg desloratadine per tablet that are a generic version of the reference product Aerius 5 mg film-coated tablets. A satisfactory account of the pha1maceutical development has been provided.

Comparative *in-vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the tablet coat Opadry blue which is controlled to a :suitable in-house specification. The indigo carmine (E132) constituent of the tablet coat is stated to comply with EU Directive 2008/128/EC (which supersedes 95/45/EC) on food additives used as colouring agents. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

**Manufacture of the product**

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale batch size and has shown satisfactory results.

**Finished Product Specification**

The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications.
Certificates of Analysis have been provided for all working standards used.

**Stability of the Product**

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years with the storage condition ‘Store in the original packaging.’.
Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

## II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of these applications from a pharmaceutical viewpoint.

# III. NON-CLINICAL ASPECTS

## III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of desloratadine 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.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

## III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

## III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

## III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

## III.5 Environmental Risk Assessment (ERA)

Since Desloratadine tablets are 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.6 Discussion on the non-clinical aspects

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.
There are no objections to the approval of these applications from a non-clinical viewpoint.

# IV. CLINICAL ASPECTS

## IV.1 Introduction

The clinical pharmacology of desloratadine is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of desloratadine.

Based on the data provided, Desloratadine orodispersible tablets can be considered bioequivalent to Aerius 2.5 mg and 5 mg orodispersible tablets (Merck Sharp & Dohme Ltd).

## IV.2 Pharmacokinetics

In support of these applications, the applicant submitted the following bioequivalence studies:

**STUDY 1**

The applicant submitted one bioequivalence study with their original submission. However, following recent regulatory action, the bioequivalence study that was performed to support this application was not considered suitable. The applicant therefore submitted two new bioequivalence studies to support these applications:

The applicant submitted the following two bioequivalence studies:

**STUDY 2**

An open-label, randomised, single-dose, crossover, oral bioequivalence study of the applicant's test product Desloratadine 5 mg film coated tablets (Bristol Laboratories Ltd) versus the reference

product Aerius 5 mg film-coated tablet (Merck Sharp & Dohme Ltd) in healthy, adult, subjects under fasting conditions.

Following an overnight fast, subjects were administered a single dose (1 x 5 mg tablet) of the test or the reference product.

Blood samples were collected for plasma levels before dosing and up to and including 72 hours after each administration. The washout period between the treatment phases was 21 days. The pharmacokinetic results are presented below:

**Table: The mean pharmacokinetic (PK) results and 90% Cl of the log-transformed PK parameters for desloratadine are presented in the table and graph below:**

**Bioequivalence Results:**

TREATMENT A vs TREATMENT B

| Parameter ( N/N ) | Geometric Means Arithmetic Means (CV %) TRT A | TRT B | Ratio of Geometric Means | 90% Confidence Interval | Intra-Subject CV (%) |
|---|---|---|---|---|---|
| AUC72 (pg.h/mL) (19 /19 ) | 44729.49 46750.70 (43.11 ) | 49870.81 54711.80 (43.73 ) | 89.68 | 84.24 - 95.47 | 11.14 |
| CMAX (pg/mL) (19 /19 ) | 2631.21 2788.33 (33.78 ) | 3123.46 3284.18 (30.72 ) | 84.24 | 78.00 - 90.98 | 13.72 |
| Tmax* (h) (19 /19 ) | 5.00 (1.50 - 6.03 ) | 3.00 (1.00 - 6.00 ) | | | |

* Presented as median and range

TRT A=test product
TRT B=reference product
$AUC_{0-72}$ area under the plasma concentration-time curve from zero to 72 hours
$C_{max}$ maximum plasma concentration

**Conclusion**
Although the 90% C.I for $AUC_{0-72}$ lie within the acceptable limits of 80.00% to 125.00%, in line with the ' Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/140I/98 Rev 1/Con**), this criteria was not met for $C_{max}$. Therefore the results failed to demonstrate that the test product desloratadine is bioequivalent to the reference product. This could probably be due to the number of drop-outs which was higher than expected, especially for desloratadine.
Based on the submitted bioequivalence study Deslomtadine 5 mg film coated tablets (Bristol Laboratories Ltd) cannot be considered bioequivalent with Aerius 5 mg Tablets (Merck Sharp & Dohme Ltd.).

**STUDY 3**
An open-label, randomised, single-dose, crossover, oral bioequivalence study of the applicant's test product Desloratadine 5 mg film coated tablets (Bristol Laboratories Ltd) versus the reference product Aerius 5 mg film-coated tablet (Merck Sharp & Dohme Ltd) in healthy, adult, subjects under fasting conditions.
Following an ovemight fast, subjects were administ1ered a single dose (I x 5 mg tablet) of the test or the reference product.

Blood samples were collected for plasma levels before dosing and up to and including 72 hours after each administration. The washout period between the treatment phases was 21 days. The pharmacokinetic results are presented below:

**Table: The mean pharmacokinetic (PK) results and 90% CI of the log-transformed PK parameters for desloratadine are presented in the table and graph below:**

**Bioequivalence Results:**

TREATMENT A vs TREATMENT B

| Parameter ( N/N ) | Geometric Means Arithmetic Means (CV %) TRT A | TRT B | Ratio of Geometric Means | 90% Confidence Interval | Intra-Subject CV (%) |
|---|---|---|---|---|---|
| AUC72 (pg.h/mL) (30 /32 ) | 58365.21<br>61370.94 (39.31 ) | 57077.04<br>62989.34 (49.22 ) | 102.26 | 97.08 - 107.77 | 12.08 |
| CMAX (pg/mL) (32 /32 ) | 3409.76<br>3612.44 (36.11 ) | 3270.22<br>3538.68 (42.92 ) | 104.24 | 98.45 - 110.36 | 13.53 |
| Tmax* (h) (32 /32 ) | 5.00<br>(1.00 - 6.50 ) | 3.00<br>(1.00 - 7.00 ) | | | |

* Presented as median and range

TRT A=test product
TRT B=reference product
$AUC_{0-72}$ area under the plasma concentration-time curve from zero to 72 hours
$C_{max}$ maximum plasma concentration

**Conclusion**

The 90% confidence intervals of the test/reference ratio for AUC and $C_{max}$ values for desloratadine for the 5 mg test product strength lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401198 Rev 1/Con**). Thus, the data support the claim that the applicant's test product Desloratadine 5 mg film-coated tablets (Bristol Laboratories Ltd) is bioequivalent to the reference product Aerius 5 mg film-coated tablets (Merck Sharp & Dohme Ltd).

## IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for applications of this type.

## IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for applications of this type.

## IV.5 Clinical safety

No new safety data were submitted and none are required.

## IV.6 Risk Management Plan

The marketing authorisation holder (MAH) has submitted a risk management plan (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 desloratadine.
A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
Summary table of safety concerns:

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | • Hypersensitivity (including anaphylaxis, angioedema, dyspnea, pruritus, rash and urticaria)<br>• Abnormal hepatic function (including hepatitis and elevated hepatic enzymes and bilirubin) |
| Important potential risks | • Seizure<br>• Movement disorder (including psychomotor hyperactivity and restlessness)<br>• Supraventricular tachyarrhythmiaHallucinations<br>• Use in patients with severe renal insufficiency<br>• Abnormal behaviour in paediatric patients (including anger, aggression and agitation)<br>• Photosensitivity<br>• QT prolongation |
| Missing information | • Effects on fertility<br>• Use in pregnancy and lactation<br>• Use in children below the age of 1<br>• Effects of desloratadine in poor metabolisers < 2 years of age |

Routine pharmacovigilance and routine risk minimisation proposed for all safety concerns.

## IV.7 Discussion on the clinical aspects

With the exception of the bioequivalence studies, no new 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.

Bioequivalence has been demonstrated between the applicant's test product Desloratadine 5 mg film-coated tablets (Bristol Laboratories Ltd) and the reference product Aerius 5 mg film-coated tablets (Merck Sharp & Dohme Ltd).
The grant of marketing authorisations is recommended for this application.

# V. USER CONSULTATION

A user consultation with target patient groups on the package Information leaflet (PIL) has been performed on the basis of a bridging report making reference to the reference product Aerius 5 mg

film-coated tablets (Merck Sharp & Dohme Ltd) for the content of the PILs and Ranitidine 300mg film-coated tablets (Bristol Laboratories Ltd; PL 17907/0030) for the style and layout of the PILs. The bridging report submitted by the applicant has been found acceptable.

# VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with desloratadine is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

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.

The application is approved. For intermediate amendments see current product information.