DESLORATADINE 5 MG FILM-COATED TABLETS

PL 24837/0035

UKPAR

TABLE OF CONTENTS

Lay Summary .................................................. Page 2
Scientific Discussion ........................................ Page 3
Steps Taken for Assessment ............................... Page 13
Steps Taken After Initial Procedure – Summary .... Page 14
Summary of Product Characteristics .................. Page 15
Patient Information Leaflet ................................. Page 16
Labelling ......................................................... Page 17
DESLORATADINE 5 MG FILM-COATED TABLETS
PL 24837/0035

SCIENTIFIC DISCUSSION

This is a summary of the public assessment report (PAR) for Desloratadine 5 mg film-coated tablets. It explains how Desloratadine 5 mg film-coated 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 Desloratadine 5 mg film-coated tablets.

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

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

Desloratadine relieves symptoms associated with allergic rhinitis (inflammation of the nasal passages caused by an allergy, for example, hay fever or an allergy to dust mites). These symptoms include sneezing, runny or itchy nose, itchy palate, and itchy, red or watery eyes. Desloratadine is also used to relieve the symptoms associated with urticaria (a skin condition caused by an allergy). These symptoms include itching and hives.

Desloratadine can be used by adults and children of 12 years of age and older.

How do Desloratadine 5 mg film-coated tablets work?
When the body reacts to allergens, such as pollen or dust mites, histamine is released and binds to H1 receptors in the body. In hay fever and other nasal allergies this results in inflammation of the nose, eyes, skin or airways, itchy watery eyes, a runny nose, sneezing and nasal congestion. In skin allergies such as urticaria histamine causes inflammation of the skin and results in an itchy rash, swelling and hives. Desloratadine belongs to a group of medicines known as the anti-histamines and works by blocking histamine receptors and preventing these allergic reactions.

How are Desloratadine 5 mg film-coated tablets used?
Desloratadine 5 mg film-coated tablets should be swallowed whole with water, with or without food. The recommended dose is one tablet once a day. The duration of treatment is dependent on the type of allergic disease and should be determined by a doctor.

The medicine can only be obtained with a prescription.

What benefits of Desloratadine 5 mg film-coated tablets have been shown in studies?
Because Desloratadine 5 mg film-coated tablets is a generic medicine, studies in patients have been limited to tests to determine that the tablets are bioequivalent to the reference medicine, Aerius 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 Desloratadine 5 mg film-coated tablets?
Because Desloratadine 5 mg film-coated tablets is a generic medicine and is bioequivalent to the reference medicine, the benefits and possible side effects of this medicine are taken as being the same as the reference medicine. For the full list of restrictions, see the package leaflet.

Why are Desloratadine 5 mg film-coated tablets approved?
It was concluded that, in accordance with EU requirements, Desloratadine 5 mg film-coated tablets have been shown to have comparable quality and to be bioequivalent to Aerius 5 mg film-coated tablets. Therefore, the MHRA decided that, as for Aerius 5 mg film-coated tablets, the benefits are greater than the risks and recommended that Desloratadine 5 mg film-coated tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Desloratadine 5 mg film-coated tablets?
A risk management plan has been developed to ensure that Desloratadine 5 mg film-coated tablets are used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Desloratadine 5 mg film-coated 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/healthcare professionals will be monitored/reviewed continuously as well.

Other information about Desloratadine 5 mg film-coated tablets
The marketing authorisation for Desloratadine 5 mg film-coated tablets was granted on 25 October 2011.

The full PAR for Desloratadine 5 mg film-coated tablets follows this summary. For more information about treatment with Desloratadine 5 mg film-coated tablets, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in 08-2014.
DESLORETADINE 5 MG FILM-COATED TABLETS
PL 24837/0035

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction ........................................... Page 4

Pharmaceutical assessment ....................... Page 6

Non-clinical assessment .............................. Page 9

Clinical assessment .................................. Page 10

Overall conclusions and risk assessment ....... Page 12
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Consilient Health Limited a Marketing Authorisation for the medicinal product Desloratadine 5 mg film-coated tablets (PL 24837/0035) on 25 October 2011. This product is a prescription-only medicine (POM), indicated for the relief of symptoms associated with:

- allergic rhinitis
- urticaria.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Aerius 5 mg film-coated tablets (Schering-Plough Europe), which was first authorised in Europe via a Centralised Procedure on 15 January 2001.

The active ingredient, 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. The selectivity is achieved because the substance is excluded from the entry into the central nervous system.

No new non-clinical data have been submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

A single-dose, bioequivalence study carried out under fasting conditions was submitted to support this application, comparing the pharmacokinetic profile of the test product, Desloratadine 5 mg film-coated tablets (Consilient Health Limited, Ireland), versus the reference product, Aerius 5 mg film-coated tablets (Schering-Plough, Europe). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new or unexpected safety concerns arose during the review of the information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Desloratadine 5 mg film-coated tablets outweigh the risks; hence the Marketing Authorisation was granted.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE
INN: Desloratadine
Chemical names: 8-chloro-6,11-dihydro-11-(4-piperidinyldene)-5Hbenzo[5, 6]cyclohepta [1,2-b]pyridine

Structure:

Molecular Formula: C_{19}H_{19}ClN_{2}
Molecular weight: 310.83
Appearance: A white to cream colour powder with pinkish tinge. Freely soluble in dichloromethane, soluble in methanol and chloroform, very slightly soluble in acetone and ethyl acetate, and practically insoluble in water.

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

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.

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

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

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

DRUG PRODUCT
Other Ingredients
Other ingredients (in the tablet core and coating) consist of the pharmaceutical excipients, namely microcrystalline cellulose (E460), hypromellose (E464), hydrochloric acid (E507), sodium hydroxide (E524), maize starch, lactose monohydrate, talc (E553b), macrogol, titanium dioxide (E171) and indigo carmine aluminium lake (E132).
Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their respective European Pharmacopoeia monographs, with the exception of Indigo carmine aluminium lake (E132). Indigo carmine aluminium lake (E132) complies with its respective in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

The specification for Indigo carmine aluminium lake (E132) is in compliance with current European Directives concerning use of colouring agents in foodstuff.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in its production is sourced from healthy animals under the same conditions as that for human consumption. In addition, the supplier has confirmed that no ruminant material is present.

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

**Pharmaceutical Development**
The objective of the development programme was to formulate safe, efficacious, stable product that could be considered a generic medicinal product of the reference product, Aerius 5 mg film-coated tablet (Schering-Plough, Europe).

Suitable pharmaceutical development data have been provided for this application.

Comparative dissolution and impurity profiles have been provided for this product and its respective reference product.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Finished Product Specification**
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**
The tablets are packaged in either:

i. polyvinylchloride/polyvinylidene chloride/aluminium(PVC/PVDC/Al) foil blisters. The blister strips are packed in cardboard boxes in pack sizes of 7, 10, 20, 30, 50, 90 and 100 film-coated tablets or

ii. high-density polyethylene (HDPE) tablet containers, with polypropylene closures, containing a dessicant in a pack size of 250 film-coated tablets.

Not all pack sizes may be marketed. However, the Marketing Authorisation holder has committed to submitting mock-ups to the UK regulatory authorities for approval before marketing any pack size.
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuff.

**Stability**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, the following shelf-life/storage conditions have been accepted:
- 2 years for product packaged in blister packs, with the storage condition, ‘store in the original package in order to protect from moisture’
- 2 years before opening and 3 months after first opening of the tablet container, for the product packaged in the HDPE tablet containers, with the storage condition ‘store in the original package in order to protect from moisture’.

**Bioequivalence/Bioavailability**
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

**Summaries of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SmPC, PIL and labelling are satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**MAA Forms**
The MAA form is satisfactory.

**Expert Report**
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
The grant of a Marketing Authorisation is recommended.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
As the pharmacodynamic, pharmacokinetic and toxicological properties of desloratadine are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT
The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the product is intended for a generic substitution with a product that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The clinical pharmacology of desloratadine is well-known. With the exception of data from the below bioequivalence study, no new pharmacodynamic or pharmacokinetic data are provided or required for this application.

Pharmacokinetics
In support of the application, the Marketing Authorisation Holder has submitted the following bioequivalence study:

A single-dose, randomized, open-label, two-period, two-sequence, two-treatment, crossover study to compare the pharmacokinetics of the test product Desloratadine 5 mg film-coated tablets (Consilient Health, Ireland) versus the reference product, Aerius 5 mg film-coated tablets (Schering-Plough, Europe) in healthy adult male subjects under fasted conditions.

The subjects received a single oral dose of either the test or the reference product, with 240 ml of water, after an overnight fast. Blood samples were taken for the measurement of pharmacokinetic parameters pre-dose and up to 72 hours post dose. The washout period between the two treatment arms was 14 days. The pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters (geometric least squares mean, ratios and confidence intervals [CI]) of desloratadine:</th>
<th>Desloratadine 5 mg (Test)</th>
<th>Aerius 5 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\text{max} (pg/ml)</td>
<td>2183.88</td>
<td>2175.36</td>
<td>100.39</td>
<td>93.64-107.63</td>
</tr>
<tr>
<td>AUC\text{0-72h} (pg.h/ml)</td>
<td>31596.52</td>
<td>32644.35</td>
<td>96.79</td>
<td>91.89-101.95</td>
</tr>
<tr>
<td>AUC\text{0-\infty} (pg.h/ml))</td>
<td>34395.68</td>
<td>35031.98</td>
<td>98.18</td>
<td>93.02-103.64</td>
</tr>
</tbody>
</table>

AUC\text{0-72h} area under the plasma concentration-time curve from time zero to 72 hours
AUC\text{0-\infty} area under the plasma concentration-time curve from time zero to infinity
C\text{max} maximum plasma concentration
90% geometric CI calculated from ln-transformed data

The 90% confidence intervals for AUC and C\text{max} for test versus reference product for desloratadine are within the acceptance criteria specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98). Thus, the data support the claim that the test product Desloratadine 5 mg film-coated tablets (Consilient Health Limited, Ireland) is bioequivalent to the reference product Aerius 5 mg film-coated tablets (Schering-Plough, Europe).

EFFICACY
The efficacy of desloratadine is well-known. No new efficacy data have been submitted and none are required for an application of this type.

SAFETY
With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for an application of this type. No new or unexpected safety issues were raised by the bioequivalence study.
SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPC, PIL and labelling are clinically acceptable. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and in-line with the current guidelines. The labelling is in-line with the current guidelines.

CLINICAL EXPERT REPORT
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person 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.

Suitable justification has been provided for not submitting a risk management plan for this product.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT
QUALITY
The important quality characteristics of Desloratadine 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. As the pharmacokinetics, pharmacodynamics and toxicology of sertraline are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new efficacy data were submitted and none are required for application of this type.

Bioequivalence has been demonstrated between the applicant’s 5 mg tablet strength and the reference product.

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for application of this type. No new or unexpected safety concerns arose from the bioequivalence study

PRODUCT LITERATURE
The SmPC, PIL and labelling are acceptable. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and in-line with the current guidelines. The labelling is in-line with the current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data provided support the claim that this product is a generic medicinal product of the reference product, Aerius 5 mg film-coated tablets (Schering-Plough, Europe). Extensive clinical experience with desloratadine is considered to have demonstrated the therapeutic value of the product. The benefit/risk is, therefore, considered to be positive.
DESLORATADINE 5 MG FILM-COATED TABLETS

PL 24837/0035

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation application on 26 January 2011.
2 Following standard checks and communication with the applicant the MHRA considered the application valid on 15 February 2011.
3 The application was determined and granted on 25 October 2011.
# DESLORATADINE 5 MG FILM-COATED TABLETS

**PL 24837/0035**

## STEPS TAKEN AFTER INITIAL AUTHORISATION – SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>17/09/2013</td>
<td>Type IB variation</td>
<td>To extend the shelf life of the product from two to three years; section 6.3 of the SmPC is updated.</td>
<td>Approved – 24/10/2013</td>
</tr>
<tr>
<td>08/04/2014</td>
<td>Type IB variation</td>
<td>To update sections 2 (Qualitative and quantitative composition), 4.2 (Posology and method of administration), 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), 4.6 (Fertility, pregnancy and lactation), 4.8 (Undesirable effects), 5.1 (Pharmacodynamic properties) and 5.2 (Pharmacokinetic properties) of the SmPC and consequentially the leaflet and label in line with the QRD template.</td>
<td>Approved – 07/07/2014</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
LABELLING

Blister:
Desloratadine 5 mg film-coated tablets

Carton with Braille: