PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Desloratadine Archie Samuel 5 mg film-coated tablets
Archie Samuel s.r.o., Czech Republic

desloratadine

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB’s knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2327/001/DC
Registration number in the Netherlands: RVG 109597

8 August 2012

Pharmacotherapeutic group: other antihistamines for systemic use
ATC code: R06AX27
Route of administration: oral
Therapeutic indication: relief of symptoms associated with allergic rhinitis and urticaria
Prescription status: prescription only
Date of authorisation in NL: 27 June 2012
Concerned Member States: Decentralised procedure with AT, BE, BG, CZ, DE, DK, FI, FR, HU, LU, PT, RO, SI, SK, UK
Application type/legal basis: Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.
I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Desloratadine Archie Samuel 5 mg film-coated tablets from Archie Samuel s.r.o. The date of authorisation was on 27 June 2012 in the Netherlands.

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 SPC.

Desloratadine is a non-sedating, long-acting histamine antagonist with selective peripheral H<sub>1</sub>-receptor antagonist activity. After oral administration, desloratadine selectively blocks peripheral histamine H<sub>1</sub>-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. Desloratidine is the major active metabolite of loratidine.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Aerius 5 mg film-coated tablets which has been registered in the EEA by Merck Sharp & Dohme Ltd. since 15 January 2001 through a centralised procedure (EU license number EU/1/00/160/001).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Aerius 5 mg film-coated tablets, registered in the EEA. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.
II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is desloratadine, an established active substance however not described in the European, British or US Pharmacopoeia (Ph.Eur., BP, USP*). It is a white to off white powder with pinkish background, which is soluble in methanol and chloroform, and insoluble in water. Desloratadine has no chiral centres. The active substance can exist in two polymorphic forms, but this has no clinical relevance as they are bioequivalent and have the same dissolution and stability profile.

The Active Substance Master File (ASMF) procedure is used for both suppliers of 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
Desloratadine is manufactured from loratadine and its structure is confirmed with chemical and spectroscopic data. Sufficient data have been provided on the synthesis.

Quality control of drug substance
The control tests and specifications for each sourced drug substance are adequately drawn up. A discussion on the potential and actual degradation products beside the synthesis impurities is provided. Batch analysis results of at least 3 batches from each manufacturer have been presented, demonstrating compliance with the proposed specification.

Stability of drug substance
Stability studies have been performed on the drug substance. No significant changes in any parameters were observed. From the stability data, the retest periods of 48 months & 36 months for respective drug substances have been accepted.

* Ph.Eur., USP and BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.

Medicinal Product

Composition
Desloratadine Archie Samuel 5 mg is a round, biconvex, blue film-coated tablet.

The film-coated tablets are packed in PVC/PVdC/aluminium blisters or HDPE bottles with PP caps.

The excipients are:
Tablet core
Poloxamer type 188
Citric acid monohydrate
Microcrystalline cellulose
Maize starch
Croscarmellose sodium
Lactose monohydrate
Talc

Tablet coat
Polyvinyl alcohol (part. hydrolyzed)
Titanium dioxide (E 171)
Macrogol/PEG 3350
Indigo carmine aluminium lake (E 132)
Talc

Pharmaceutical development
The objective was to develop a tablet formulation containing desloratadine that is essentially similar to the reference product Aerius 5mg film-coated tablets. The choice of packaging and excipients is usual for this dosage form. Trial formulations have been prepared by direct compression and wet granulation. Comparative dissolution testing was performed against the innovator at three different pH values. Comparable results were obtained. The pharmaceutical development has been sufficiently explained.

Manufacturing process
The product is manufactured by wet granulation, tablet compression and tablet coating. Sufficient in-process controls have been laid down. Process validation has been performed on 3 production batches. The validation results are acceptable.

Control of excipients
The excipients used are well-known and of pharmacopoeial quality. The colour coating is tested according to an in-house monograph. These specifications are acceptable.

Quality control of drug product
The drug product specifications cover appropriate parameters for the dosage form and include tests for description, identification, average weight, moisture content, content uniformity, related substances, dissolution, assay and microbiological purity. An overview of potential degradation products and actual found impurities is presented. Validations of analytical methods have been presented. Batch analysis results were provided on four pilot-scale batches. The results show that the finished products meet the specifications proposed.

Stability of drug product
Stability studies according to ICH conditions have been performed on 4 pilot batches of the drug product. The tablets were stored at 25°C/60% RH (36 months) and RH 40°C/75% RH (6 months) in both PVC/PVdC/aluminium blisters and HDPE bottles. All results were in compliance with the specifications. There were no significant trends observed. A photostability study was performed in conformity with ICH topic Q1B. Photostability testing showed no important degradation. Based on the data provided, a shelf-life of 48 months for blister and bottles was granted. For bottles no special storage condition is required. For blisters the storage condition “Store in the original package in order to protect from moisture” applies. An in-use stability study has been performed on 2 pilot batches packed in open HDPE bottles (500 tablets) and stored for 6 months at 25°C/60%RH. In-use stability of 6 months has been demonstrated.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
TSE certificates have been provided for lactose monohydrate, talc, poloxamer 188, citric acid monohydrate, sodium croscarmellose and microcrystalline cellulose.

II.2 Non-clinical aspects

This product is a generic formulation of Aerius, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.
Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of desloratadine released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Desloratadine is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Desloratadine Archie Samuel 5 mg (Archie Samuel s.r.o., Czech Republic) is compared with the pharmacokinetic profile of the reference products Aerius 5 mg film-coated tablets (Schering-Plough, France) and Aerius 5 mg (Schering-Plough, Canada). Only the data of the comparison with the French reference product are given as the comparison with the Canadian product is of no relevance for the EU.

The choice of the reference product
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.

Design
A single-dose, randomised, three-period, three-treatment, three-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy subjects (9 males, 15 females), aged 19-42 years. Each subject received a single dose (5 mg) of one of the 3 desloratadine formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. Fasting was continued for 4 hours after dosing. Drinking water was not allowed for 2 hour pre-dose to 2 hours post-dose. Thereafter, it was allowed at all times. There were 3 dosing periods, separated by a washout period of 21 days. Blood samples were collected pre-dose and at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 8.00, 12.0, 24.0, 48.0 and 72.0 hours after administration of the products.

Overall, the study design is appropriate for a bioequivalence study of an oral immediate-release formulation.

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
All subjects completed the study. One subject missed the 72-hour blood sample and was excluded from analysis, as per protocol. The remaining twenty-three subjects were included in the pharmacokinetic and statistical analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_max (median, range)) of desloratadine under fasted conditions.

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<th>Treatment</th>
<th>AUC_0-t</th>
<th>AUC_0-∞</th>
<th>C_max</th>
<th>t_max</th>
<th>t_1/2</th>
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<td>N=23</td>
<td>pg.h/ml</td>
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The 90% confidence intervals calculated for $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{\text{max}}$ are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25. Based on the pharmacokinetic parameters of desloratadine under fasted conditions, it can be concluded that Desloratadine Archie Samuel 5 mg and Aerius 5 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Desloratadine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of desloratadine. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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).

**Risk management plan**

Desloratadine was first approved in 2001, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of desloratadine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

**Product information**

**SPC**

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Aerius.

**Readability test**

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. A total of 17 questions was asked: 14 specific to the medicine and 3 general questions about the format of the leaflet. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The 1st round of testing showed that the information to answer each question was traced 100% of the time. Each question was answered correctly 100% of the time.

The 2nd round of testing showed that 100% of the participants were able to trace the information for the questions 100% of the time. Each of these participants showed they understood the information by answering the questions correctly 100% of the time. The 2nd round of testing showed that the information to answer each question was traced 100% of the time. Each question was answered correctly 100% of the time. Based on the test results, no revisions were made. The readability test has been sufficiently performed.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Desloratadine Archie Samuel 5 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Aerius 5 mg. 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Desloratadine Archie Samuel 5 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 23 February 2012. Desloratadine Archie Samuel 5 mg film-coated tablets was authorised in the Netherlands on 27 June 2012.

The date for the first renewal will be: 29 June 2016.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product
- The MAH committed to finish the ongoing stability studies.
- The MAH committed to perform an in-use stability study on a second batch at the end of shelf-life.
- The MAH committed to review the dissolution limit when more results from the 30 minutes time point become available.
List of abbreviations

ASMF  Active Substance Master File
ATC   Anatomical Therapeutic Chemical classification
AUC   Area Under the Curve
BP    British Pharmacopoeia
CEP   Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP  Committee for Medicinal Products for Human Use
CI    Confidence Interval
C\text{max} Maximum plasma concentration
CMD(h) Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV    Coefficient of Variation
EDMF  European Drug Master File
EDQM  European Directorate for the Quality of Medicines
EU    European Union
GCP   Good Clinical Practice
GLP   Good Laboratory Practice
GMP   Good Manufacturing Practice
ICH   International Conference of Harmonisation
MAH   Marketing Authorisation Holder
MEB   Medicines Evaluation Board in the Netherlands
OTC   Over The Counter (to be supplied without prescription)
PAR   Public Assessment Report
Ph.Eur. European Pharmacopoeia
PIL   Package Leaflet
PSUR  Periodic Safety Update Report
SD    Standard Deviation
SPC   Summary of Product Characteristics
t\frac{1}{2} Half-life
t_{\text{max}} Time for maximum concentration
TSE   Transmissible Spongiform Encephalopathy
USP   Pharmacopoeia in the United States
### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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<th>Scope</th>
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<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
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