CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Desloratadine Teva 0.5 mg/ml, oral solution
Teva Nederland B.V., the Netherlands

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/2478/001/DC
Registration number in the Netherlands: RVG 110902

19 September 2013

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:	4 September 2013
Concerned Member States:	Decentralised procedure with BE, BG, CY, CZ, DE, DK, EL, ES, FR, HU, RO, 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 Teva 0.5 mg/ml, oral solution from Teva Nederland B.V. The date of authorisation was on 4 September 2013 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_1-receptor antagonist activity. After oral administration, desloratadine selectively blocks peripheral histamine H_1-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 0.5 mg/ml oral solution, registered in the EEA by Merck Sharp & Dohme Ltd., for which the first marketing authorisation was obtained on 15 January 2001 through a centralised procedure (EU license number EU/1/00/160/061-069).

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 0.5 mg/ml oral solution, registered in the EEA and obtained from Belgium. 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*). The active substance is a white to off-white crystalline powder, and is slightly soluble in water. Desloratadine has no chiral centres. The active substance is predominantly polymorphic form I and may also contain form II. Polymorphic forms do not affect the efficiency of the product, as it contains desloratadine in a dissolved form. Adequate limits are applied.

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
The manufacturing process of desloratadine consists of five steps. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The drug substance specification has been established in-house. The drug substance specification is in line with the DMF holder's, with additional requirements for particle size and microbiological quality. The specification is 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 for one full-scale batch.

Stability of drug substance
Stability data on the active substance have been provided for four full-scale batches stored at 25°C/60% RH (60 months) and at 40°C/75% RH (6 months). A slight positive trend was observed in polymorph I.
Based on the stability data provided the proposed re-test period of 60 months without special storage conditions can be granted.

** 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 Teva 0.5 mg/ml is a clear, colourless aqueous solution with a bubble-gum odour.

The oral solution is packed in amber colour glass bottles with white child-resistant polypropylene (PP) closures and yellow tamper evidence rings. Packs of 50, 60, 100, 120 and 150 ml amber glass bottles are available. All packages are supplied with a HDPE measuring spoon, marked for doses of 2.5 ml and 5 ml.

The excipients are: 150 mg/ml liquid sorbitol (non-crystallising) (E420), 100 g/ml propylene glycol (E1520), sucralose (E955), hypromellose (E464), sodium citrate (E331), N&A Bubblegum type FL #25685 flavour, citric acid anhydrous (E330), purified water.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The concentration of propylene glycol in the product is considered acceptable for paediatric patients.

The main development studies were formulation trials. Formulation trials were performed to investigate different sweeteners, different types of hypromellose, different concentrations of flavouring agent and different concentrations of disodium edetate. The choice of manufacturing process and packaging has been adequately justified. The amber glass bottle is considered suitable.

The batch used in the bioequivalence study has the same composition and is manufactured in the same way as the future commercial batches. The bioequivalence batch is of sufficient size in relation to the intended commercial batch size. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process is divided into the following steps: dissolution of the active substance and excipients, adjustment to the final volume, filtration and filling. The product is manufactured using conventional manufacturing techniques. Adequate process validation data of one pilot batch has been provided. Given the simplicity of the manufacturing process this is considered sufficient.

Process validation for batches of the maximum production scale will be performed post authorisation.

Control of excipients

The excipients comply with relevant Ph.Eur. monographs, except for bubblegum flavour. The in-house specification for the bubblegum flavour has been provided. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identification of desloratadine, uniformity of mass of delivered doses from multidose containers, deliverable volume, pH, assay of desloratadine, related substances and microbiological quality. The release and shelf life limits are identical. The drug product specification is acceptable. The analytical methods have been adequately described and validated.

Batch analytical data from the proposed production site have been provided on two pilot-scale batches of each fill volume, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for two pilot-scale batches of the 50 ml and 150 ml bottles stored at 25°C/60% RH (12 months) and at 40°C/75% RH (6 months) both upright and inverted. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed marketing packaging.

All parameters tested remained relatively stable in both container sizes, at both conditions in both orientations. All results remained well within specification limits. From a forced degradation study it is concluded that the drug product is not photostable.

Based on the stability data provided the proposed shelf life of 24 months with storage conditions ‘Do not refrigerate or freeze’ and ‘Store in the original bottle in order to protect from light’ can be granted.

In-use stability data has been provided demonstrating that the product remains stable for 2 months following first opening.

Several post-approval commitments have been made with regard to the drug product; these are listed on page 8 of this report.

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.

II.2 Non-clinical aspects

This product is a generic formulation of Aerius, which is available on the European market. 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 member states agreed that no further non-clinical studies are required.

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.
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 member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Desloratadine Teva 0.5 mg/ml (Teva Nederland B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Aerius 0.5 mg/ml oral solution (SP Europe, Belgium).

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, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy subjects (11 males and 13 females), aged 24-55 years. Each subject received a single dose (0.5 mg/ml) of one of the 2 desloratadine formulations. After an overnight fast, 5 mg desloratadine in 10 ml syringe was dispensed into the subject's mouth. The syringe was then filled (past the 10 mL) with water taken from a cup containing 240 mL room temperature water, dispensed back into the cup, and then the mixture was stirred with the tip of the syringe. The subject was instructed to briefly swish the inside of their mouth with some of the water/solution mixture to ensure no study drug remained in the oral cavity, and then consume the entire 240 ml water/solution mixture. There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 12, 16, 24, 48 and 72 hours after administration of the products.

This single dose, cross-over study under fasted conditions is the correct design to establish bioequivalence between two formulations. Although the test and reference products are aqueous liquid preparations, both contain the same amount of sorbitol as excipient which may affect the absorption of desloratadine. Therefore, the MAH submitted a comparative bioavailability study under fasted conditions to demonstrate bioequivalence between Desloratadine Teva 0.5 mg/ml solution and Aerius 0.5 mg/ml solution as the reference product. Desloratadine has a terminal elimination half-life of approximately 27 hours. Instead of AUC_{0-t} a truncated AUC (AUC_{0-72}) was estimated. This is in accordance with the guidance on investigation of bioequivalence. Wash-out period of 21 days is long enough, all pre-dose

concentrations were smaller than the lower limit of quantification. Samples time schedule was adequate to determine C_{max} accurately.

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 twenty-four subjects completed the study and are included in the pharmacokinetic and statistical analyses.

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

Treatment N=24	**AUC_{0-72}** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h
Test	43600 ± 17795	2392 ± 842	4.50 (1.00-6.00)
Reference	42335 ± 15532	2410 ± 805	4.50 (1.50-6.07)
***Ratio (90% CI)**	1.02 (0.96-1.09)	0.99 (0.92-1.07)	--
CV (%)	13	16	--
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration			

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-72} and C_{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 Teva 0.5 mg/ml and Aerius 0.5 mg/ml oral solution are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

No serious adverse events were reported during the conduct of this study. There were 17 adverse events involving 9 subjects in the study. All adverse events were judged to be mild in severity. They were equally divided between test and reference treatment.

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 not been evaluated via a user consultation study. A bridging report was submitted with reference to the successfully user tested PL of Desloratadine 5 mg Teva film-coated tablets. This is acceptable. Layout and design are the same. Separate user testing is not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Desloratadine Teva 0.5 mg/ml, oral solution has a proven chemical-pharmaceutical quality and is a generic form of Aerius 0.5 mg/ml oral solution. 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 Teva 0.5 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 4 March 2013. Desloratadine Teva 0.5 mg/ml, oral solution was authorised in the Netherlands on 4 September 2013.

The date for the first renewal will be: 31 July 2017.

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

<u>Quality - medicinal product</u>

- The MAH committed to validate the first three production batches of the proposed batches sizes.
- The MAH committed to provide batch analysis data of the first full-scale batches.
- The MAH committed to continue the on-going long term stability studies up to 36 months.
- The MAH committed to put production scale batches on long-term and accelerated stability studies.
- The MAH committed to perform in-use stability testing on a second batch towards the end of its shelf-life (24 months).

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_{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
$t_{½}$	Half-life
t_{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

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached