COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Desloratadine 2.5 mg and 5 mg Focus, orodispersible tablets

(desloratadine)

NL Licence RVG 125540-125541

Date: 10 December 2020

This module reflects the scientific discussion for the approval of Desloratadine 2.5 mg and 5 mg Focus, orodispersible tablets. The marketing authorisation was granted on 4 August 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

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 Desloratadine 2.5 mg and 5 mg Focus, orodispersible tablets from Focus Care Pharmaceuticals B.V.

The product is indicated in adults, adolescents aged 12 years and older and children aged 6-11 years for the relief of symptoms associated with:

- allergic rhinitis
- urticaria

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

This national procedure concerns a generic application claiming essential similarity with the innovator product Aerius 2.5 mg and 5 mg orodispersible tablet. The reference product Aerius has been authorised in the Netherlands by Merck Sharp & Dohme B.V. through centralised procedure EU/1/00/160 since 15 January 2001.

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

II. QUALITY ASPECTS

II.1 Introduction

Desloratadine 2.5 mg Focus is a red, round, flat tablet with beveled edges and '2.5', embossed on one side.
Desloratadine 5 mg Focus is a red, round, flat tablet with beveled edges and '5' embossed on one side.
Each orodispersible tablet contains as active substance 2.5 or 5 mg of desloratadine.

The orodispersible tablets are packed in Al/Al blisters.

The excipients are: prolacrilin potassium, citric acid monohydrate, red iron oxide (E 172), magnesium stearate, croscarmellose sodium, aspartame (E 951), microcrystalline cellulose, mannitol, maltodextrin, propylene glycol (E 1520), modified starch, flavouring agent tutti-frutti (flavouring substances, maltodextrin, propylene glycol (E 1520), modified starch (E 1450)).

The two tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is desloratadine, an established active substance described in the European Pharmacopoeia (Ph. Eur.). The active substance shows polymorphism and is very slightly soluble in water. The polymorphic form is a mixture of form I and form II. For the reference product Aerius it is known that the active substance can exist in two polymorphic forms, but this has no clinical consequence.

The CEP procedure is used for both manufacturers of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The specifications are adopted from the Ph. Eur. monograph desloratadine and the CEPs with additional requirements for residual solvents and particle size. 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 three full-scale batches per drug substance manufacturer.

Stability of drug substance
Stability data on the active substance has been provided for drug substance manufacturer I. Six production-scale batches were stored at 25°C/60% RH (12 or 24 months), seven production-scale batches were stored at 30°/65% RH (24 or 36 months) and nine production-scale batches were stored at 40°C/75% RH (6 months). The stability results show no trends or significant changes. The retest period of 36 months at less than 25°C is justified.

The active substance of manufacturer II is stable for 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The pharmaceutical development of the product has been adequately performed. Desloratadine orodispersible tablets are a generic form of the

marketed tablet Aerius. The qualitative composition of both tablets is not identical. The products used in the bioequivalence study are acceptable. Comparative dissolution data complementary to the bioequivalence study have been provided. The dissolution tests have been done at three different pHs (pH 1.2, pH 4.5 and pH 6.8). At pH 4.5 and 6.8 the dissolution profiles of test biobatch and reference product are not equivalent. Bioequivalence was however demonstrated *in vivo*. The dissolution data in support of the biowaiver for the 2.5 mg strength are acceptable from a chemical-pharmaceutical point of view.

Manufacturing process

The orodispersible tablets are manufactured by direct compression. The product is manufactured using conventional manufacturing techniques. The manufacturing process is a standard manufacturing process. Process validation data on the product has been presented for two batches of the lower end of the commercial batch size range. These are appropriate. Additional process validation for full-scale batches will be performed post authorisation.

Control of excipients

The excipients comply with the Ph. Eur. requirements. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, diameter, thickness, identification, water content, average weight, disintegration, dissolution, assay, uniformity of dosage units, related substances, identification of colouring agent and microbiological quality. Release and shelf-life requirements are identical except for water content. The 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 full-scale batches per strength and per drug substance manufacturer.

Stability of drug product

Stability data on the product has been provided on two pilot-scale and eleven production-scale batches stored at 25°C/60% RH (36 months) 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 aluminium/ peelable aluminium blisters. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. The results show no out-of-specifications or trends at the tested storage conditions. The proposed shelf life of 36 months is acceptable.
The results support the shelf-life and storage condition of 3 years, in Al/Al blister packaging, with storage condition ‘Store in the original blister packaging to protect from moisture’.

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Desloratadine 2.5 mg and 5 mg Focus, orodispersible tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Desloratadine Focus 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

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 MEB agreed 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 Desloratadine 5 mg Focus (Focus Care Pharmaceuticals B.V., the Netherlands) is

compared with the pharmacokinetic profile of the reference product Aerius 5 mg orodispersible tablets (Merck Sharp & Dohme B.V., the Netherlands).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The MAH applied for a biowaiver for the 2.5 mg tablet. Both strengths are manufactured by the same manufacturing process. The qualitative composition of both strengths is the same and the composition of strengths is quantitatively proportional. Dissolution studies were performed using paddle apparatus, at 50 rpm and using 900 mL medium volume, at pH 1.2 (HCl 0.1N), pH 4.5 (acetate buffer) and pH 6.8 (phosphate buffer). The biowaiver has been granted.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 30 healthy male and female subjects, aged 21-64 years. Each subject received a single dose (5 mg) of one of the 2 desloratadine formulations. Prior to drug administration, each subject rinsed his/her mouth for approximately 5 seconds with approximately 20 mL of room temperature water, and then swallowed this water. Subjects were instructed to swallow saliva before dosing. Subsequently, staff placed the orodispersible tablet directly on the subject's tongue and asked the subject to close his/her mouth in a natural way, without swallowing, chewing, biting or breaking the tablet. Water was not permitted from 1 hour prior to drug administration until 1 hour post-dose. 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, 4.33, 4.67, 5, 6, 8, 12, 16, 24, 48 and 72 hours after administration of the products.

The design of the study is acceptable. According to the SmPC of Aerius 5 mg orodispersible tablets, desloratadine can be taken with or without food. A bioequivalence study under fasting conditions is appropriate. The wash-out period of minimally 21 days was long enough (elimination half-life is approximately 27 h). Pre-dose concentrations were reported in period 2 in 2 subjects (43.27 pg/mL and 25.01 pg/mL). One of these values was only slightly above the LLOQ (25.00 pg/mL). These values were less than 5% of C_{max}. The sampling period (up to 72 h post-dose) was in line with the Guideline on the investigation of bioequivalence. T_{max} of desloratadine is approximately 3 h. The sampling scheme was therefore adequate to estimate PK parameters.

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

Two subjects were withdrawn during the study, one at the check-in of period 2 due to a positive alcohol test, and one after period 1 because approximately 5 mL of saliva was spilled from the mouth during dosing. A total of 28 subjects (14 males, 14 females) completed the study and were 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=28	AUC_{0-72} (pg.h/ml)	$AUC_{0-\infty}$ (pg.h/ml)	C_{max} (pg/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	60932 ± 55.6	--	3098 ± 27.4	5.0 (1.5 – 8.0)	--
Reference	62927 ± 52.8	--	3041 ± 27.1	5.0 (2.0-12.0)	--
***Ratio (90% CI)**	0.97 (0.90 – 1.04)	--	1.02 (0.96 – 1.07)	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80–1.25. Based on the submitted bioequivalence study Desloratadine 5 mg Focus is considered bioequivalent with Aerius 5 mg orodispersible tablets.

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 Desloratadine Focus.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity (including anaphylaxis, angioedema, dyspnoea, pruritus, rash and urticarial)

	• Abnormal hepatic function (including hepatitis and elevated hepatic enzymes and bilirubin)
Important potential risks	• Convulsion • Movement disorder (including psychomotor hyperactivity and restlessness) • Supraventricular tachyarrhythmia • QT prolonged • Hallucination • Abnormal behaviour including aggressive reactions • Photosensitivity
Missing information	• Effects on fertility • Use in pregnancy • Use in lactation • Use in children less than 6 years of age

The MEB agrees 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to the user tested PL for Aerius (centralised procedure EU/1/00/160/037-048). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Desloratadine 2.5 mg and 5 mg Focus, orodispersible tablets have a proven chemical-pharmaceutical quality and are generic forms of Aerius 2.5 mg and 5 mg orodispersible 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 with the reference product, and has therefore granted a marketing authorisation. Desloratadine 2.5 mg and 5 mg Focus was authorised in the Netherlands on 4 August 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/ Justification for refuse