LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Desloratadin Orion
(desloratadine)

SE/H/2599/01-02/DC

This module reflects the scientific discussion for the approval of Desloratadin Orion. The procedure was finalised at 2025-09-17. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Desloratadin Orion, 2,5 mg, 5 mg, Orodispersible tablet.

The active substance is desloratadine. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Desloratadine is a second generation orally administered, non-sedating, tricyclic histamine antagonist. Following oral administration, it selectively blocks peripheral histamine H1 receptors and inhibits histamine release from mast cells.

Pharmacological classification
Pharmacotherapeutic group: Other antihistamines for systemic use
ATC code: R06AX27

Claimed therapeutic indications

5 mg orodispersible tablets:
Desloratadin Orion is indicated in adults and adolescents aged 12 years and older for the relief of symptoms associated with:
- allergic rhinitis (see section 5.1)
- urticaria (see section 5.1).

2.5 mg orodispersible tablets:
Desloratadin Orion is indicated in adults, adolescents aged 12 years and older and children aged 6–11 years old for the relief of symptoms associated with:
- allergic rhinitis (see section 5.1)
- urticaria (see section 5.1).

II.2 General comments on the submitted dossier

The application for Desloratadin Orion, 2,5 mg and 5 mg, Orodispersible tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS). DK, FI, and NO are concerned member states (CMS) in the application for 2,5 mg, Orodispersible tablet, and DK is concerned member state (CMS) in the application for 5 mg, Orodispersible tablet.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Aerius, 5 mg, Film-coated tablet authorised in the Union since 2001, with N.V. Organon as marketing authorisation holder.

The reference product used in the bioequivalence study is Aerius, 5 mg, Film-coated tablet from Norway with N.V. Organon as marketing authorisation holder.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
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.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP
A statement on the application of appropriate GCP standards in the submitted study has been provided. The Applicant provided inspection reports from inspections performed by Germany and the Netherlands in 2024 where the GCP quality was considered sufficient.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

Drug Product
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of desloratadine are well known. As desloratadine is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Shortly, desloratadine is a second-generation non-sedating antihistamine (and an active metabolite of loratadine). It primarily targets histamine H1-receptors and has only limited movement over the blood-brain barrier. In mature rats, desloratadine is widely distributed in the liver, spleen, thymus, heart, adrenal glands, and pituitary gland. The primary pathways for desloratadine metabolism involved hydroxylation at the 3-, 5-, or 6-positions (in humans and non-clinical animal models) – although the proportions of metabolites differ somewhat between species.

Toxicologically, there are no indications that desloratadine is genotoxic (based on Ames test, human peripheral blood lymphocyte clastogenicity assay and mouse bone marrow micronucleus assay). In carcinogenicity tests (2-year dietary exposures) with loratadine, mice did not manifest any increase in neoplasms whereas rats demonstrated a significantly higher incidence of hepatocellular neoplasms (combined adenomas and carcinomas) in males at 10 mg/kg/day and in both males and females at 25 mg/kg/day (roughly 7x the AUC in humans at the recommended daily oral dose). The clinical significance of these findings during long-term use of desloratadine is not known. There was no desloratadine effect on female rat fertility at doses up to 24 mg/kg/day (corresponding to an animal-to-human exposure margin around 506x times). Some study results indicate that desloratadine may cause decreased fertility in male rats (decreases in sperm numbers and motility and histopathologic testicular changes) at 12 mg/kg (corresponding to a systemic animal-to-human exposure margin of ~175x). The male reproductive toxicity effects have been reported with other antihistamines and appear, so far, to be rat-specific. Desloratadine was not teratogenic (in terms of malformations and embryofetal mortality) in rat or rabbit EFD studies (giving an approximately 210x to 230x exposure margin to humans) but there have been outcomes of increased pre-implantation loss and a decreased number of implantations and foetuses in rats at an exposure margin of 120x. Reduced body weight and slow righting reflex were reported in pups at approximately 50 times or greater than the AUC in humans at the recommended daily oral dose. Desloratadine had no effect on pup development at approximately 7 times the AUC in humans at the recommended daily oral dose. Overall, at likely human exposure levels and with some margin, desloratadine is not genotoxic or a developmental toxicant.

Environmental Risk Assessment (ERA)
The procedure was initiated after 1st Sept 2024 and the 2024 CHMP ERA GL is therefore in force. The applicant has provided an ERA document for ‘Desloratadine Orodispersible Tablets 2.5 mg and 5 mg’ dated to Sept 2024. The relevant CMS are SE (RMS), DK, FI and NO. Arguments have been provided that the approval and indication conditions for the present proposed product do not differ in any relevant way with regard to the ERA and the differences between the 2006 CHMP ERA GL (‘old ERA GL’, relevant for the Aerinaze ERA) and the new ERA GL (relevant for this procedure). Aerinaze was approved for a maximum of 2 x 2.5 mg tablets per day whereas this procedure also allows 1 x 5 mg tablets per day, so the applicants argument is acceptable. Overall, the ERA document with its argument that the relevance of the conclusions in the Aerinaze ERA remain applicable is considered acceptable and there are no indications that desloratadine is an environmental risk (or an PBT/vPvB substance).

There are no objections to approval of Desloratadin Orion from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted a single bioequivalence study comparing Desloratadin Orion ODT with the reference product Aerius tablets.

Pharmacokinetic properties of the active substance
Absorption
The pharmacokinetics of desloratadine is not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator.
Desloratadine plasma concentrations can be detected within 30 minutes of administration. Desloratadine is well absorbed with maximum concentration achieved after approximately 3 hours; the terminal phase half-life is approximately 27 hours. The
bioavailability of desloratadine was dose proportional over the range of 5 mg to 20 mg.

Distribution
Desloratadine is moderately bound (83 % - 87 %) to plasma proteins.

Biotransformation
The enzyme responsible for the metabolism of desloratadine has not been identified yet, and therefore, some interactions with other medicinal products cannot be fully excluded. Desloratadine does not inhibit CYP3A4 in vivo, and in vitro studies have shown that the medicinal product does not inhibit CYP2D6 and is neither a substrate nor an inhibitor of P-glycoprotein.

Study
Methods
This was a single-dose, two-way crossover study conducted in 24 healthy volunteers, comparing Desloratadine Orion, 5 mg, orodispersable tablet with Aerius, 5 mg, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of desloratadine were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 5 February 2024 and 3 March 2024.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for desloratadine, n=24.

Treatment	AUC_{0-72} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	43470 ± 15504	2898± 1118	3.00 (1.33 - 5.50)
Reference	43183 ± 16608	2888 ± 1108	2.33 (0.67 - 5.00)
***Ratio (90% CI)**	101.60 (94.48 - 109.26)	100.44 (92.28- 109.32)	-
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 plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-72} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strength of 2.5 mg.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Absence of studies with the additional strength of 2.5 mg is acceptable, as all conditions for biowaiver for additional strength, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of desloratadine is linear.

Based on the submitted bioequivalence study, Desloratadine Orion is considered bioequivalent with Aerius.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system

Proposed MAH: Orion Corporation

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 Desloratadin Orion.

Part II Safety specification
The MAH has submitted the version 1 RMP dated 2.9.2024 and proposed the following safety concerns:

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 1 signed 2.9.2024 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall

continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.>

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Desloratadin Orion, is found adequate. There are no objections to approval of Desloratadin Orion, from a non-clinical and clinical point of view.

Bioequivalence between the test and reference product has been adequately demonstrated.

The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments
N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to

- Desloratadine Actavis 5 mg filmcoated, EMEA/H/C/002435, for content.
- Burana 50 mg/g gel, DE/H/5281/01/DC, for layout.

The bridging report submitted by the applicant has been found acceptable.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-