LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Desloratadin Evolan
# (desloratadine)

# 2024-0541

**This module reflects the scientific discussion for the approval of Desloratadin Evolan. The procedure was finalised on 2025-04-07. For information on changes after this date please refer to the module 'Update'.**

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# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Desloratadin Evolan, 5 mg, Film-coated tablet.

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

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Desloratadin Evolan, 5 mg, Film-coated tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies for a marketing authorisation in Sweden through a National Procedure.

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 Union since 2001, with N.V. Organon of the originator product as marketing authorisation holder.

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

**Potential similarity with orphan medicinal products**
N/A

# II. QUALITY ASPECTS

## II.1 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.

## II.2 Medicinal 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. 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.

**Environmental Risk Assessment (ERA)**
Since Desloratadin Evolan is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

# IV. CLINICAL ASPECTS

**Pharmacokinetics**
To support the marketing authorisation application the applicant has submitted reports of two bioequivalence studies comparing Desloratadin Evolan, 5 mg, film-coated tablet with the reference product Aerius, 5 mg, film-coated tablet.

A total of three bioequivalence studies have been conducted with the new drug formulation. The first study, 210-10, is not considered reliable since the responsible CRO was found to be non-GCP compliant. The second study, 1766, failed to demonstrate bioequivalence for Cmax. An additional study, 1818, was therefore conducted using an increased sample size. Study 1818 is thus considered as pivotal for the application.

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 degree of accumulation of desloratadine was consistent with its half-life (approximately 27 hours) and a once daily dosing frequency. The bioavailability of desloratadine was dose proportional over the range of 5 mg to 20 mg.
In a pharmacokinetic trial in which patient demographics were comparable to those of the general seasonal allergic rhinitis population, 4 % of the subjects achieved a higher concentration of desloratadine. This percentage may vary according to ethnic background. Maximum desloratadine concentration was about 3-fold higher at approximately 7 hours with a terminal phase half-life of approximately 89 hours. The safety profile of these subjects was not different from that of the general population

Distribution
Desloratadine is moderately bound (83 % - 87 %) to plasma proteins. There is no evidence of clinically relevant medicine accumulation following once daily dosing of desloratadine (5 mg to 20 mg) for 14 days.

Metabolism
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.

Elimination
In a single dose trial using a 7.5 mg dose of desloratadine, there was no effect of food (high-fat, high caloric breakfast) on the disposition of desloratadine. In another study, grapefruit juice had no effect on the disposition of desloratadine.

Study 1766
*Methods*
This was a single-dose, two-way crossover study conducted in 19 healthy volunteers, comparing Desloratadine Evolan, 5 mg, film-coated tablets with Aerius, 5 mg, film-coated tablets 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 Oct 27, 2014, and Nov 21, 2014.

*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=19.**

| Treatment | $AUC_{72}$ pg*h/ml | $C_{max}$ pg/ml | $t_{max}$ h |
|---|---|---|---|
| **Test** | **48751 ± 21017** | **2788 ± 942** | **5.00 1.50-6.03** |
| **Reference** | **54712 ± 23927** | **3284 ± 1009** | **3.00 1.00-6.00** |
| ***Ratio (90% CI)** | **89.68 (84.24-95.47)** | **84.24 (78.00-90.98)** | **-** |

**$AUC_{0-t}$** 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*

Bioequivalence was demonstrated for AUC but not for $C_{max}$. For $C_{max}$ the 90% CI for the ratio of the test and reference products were 78.00-90.98 and fell outside the conventional acceptance range of 80.00-125.00%.

Study 1818
*Methods*
This was a single-dose, two-way crossover study conducted in 32 healthy volunteers, comparing Desloratadine Evolan, 5 mg, film-coated tablets with Aerius, 5 mg, film-coated tablets 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 Jan 15, 2015, and Feb 12, 2015.

*Results*

The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

**Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range) for desloratadine, n=32.**

| Treatment | $AUC_{72}$ pg*h/ml | $C_{max}$ pg/ml | $t_{max}$ h |
|---|---|---|---|
| **Test** | **61371 ± 24128** | **3612 ± 1304** | **5.00 1.00-6.50** |
| **Reference** | **62989 ± 31006** | **3539 ± 1519** | **3.00 1.00-7.00** |
| ***Ratio (90% CI)** | **102.26 (97.03-107.77)** | **104.24 (98.45-110.36)** | **-** |
| $AUC_{0-t}$ area under the plasma concentration-time curve from time zero to t hours<br>$C_{max}$ maximum plasma concentration<br>$t_{max}$ time for maximum plasma concentration | | | |

**calculated based on ln-transformed data*

For $AUC_{0-t}$ 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%.

Discussion and overall conclusion

In study 1766, bioequivalence was not demonstrated for $C_{max}$. The study was therefore repeated (study 1818) by increasing the number of enrolled subjects and bioequivalence was demonstrated for both AUC and $C_{max}$. Thus, based on the results from study 1818, Desloratadine 5 mg film-coated tablet is considered bioequivalent with Aerius 5 mg film-coated tablets.

**Pharmacodynamics/Clinical efficacy/Clinical safety**

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

**Risk Management Plan**

The MAH has submitted an updated 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 Evolan, film-coated tablets.

Part II Safety specification

| Summary of safety concerns | |
|---|---|
| Important identified risks | • None |
| Important potential risks | • None |
| Missing information | • None |

No safety concerns, that require additional pharmacovigilance activities or additional risk minimisation measures, are presented.

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 3.1, signed 08 October 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.

# V. USER CONSULTATION

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 Cipla 5 mg film-coated tablets (SE/H/1136/01/DC) for the content and to
- Kalcium/Kolekalciferol Evolan film-coated tablets (nationally approved in Sweden 2021-04-19, MAno: 60612 and 60613) for the layout.

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

# VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Desloratadin Evolan, is found adequate. There are no objections to approval of Desloratadin Evolan, 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.

**List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment**

N/A

**List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC**

N/A

# VII. APPROVAL

Desloratadin Evolan, 5 mg, Film-coated tablet was approved in the national procedure on 2025-04-07.

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# Public Assessment Report – Update

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

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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