IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Deslor 5 mg Film-Coated Tablets
Desloratidine
PA0711/202/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number DK/H/2038/001 with Denmak as RMS. The responsibility of RMS was transferred to Ireland on 23 March 2021 under procedure number IE/H/1186/001

Please note the following detail for the product in IE:

Marketing Authorisation Number: PA0711/202/001
Marketing Authorisation Holder: Rowex Ltd

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The Danish public assessment report published at the time of the initial marketing authorisation is provided herein.

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Deslor 5 mg film-coated tablets, from Rowex Ltd.

The product is indicated for the relief of symptoms associated with allergic rhinitis and urticaria. A comprehensive description of the indications and posology is given in the SmPC.

Desloratadine is a non-sedating, long-acting antihistamine with selective peripheral H1-receptor antagonist activity. After oral administration, desloratadine selectively blocks peripheral histamine H1- receptors because the substance is excluded from entry to the central nervous system.

This decentralised procedure concerns a generic application claiming essential similarity with the reference product Aerius 5 mg film-coated tablets, which has been registered in Europe by SP Europe since 2001.

II. QUALITY ASPECTS

II.1 Introduction

Each tablet contains 5 mg desloratadine.

The tablets are light blue, round shaped, biconvex film-coated tablets, with "5" debossed on one side. Diameter 6.50 ± 0.10 mm.

The tablets are supplied in blister packs comprising of OPA/ALU/PVC/ALU and in blister packs comprising of PVC/Aclar ALU.

The following pack-sizes are approved: Unit dose: 30x1 film-coated tablets.
Not unit dose: 30 film-coated tablets. However, not all pack sizes may be marketed.

The tablet core contains: Maize starch; Cellulose, microcrystalline; Hypromellose; Silica, Colloidal anhydrous and Hydrogenated vegetable oil (Type 1).
The tablet coating consists of: Opadry Blue *03B50689*(Hypromellose E464; Titanium dioxide E171; Macrogol 400 E1521 and Indigo Carmine Aluminum Lake E132).

The RMS 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.

II.2 Drug Substance

The active substance, desloratadine, is not described in the European Pharmacopoeia. It is a white to off-white powder with pinkish background powder. It is soluble in chloroform and insoluble in water. It is not optically active.

Chemical name(s): 8-Chloro-6,11-dihydro-11-(4-piperidinylidene)-5H-benzo [5,6] cyclohepta [1,2-b] Pyridine

Molecular formula: $C_{19}H_{19}ClN_2$
Molecular mass: 310.83

The documentation on the active substance is presented as a Drug Master File.

The defined starting materials are found acceptable. The control tests and specifications for the drug substance are adequately drawn up and the analytical procedures have been sufficiently validated.

Stability studies according to ICH guidelines have been performed and an appropriate retest period has been set.

Adequate specifications, validation of analytical procedures and certificates of analysis of the active substance issued by the finished product manufacturer are provided.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained. All excipients are described in Ph. Eur. except hydrogenated vegetable oil, which complies with USP/NF. Dissolution testing has been performed with the batches used in the bioequivalence study. Dissolution profiles are provided.

The manufacturing process is a standard wet granulation process. It has been adequately described and validated on 3 pilot scale batches.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented and are found sufficient.

Batch analysis has been performed on 3 batches. The batch analysis results show that the finished product meets the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The proposed shelf-life of 24 months with the storage condition "no special precautions for storage" is acceptable.

III. NON-CLINICAL ASPECTS

III.1 Introduction
Pharmacodynamic, pharmacokinetic and toxicological properties of desloratadine are well known. As desloratadine is a widely used, well-known active substance, the MAH has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview report refers several publications up to year 2009. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.2 Ecotoxicity/environmental risk assessment (ERA)
Since Deslor 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

IV. CLINICAL ASPECTS

IV.1 Introduction
Desloratadine is a well-known active substance with established efficacy and tolerability. As desloratadine is a widely used, well-known active substance, the MAH has not provided additional studies (apart from a supportive bioequivalence study referenced below) and further studies are not required. Overview based on literature review is, thus, appropriate.

The clinical report refers several publications up to year 2010. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

IV.2 Pharmacokinetics

To support the application, the MAH has submitted as report one bioequivalence study. Deslor 5 mg film-coated tablets has been compared to Aerius 5 mg film-coated tablets, Schering-Plough, from the Dutch market.

The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting with a wash out period of 16 days between the two administrations. 5 mg was administered in each period.

36 healthy male subjects were enrolled in the study, 28 subjects completed the study. The primary variables for the evaluation of bioequivalence were AUC0-72 and Cmax.
The 90% confidence interval for the ratio between the ln-transformed AUC0-72 and Cmax for the test product and the reference product should be within 80% to 125% in order to conclude bioequivalence.

Results

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

N= 28

DESLORATADINE					
Treatment	**AUC_{0-72}** pg/ml/h	**$AUC_{0-\infty}$** pg/ml/h	**C_{max}** pg/ml	**t_{max}** h	**$T_{1/2}$** h
Test	42377.515 ± 14835.9616	45657.081 ± 15834.0717	2463.949 ± 866.9520	4.500 1.00 – 5.50	19.231 ± 3.6932
Reference	43173.507 ± 19865.4591	46716.616 ± 21516.9071	2366.186 ± 974.1925	4.500 1.00 – 6.00	19.929 ± 3.6704
***Ratio (90% CI)**	100.41 (93.31 – 108.05)		105.17 (97.27 – 113.71)		
CV (%)	16.19 %		17.25 %		

$AUC_{0-\infty}$	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

*ln-transformed values

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

N= 28

3-Hydroxy Desloratadine					
Treatment	**AUC_{0-72}** pg/ml/h	**$AUC_{0-\infty}$** pg/ml/h	**C_{max}** pg/ml	**t_{max}** h	**$T_{1/2}$** h
Test	44963.026 ± 12648.6790	54084.042 ± 16871.2777	1876.645 ± 529.4468	5.000 1.50 – 5.00	29.574 ± 5.7407
Reference	43681.472 ±	52723.463 ±	1782.600 ±	5.000	29.693 ±
	12714.4562	16896.0919	481.4279	1.00 – 5.00	7.4202
***Ratio (90% CI)**	103.16 (99.84 – 106.59)		105.34 (100.23 – 110.70)		
CV (%)	7.18 %		10.92 %		

$AUC_{0-\infty}$	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

*ln-transformed values

The data demonstrates bioequivalence between the test and reference products, as the 90% CI are within 80.00 %-125.00 % for ln transformed Cmax and AUC0-72h for the parent compound desloratadine and the metabolite 3-hydroxy deloratadine.

Pharmacokinetic conclusion

The presented bioequivalence study indicates that Deslor 5 mg, film-coated tablets is bioequivalent with Aerius 5 mg film-coated tablets.

The RMS 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

As the dossier in question refers to a generic product with an active substance which has been marketed throughout the EU for more than 10 years and of which the safety profile has not been disputed so far, the MAH considers routine pharmacovigilance sufficient without any need for further risk minimisation measures. The RMS endorses this position.

V. OVERALL CONCLUSIONS

Deslor 5 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Aerius. 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.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity had been demonstrated for Deslor with the reference product, and therefore granted a marketing authorisation. The decentralised procedure was finalised on 20 March 2012. Deslor was authorised in Denmark on 12 September 2012.

According to the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs), PSURs should be submitted every 5 years. The next PSUR should be submitted with a DLP of 15 July 2016.

The date for the first renewal will be: 20 March 2017.

There were no post-approval commitments made during the procedure.

VI. REVISION DATE

24 April 2024

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From DK/H/2038/001 to IE/H/1186/001	N/A	23 March 2021	N/A