COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Desloratadine Double-e Pharma 5 mg, film-coated tablets

(desloratadine)

NL/H/4392/001/DC

Date: 2 November 2020

This module reflects the scientific discussion for the approval of Desloratadine Double-e Pharma 5 mg, film-coated tablets. The procedure was finalised at 13 February 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
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 Member States have granted a marketing authorisation for Desloratadine Double-e Pharma 5 mg, film-coated tablets, from Double-E Pharma Limited.

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

- allergic rhinitis
- urticaria

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

This decentralised procedure is a duplicate application for product Desloratadine Teva 5 mg film-coated tablets that was originally authorised through the centralised procedure by Teva Pharma B.V. It is required to be divested to a third party as part of certain regulatory commitments that Teva have entered into with the European Commission (Case M. 7746) as a consequence of a acquisition in August 2016. This submission is based upon the original CP licence number EMEA/H/C/2419.

Teva was allowed by the Coordination group for Mutual recognition and Decentralised procedure for human medicinal products (CMDh) to apply for duplicate registrations with a consolidated dossier via the decentralised procedure for products registered via the centralised procedure, to accommodate the regulatory commitments as required by the European commission. In such decentralised procedure, only the regional administrative information would be subjected to assessment, whereas for the quality, non-clinical and clinical modules reference to the EPAR[1] of the product registered via the centralised procedure should be made by the RMS.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Aerius 5 mg, film-coated tablets which has been registered in the EEA by Merck Sharp & Dohme B.V. since 15 January 2001 through a centralised procedure (EMEA/H/C/000313).

The concerned member states (CMS) involved in this procedure was Finland.

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

[1] Public Assessment Report for Desloratadine Teva 5 mg film-coated tablets (https://www.ema.europa.eu/en/documents/assessment-report/desloratadine-teva-epar-public-assessment-report_en.pdf)

II. QUALITY ASPECTS

II.1 Introduction

Desloratadine Double-e Pharma blue, round , biconvex film-coated tablet printed in with ink: "D5" on one side and plain on the other side. Each tablet contains 5 mg of desloratadine.

The film-coated tablets are packed in OPA/Alu/PVC – Aluminium blisters.

The excipients are:
Tablet core - microcrystalline cellulose, pregelatinised maize starch, talc and silica colloidal anhydrous
Tablet coating - lactose monohydrate, hypromellose, titanium dioxide (E171), macrogol 400, and indigo carmine (E132)
Printing ink – shellac, titanium dioxide (E171) and propylene glycol

II.2 Drug Substance

At the time of the CHMP opinion, the active substance desloratadine is not described in the European Pharmacopoeia. The substance is slightly soluble in water, sparingly soluble in methanol, ethanol, propylene glycol, acetonitrile and toluene. In acidic environments the solubility increases. Desloratadine exists in different polymorphic forms. The active substance is sourced from one manufacturer. The manufacturing process produces consistently the same crystalline form or ratio of crystalline forms of desloratadine. Both crystalline

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.

<u>Manufacturing process</u>
The manufacturing process of desloratadine includes five steps. During evaluation of this dossier, the starting materials have been re-defined to an earlier point of the synthesis and consequently additional information has been included in the Restricted and Applicant's parts of the ASMF. The sources of the starting material have also been clarified. In the detailed description of manufacturing process of desloratadine reaction conditions, equipment and quantities of the used materials are provided precisely. Organic and inorganic impurities as well as residual solvents of desloratadine active substance are well

discussed. Adequate in process controls are in place and appropriate specifications have been adopted for the starting materials, solvents and reagents. The validation procedures are in compliance with ICH Q2 requirements, so the methods are considered adequate for the control of the active substance on a routine basis.

Quality control of drug substance

Specifications have been set that are appropriate in view of the Ph. Eur. Monograph 'Substances for Pharmaceutical use', the Q6A Guideline on Setting Specifications and the impurity discussion. The specification includes tests for identification (IR and HPLC), polymorphism (XRD), water, sulphated ash, heavy metals, residual acetic acid, related substances, assay (HPLC) and residual solvents. Limits of specified and unspecified related substances are set in line with ICH Q3A guidelines. The maximum level of total impurities is set at not more than 0.50%. The limits for residual solvents are lower than ICHQ3C and Ph. Eur. requirements and are considered justified. The limits for assay are based on general pharmacopoeial limits for APIs measured by HPLC. Analytical tests are correctly drawn up and validated according ICH. Batch results confirm batch to batch consistency and uniformity of the quality of the substance and indicate that the process is under control.

Stability of drug substance

Satisfactory stability data of twelve batches of desloratadine, stored in their proposed commercial packaging for up to 60 months at 25° ± 2°C/ 60 % ± 5 % RH and 6 months at 40° ± 2°C/ 75 % ± 5 % RH, have been provided that justify the proposed re-test period of 60 months without any special storage condition.

II.3 Medicinal Product

Pharmaceutical development

The aim of the product development was to formulate tablets which are robust, stable and are bioequivalent to the reference medical product marketed in Europe by Schering-Plough Labo N.V. as Aerius/Neoclarityn 5 mg tablets

Desloratadine Double-e Pharma 5 mg film-coated tablets are conventional immediate release medicinal products. The active substance exists in different polymorphic forms. The polymorphic forms have almost the same solubility characteristics, therefore the differences in the two active substance sources are not relevant for the product performance. The excipients used are all standard and commonly used in the pharmaceutical industry. All excipients used in the manufacture of the finished product comply with official Ph. Eur. monographs except Opadry II Blue and Opacode white. Microcrystalline cellulose and pregelatinized maize starch used intragranular, colloidal anhydrous silica and talc used extragranular are applied in the tablet core. Opadry II Blue is a hypromellose based film coating. Satisfactory comparative impurity profiles have been presented for the test and reference products. Comparative dissolution profiles of reference and test biobatches were performed in three different dissolution media: 0.1 M Hydrochloric acid, Phosphate buffer pH 4.5, Phosphate buffer pH 6.8. In all three media dissolution of the drug substance from the reference and test product is fast and complete and profiles are proved to be similar since the amount of the dissolved desloratadine is higher than 85% at 15 minutes.

Manufacturing process

The manufacturing process is a conventional wet granulation technology followed by mixing and tabletting steps and film coating with ready to use mixtures and printing. The manufacturing formula, flow chart and description of the manufacturing process are presented The presented documentation contains results of process qualification for one batch. The results obtained for the critical parameters tested on the qualification batch proved that the manufacturing process of Desloratadine Double-e Pharma 5 mg film-coated tablets is qualified. The main process steps are supervised by suitable in-process controls and their acceptance criteria are specified. Batch analysis data on three pilot batches were within the specification limits and confirm both the consistency of production and good performance of the analysis methods. Therefore, the analytical tests are considered suitable, manufacturing process and analysis are well controlled.

Quality control of drug product

The specification of the finished medicinal product is acceptable and includes tests for description, identification (UPLC, UV), identification of titanium dioxide, identification of indigo carmine, uniformity of dosage units, dissolution, assay (UPLC), impurities/degradation products and microbiological quality. The proposed test procedures and acceptance criteria comply with the requirements of the Ph.Eur. and ICH guidelines. All tests included in the specification have been satisfactorily described and validated.
Certificates of analysis and typical IR spectra are presented. The batch analysis results of pilot batches confirm that the finished product meets the proposed specifications.

Stability of drug product

The conditions used in the stability studies are in accordance with the ICH stability guideline. The control tests and specifications of active product are adequately drawn up. Photostability results demonstrated that the product is not sensitive to light.

Based on the stability results provided, the proposed shelf-life and storage conditions as defined in the SmPC are justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Material of animal origin used in the production of Desloratadine Double-e Pharma is lactose monohydrate, for which statements from suppliers confirm that is Bovine Spongiform Encephalopathy (BSE)/ Transmissible Spongiform Encephalopathies (TSE) free.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

No Environmental Risk Assessment was submitted. This was justified by the MAH as the introduction of Desloratadine Double-e Pharma 5 mg film-coated tablets manufactured by Teva is considered unlikely to result in any significant increase in the combined sales volumes for all desloratadine containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

III.2 Discussion on the non-clinical aspects

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable. Therefore, the CHMP agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

This is an application for film-coated tablets containing desloratadine. To support the marketing authorisation application the applicant conducted a bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment. The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of desloratadine based on published literature. No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study.

Table 1. Tabular overview of clinical studies

Type of study	BE
Study identifier	1262
Objectives of the study	Compare the desloratadine from Desloratadine 5 mg Film-Coated Tablets (Teva Pharmaceutical Works Private Limited Company, Hungary) and Aerius 5 mg Film-Coated Tablets (Manufactured by Schering- Plough Ltd., Belgium for Essex Pharma GmbH, Germany
Study design and type of control	Pivotal, single dose, randomized, open-label, two-period, two-sequence, two-treatment, single- centre, crossover, comparative bioavailability study.
Test product(s); dosage regimen	Test Product: Desloratadine 5 mg Film-Coated
Route of administration	Tablets; Lot No: 0190310; (Teva Pharmaceutical Works Private Limited Company, Hungary) Dose: 1 x 5 mg Mode of Administration: Oral under fasting
Number of subjects	Thirty-six (36) subjects were enrolled and dosed in Period 1. Thirty-two (32) subjects completed the study. Twenty-nine (29) subjects were included in the statistical analysis.
Healthy subjects or diagnosis of patients	36 subjects enrolled. Healthy, nonsmoking male and female volunteers, 18 years of age or older, with a BMI within 18.5-30.0 kg/m2, inclusive.
Duration of treatment	The study consisted of two study periods. Each study period included a single-dose drug administration of either the test or the reference product. There was a washout period of 14 days between each drug administration. Subjects were confined to the clinic the day prior to dosing.
Study status; type of report	Complete

IV.2 Pharmacokinetics

Study Design

Study 1262 was a pivotal, single dose, randomized, open-label, two-period, two-sequence, two-treatment, single- centre, crossover, comparative bioavailability study in August 2010. The products were studied using a crossover design with 36 healthy male and female non-smoking volunteers being administered an oral dose of 1 × 5 mg under fasting conditions. The study consisted of two study periods. Each study period included a single-dose drug administration of either the test or the reference product. There was a washout period of 14 days between each drug administration. Subjects were confined to the clinic the day prior to dosing. Thirty-six (36) subjects were enrolled and dosed in Period 1. Thirty-two (32) subjects completed the study. Twenty-nine (29) subjects were included in the statistical analysis. Each subject received either a desloratadine 5mg film-coated tablet (test A) or an Aerius 5mg film-coated tablet (reference B) with 240ml water, after an overnight fast, according to

a computer generated randomisation list. Following a washout period of 14 days, the subjects received the alternative formulation under identical conditions. During each study period, blood samples were taken pre-dose and at 0.5, 1.0, 2.0, 2.33, 2.67, 3.0, 3.33, 3.67, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72 hours after dosing at pre-defined times. Plasma was harvested from these samples and assayed for desloratadine.

Test and reference products

Thirty-six healthy adult male (n = 18) and female (n = 18) subjects aged between 18 and 73 years (mean 41 ± 11), with a body mass index (BMI) of between 20.7 and 29.9 (mean 25.3 ± 2.9) and a weight range of 47.3 to 99.4kg (mean 71.2 ± 14.2) participated in the study. Seventeen subjects were White, 8 were Hispanic/Latino, 8 were Black and 3 were Asian. All female subjects were surgically sterile, post-menopausal or taking adequate contraceptive precautions. Of the 36 subjects who entered the study, 32 completed the study in its entirety: - Subject 14 withdrew from the study prior to period 2 due to work related issues. - Subjects 21 and 28 failed to report for period 2. - Subject 05 was dismissed from the study prior to period 2 due to non compliance. Of these 32 subjects, a total of 29 subjects were included in the pharmacokinetic and statistical analyses. Subjects 07, 19 and 36 were excluded from the pharmacokinetic/statistical analysis as these subjects had pre-dose concentrations detected in period 2 which were greater than 5% of the C_{max} value reported for period 2. This is in line with the applicable bioequivalence guideline.

Analytical methods

An LC/MS/MS assay for the determination of desloratadine in human plasma was developed and validated at Warnex Bioanalytical Services in Laval, Québec. The analytical method was calibrated between 25.0 to 6250 pg/mL. Precision and accuracy criteria were adequately set. The results of the stability investigations were satisfactory. Overall, the bioanalytical method was considered adequately validated.

Pharmacokinetic variables

The pharmacokinetic parameters of interest in this study were $AUC_{0\text{-}72h}$ and C_{max}. Other pharmacokinetic parameters, such as AUC_{inf}, AUC_t/AUC_{inf}, K_{el}, and T_{max} were to be given for information purpose only.

Statistical methods

Analysis of variance (ANOVA) including sequence, subjects nested within sequence, period and treatment was performed on the log-transformed data for $AUC_{0\text{-}72h}$ and C_{max}. T_{max} was analysed using a non-parametric test (Wilcoxon test)The 90% confidence intervals of the test/reference ratios of geometric means for $AUC_{0\text{-}72h}$ and C_{max} were calculated based on the least squares means and estimate of the ANOVA.

Bioequivalence was established if the 90% confidence interval for the ratio (test/reference) of the geometric least squares means for the log-transformed parameters $AUC_{0\text{-}72h}$ and C_{max} were within the internationally accepted range of 80.00% to 125.00%.

Results

Summary of the pharmacokinetic results and the statistical analysis

Desloratadine: (N=29)

Parameter (N/N)	Geometric Means Arithmetic Means (CV %) TRT A		TRT B		Ratio of Geometric Means	90% Confidence Interval	Intra-Subject CV (%)
AUC72 (pg.h/mL) (29 /29)	52045.2 56183.7	(43.27)	51291.2 55294.1	(44.14)	101.47	97.44 - 105.66	9.08
Cmax (pg/mL) (29 /29)	2890.7 3035.5	(33.77)	3053.6 3197.6	(35.42)	94.66	90.61 - 98.90	9.82
Tmax* (h) (29 /29)	5.00 (1.50 - 8.00)		3.00 (1.50 - 16.00)				
Lambda** (1/h) (29 /29)	0.0322 (26.90)		0.0327 (22.83)				
T1/2** (h) (29 /29)	23.80 (40.37)		22.69 (32.13)				
AUC72/AUCinf** (29 /29)	0.8989 (9.90)		0.9073 (8.26)				

** Presented as arithmetic mean (CV%) only
* Presented as median and range

TRT A: Desloratadine 5 mg Film-Coated Tablets; Lot No: 0190310; (Teva Pharmaceutical Works Private Limited Company, Hungary)
TRT B: Aerius® 5 mg Film-Coated Tablets; Lot No: 9STBAB2B01; (Manufactured by Schering-Plough Ltd., Belgium for Essex Pharma GmbH, Germany)

The geometric 90% confidence intervals for the ratios of AUC_{0-72} and C_{max} for the test and reference products fall within the pre-specified acceptance range for bioequivalence of 80.00 to 125.00%.

Safety data

A total of 8 mild adverse events (AEs) were experienced by the subjects after taking the Test product. A total of 6 mild AEs were experienced by the subjects after taking the Reference product. The most common adverse events were somnolence, headache and catheter site pain/oedema and were all mild in severity. There were no AEs associated with clinical laboratory tests at post-study. No serious adverse events were reported during the conduct of this study.

Conclusion

Based on the presented bioequivalence study Desloratadine 5 mg film-coated tablets is considered bioequivalent with Aerius 5 mg film-coated tablets.

IV.3 Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

IV.4 Additional data

Dissolution studies were performed in order to demonstrate the equivalence between the reference and the test product with regard to desloratadine release. All the dissolution studies were carried out using 6 or 12 tablets of each compared product using basket apparatus (500 ml of 0.1 M HCl, 100 rpm, 37.0 ± 0.5°C). All batches of Desloratadine 5 mg Film-coated Tablets conform to the specification. Aerius 5 mg Filmtabletten (batch no.: 9STBAB2B01, biobatch, Schering-Plough Labo N.V, DE) and Desloratadine 5 mg Film-coated Tablets (batch no.: 0190310) used in the biostudy showed almost the same dissolution profiles.

IV.5 Discussion and conclusions on clinical aspects

To support this generic application, a single bioequivalence study has been performed. The design of this study as a cross-over, two-period, two-sequence, open-label study is adequate. The study was conducted in fasting state, which is generally considered the most discriminatory approach for such immediate release preparations, and desloratadine was the analyte for the pharmacokinetic assessment including conclusions on bioequivalence. Truncated AUC (AUC0-72h) has been used as sampling period. This is in accordance with the applicable bioequivalence guideline which says that a sampling period longer than 72 hours is not considered necessary for any immediate release formulation. Hence for drugs with a long half-life, comparison of extent of exposure using truncated AUCs at 72 hours is acceptable. The calculation of the pharmacokinetic parameters as well as their statistical evaluation is acceptable. Overall, the study is in line with the requirements of the applicable bioequivalence guideline. The 90% confidence interval for the ratio (test/reference) of the geometric least squares means for the log-transformed parameters AUC0-72h and Cmax were within the range of 80.00% to 125.00%. Bioequivalence between test product Desloratadine Double-e Pharma 5mg film-coated tablets with the reference product Aerius 5mg film-coated tablets was therefore established. The dissolution studies supported that the test and the reference product have similar dissolution profiles.

V. 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 Double-e Pharma.

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	• Use in pregnancy • Use in lactation • Use in children less than 6 months of age

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

VI. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VII. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Desloratadine Double-e Pharma 5 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Aerius 5 mg, film-coated 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. Reference was made to the dossier of already registered and approved product Desloratadine Teva 5 mg film-coated tablets.

The Board followed the advice of the assessors.

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 Double-e Pharma with the reference product, and have

therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 February 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse