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SCIENCE MEDICINES HEALTH

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Assessment report

Desloratadine ratiopharm

International nonproprietary name: desloratadine

Procedure No. EMEA/H/C/002404

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of Abbreviations

AUC _{0-72h}	Area under the plasma concentration-time curve from time zero to 72 hours
AUC _{inf}	Area under the plasma concentration-time curve from time zero to infinity
BE	Bioequivalence
BMI	Body Mass Index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CV	Coefficient of variation
ERA	Environmental Risk Assessment
EU	European Union
GCP	Good Clinical Practice
K _{el}	Elimination rate constant
LC	Liquid chromatography
MA	Marketing Authorisation
MS	Mass spectrometry
SmPC	Summary of Product Characteristics
T _{1/2}	Elimination half-life
T _{max}	Time to maximum plasma concentration

1 Background information on the procedure

1.1 Submission of the dossier

The applicant ratiopharm GmbH submitted on 31 January 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Desloratadine ratiopharm, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– ‘Generic of a Centrally authorised product’. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 September 2010.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication: Relief of symptoms associated with allergic rhinitis and urticaria.

The legal basis for this application refers to:

Article 10(1) of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Aerius instead of non-clinical and clinical data unless justified otherwise.

Information on Paediatric requirements

Not applicable.

Information relating to Orphan Market Exclusivity

Not applicable.

Market Exclusivity

Not applicable.

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
 - Product name, strength, pharmaceutical form: Aerius, 5 mg, Film-coated tablets
 - Marketing authorisation holder: Schering-Plough Europe
 - Date of authorisation: 15/01/2001
 - Marketing authorisation granted by:
 - Union
 - Union Marketing authorisation number: EU/1/00/160/001
- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
 - Product name, strength, pharmaceutical form: Aerius, 5 mg, Film-coated tablets
 - Marketing authorisation holder: Schering-Plough Europe

- Date of authorisation: 15/01/2001
- Marketing authorisation granted by:
 - Union
 - Union Marketing authorisation number: EU/1/00/160/001
- Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:
 - Product name, strength, pharmaceutical form: Aeries, 5 mg, Film-coated tablets
 - Marketing authorisation holder: Schering-Plough Europe
 - Date of authorisation: 15/01/2001
 - Marketing authorisation granted by:
 - Union
 - Union Marketing authorisation number(s): EU/1/00/160/001
 - Bioavailability study number(s): Study DEV353901-3DES08 80188 & 90044

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2 Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Pieter Neels.

- The application was received by the EMA on 31 January 2011.
- The procedure started on 23 February 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 May 2011.
- During the meeting on 20-23 June 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 27 June 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 July 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 02 September 2011.
- During the CHMP meeting on 19 – 22 September 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 28 September 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 05 October 2011.
- During the CHMP meeting on 17 – 20 October, the CHMP agreed on a revised list of outstanding issues to be addressed in writing and by the applicant.
- The applicant submitted the responses to the CHMP revised consolidated List of Outstanding Issues on 26 October 2011.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the revised List of Outstanding Issues to all CHMP members on 03 November 2011.
- During the meeting on 14 -17 November 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Desloratadine ratiopharm on 17 November 2011.

2 Scientific discussion

2.1 Introduction

The Marketing Authorization Application of Desloratadine ratiopharm 5 mg film-coated tablet is made under article 10(1) of directive 2001/83/EC. The drug product is a generic of the centrally authorised medicinal product Aerius 5 mg film-coated tablet. This reference medicinal product (MA holder Schering-Plough Europe) was authorised on 15th January 2001 via the centralised procedure in accordance to Article 8 of Directive 2001/83/EC.

The reference medicinal product Aerius is indicated for the relief of symptoms associated with allergic rhinitis and urticaria, like those proposed for Desloratadine ratiopharm. The recommended daily dose is 5 mg in adults and adolescents.

The active substance of the medicinal product is desloratadine. Desloratadine is a non-sedating, long-acting histamine antagonist with selective peripheral H1-receptor antagonist activity. After oral administration, desloratadine selectively blocks peripheral histamine H1-receptors. The selectivity is achieved because the substance is excluded from the entry into the central nervous system.

This application is a generic application, therefore, demonstration of therapeutic equivalence is shown by means of pharmacokinetic studies. The relative oral bioavailability of Desloratadine ratiopharm 5 mg film-coated tablets and the European brand product Aerius 5mg film-coated tablets (manufactured by SP Europe, Belgium) was established by comparing the single dose pharmacokinetics of desloratadine from the two formulations, under fasting conditions, in a randomised crossover study.

Desloratadine ratiopharm is presented in twelve pack sizes: blisters of 7, 10, 14, 15, 20, 30, 40, 50, 60, 90 and 100 tablets and bottles containing 250 tablets. At the time of the CHMP opinion, the 250 tablets pack size does not exist for the reference product. The highest pack size of the reference product contains 100 tablets. Nevertheless, the proposed pack sizes are consistent with the dosage regimen and duration of use.

2.2 Quality aspects

2.2.1 Introduction

Desloratadine ratiopharm is available as 5 mg film-coated tablets for oral administration containing desloratadine as the active ingredient. The full list of ingredients is defined in section 6.1 of the SPC. The film-coated tablets are blue, round biconvex plain on both sides packed either in PVC/PVdC/Alu blister or HDPE bottles with PP caps with desiccant.

2.2.2 Active Substance

At the time of the CHMP opinion, the active substance desloratadine is not described in the European Pharmacopoeia. The ASMF procedure is applied.

The substance is freely soluble in dichloromethane, soluble in methanol and chloroform, very slightly soluble in acetone and ethyl acetate and practically insoluble in water. Desloratadine exists in two different polymorphic forms: Form I and Form II, but this has no clinical relevance as they are bioequivalent and have the same dissolution and stability profile.

The active substance is sourced from two different manufacturers. The manufacturing processes produce consistently the same ratio of crystalline forms of desloratadine.

Manufacture

The synthetic processes of desloratadine include one chemical step followed by purification.

The satisfactory quality of the starting material (loratadine) supplied by different manufacturers is supported by either a Certificate of Suitability from EDQM or by the ASMF. In the detailed description of manufacturing process of desloratadine reaction conditions, equipments and quantities of the used materials are provided precisely. Organic impurities and residual solvents are discussed. Impurity profiles of drug substance batches from both manufacturers are also provided. A specific discussion is provided with regard to genotoxic impurities. Based on the synthetic process, raw materials used and impurity profile of desloratadine, no potential genotoxic impurities are identified.

Specification

Specifications have been set that are appropriate in view of the Ph Eur Monograph 'Substances for Pharmaceutical use', ICH guidance.

The specifications of the active substance as tested by the finished product manufacturer include the following test parameters: description, solubility, identification (HPLC and IR), water content (KF), residue on ignition, heavy metals, related substances (HPLC), assay (HPLC), particle size and residual solvents (GC).

Batch analysis results of at least 3 batches from each manufacturer demonstrate compliance with the proposed specification and indicate that the manufacturing process followed by both manufacturers is under control.

Stability

Satisfactory stability data of three batches from each manufacturer of the active substance stored in their proposed commercial packaging at 25°C/ 60 % RH or 30°C/ 65 % RH and 40°C/ 75 % RH, have been provided to support the proposed re-test period of 24 months and 36 months without any special storage condition. All results comply with the specifications and no trends are observed.

2.2.3 Finished Medicinal Product

Pharmaceutical Development

Desloratadine ratiopharm 5 mg film-coated tablets are a conventional immediate release pharmaceutical form. The objective was to develop a tablet formulation containing desloratadine that is essentially similar to the reference product Aerius 5mg film-coated tablets.

The drug substance desloratadine is slightly soluble in water, soluble in toluene, isopropanol, 0.1M HCl, ethanol and very soluble in methanol. Desloratadine can exist in two known polymorphic forms (i.e. form I & II). Both forms are stable and bioequivalent. The two forms have been characterized with infrared spectroscopy and differential scanning calorimetry. Particle size distribution is controlled by the drug product manufacturer in the drug substance.

The chosen excipients are microcrystalline cellulose and lactose monohydrate, maize starch, poloxamer, citric acid monohydrate, sodium croscarmellose, talc, purified water and Opadry II Blue film-coating including indigo carmine (E132) as colorant for product identification. All the excipients are compendial grade. There are no compatibility concerns with the proposed excipients, as is

demonstrated in long-term and accelerated testing and supporting compatibility screening studies during 4 weeks at 50°C & 40°C/75% RH.

The primary packaging for Desloratadine Ratiopharm 5mg film-coated tablets consists of PVC/PVdC/Alu blister packs.. The two are sealed together to form the blister pack. Technical specifications describe the requirements to which the specified blister pack lid and bottom foils have to comply: visual inspection of material and dimensions. IR-spectra are provided. Certificates of analysis of the packaging materials issued from the supplier are presented.

The drug product is also packed in white 50 ml HDPE bottles closed with twist-off cap in PP with desiccant. Technical specifications describe the requirements to which the HDPE bottles and twist-off caps have to comply: dimensions. IR-spectra are provided. Certificates of conformance of the packaging materials issued from the supplier are presented. The HDPE and PP materials fulfill the Ph. Eur. requirements 3.1.3. & 3.2.2. and EC regulation 2002/72 EEC.

Adventitious agents

The applicant declares that lactose monohydrate is derived from milk and is therefore compliant with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and Veterinary Medicinal Products (EMA/410/01 Rev. 2). No excipients derived from human origin have been used.

Manufacture of the product

The manufacturing process is a conventional granulation technology consisting of granulation followed by mixing and tableting steps and film coating. The manufacturing formula and flow chart are presented. The main process steps are supervised by suitable in-process controls and their acceptance criteria are specified.

The process validation results of production batches were not provided, the process validation protocol at production scale is however provided. The first three commercial batches will be produced and subjected to validation as outlined in the validation protocol. Process evaluation has been carried out on pilot scale batches. Results of tested parameters are batch to batch comparable and are within proposed limits. The results verify that the process assures adequate batch to batch consistency.

Product Specification

The specification of the drug product are acceptable and include: appearance, assay (HPLC), uniformity of dosage units, identification by HPLC and UV, related substances (HPLC), dissolution and microbiological purity. The finished product specifications are standard for immediate release tablets. 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 of pilot batches manufactured with the source of active substance are provided. The batch analysis results show that the finished product meets the proposed specifications and confirm the consistency & uniformity of manufacture indicating that the process is under control.

Stability of the product

The conditions used in the stability studies are in accordance with the ICH stability guideline (25°C/ 60 % RH and 40°C/ 75 % RH) and the packaging similar to that proposed for the market. The control

tests and specifications of drug product are adequately drawn up. Photostability tests were performed on two batches and showed no significant degradation. Based on the stability data provided the proposed shelf-life of 3 years can be granted.

In-use stability study has been performed on 2 pilot batches packed in open HDPE bottles stored for 6 months at 25°C/60%RH. The tested parameters are appearance, identity, moisture content, assay and degradation products, dissolution and microbial purity. No trend in stability is observed during storage in open bottles. Based on these stability data in open bottles, an in-use shelf life of 6 months is set.

2.2.4 Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance.

2.2.5 Conclusions on the 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 SPC. 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 viral/TSE safety.

2.2.6 Recommendation(s) for future quality development

Not applicable.

2.3 Non- Clinical aspects

2.3.1 Introduction

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.

2.3.2 Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment (ERA) was submitted. This was justified by the applicant as the introduction of Desloratadine ratiopharm 5 mg film-coated tablets manufactured by ratiopharm GmbH 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.

2.3.3 Conclusion on the non-clinical aspects

The CHMP agreed that no further non-clinical studies are required. The ERA is expected to be similar and not increased.

2.4 Clinical Aspects

2.4.1 Introduction

This is an application for film-coated tablets containing desloratadine. To support the marketing authorisation application the applicant conducted one pivotal single dose bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment. In addition, one pilot comparative bioavailability study was conducted.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment the *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 pilot bioavailability study and one pivotal bioequivalence study.

The pilot bioavailability study, which was a single center, randomised, single-dose, open-label, 3-way crossover study, was performed to compare the rate and extent of absorption of two test desloratadine formulations versus Aterius, the reference 5 mg desloratadine tablet, under fasting conditions.. The objective was to assess the variability of the drug and to optimize the study design for the definitive bioequivalence study. The formulation of Test 1 (A) in the pilot study was identical to the formulation of the test medication in the pivotal study.

The design of the pivotal bioequivalence study is described in Table 1. It should be noted that two reference products were investigated, one of which was from the EU which is therefore the only one relevant for the present application.

Table 1. Tabular overview of clinical studies

Type of Study	BE
Study Identifier	90044
Objective(s) of the Study	Compare the rate and extent of absorption of desloratadine ratiopharm 5 mg film-coated tablet and Alerius 5 mg film-coated tablet (Reference 1 from Schering Canada Inc., Canada and Reference 2 from Schering-Plough, France), administered as a 1 x 5 mg tablet, under fasting conditions.
Study Design and Type of control	Single centre, randomised, single-dose, blinded, 3-way crossover bioequivalence study
Test Product(s); Dosage Regimen; Route of Administration	Test (A): Desloratadine ratiopharm 5 mg film-coated tablets; Dose: 1 x 5 mg Route of Administration: Oral Reference 1 (B): Alerius 5 mg film-coated tablets; (Schering-Plough Canada Inc., Canada) Dose: 1 x 5 mg Route of Administration: Oral Reference 2 (C): Alerius 5 mg immediate-release film-coated tablets; (Schering-Plough, France) Dose: 1 x 5 mg Route of Administration: Oral
Number of subjects	Enrolled and randomised: 24 (15 females and 9 males) Drop-out: 0 (elected to withdraw) Withdrawal: 0 (was withdrawn) Completed: 24 Safety population: 24 Pharmacokinetic population : 24
Healthy Subjects or Diagnosis of Patients	The 24 subjects enrolled and randomised were healthy, adult subjects, aged ≥ 18 and ≤ 55 years; body mass indices ≥ 19.0 and < 29.0 kg/m ² .
Duration of Treatment	A single oral dose of desloratadine as a 1 x 5 mg tablet was administered in each study period. The treatment phases were separated by washout periods of 21 days.

Study status; Type of Report	Complete
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2.4.2 Pharmacokinetics

Methods

Study design

Study 90044 was a single centre, randomised, single-dose, blinded, 3-way crossover bioequivalence study under fasting conditions.

Twenty-four healthy male (n=9) and female (n=15) subjects, aged 21-55 years, were enrolled into the study. Each subject received a single dose (5 mg) of the test (A), reference 1 (B) and reference 2 (C) desloratadine formulations. The subjects were confined within the facility at least 10 hours prior to dose and until 24 hours post-dose during each period. A randomisation scheme was included in the report. After an overnight fast of at least 10 hours, subjects were administered the study drug (a single oral dose of test or the reference product as per randomization schedule) with approximately 240 mL of drinking water in each period. Fasting was continued for 4 hrs after dosing. Drinking water was not allowed for 2 hour pre-dose to 2 hours post-dose. Thereafter, it was allowed at all times. For each subject, there were 3 dosing periods, separated by a washout period of 21 days.

All blood samples were drawn into blood collection tubes (1 x 6 mL) containing EDTA prior to drug administration and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 12, 24, 48, and 72 hours post-dose in each period. There were two ambulatory visits at 48.00 and 72 hours post dose in each period.

Blood samples were cooled in an ice bath and centrifuged. Aliquots were transferred to a freezer, pending transfer to the bioanalytical facility.

The study was conducted by Anapharm Inc., Québec, Canada, between 20/4/2009 and 4/6/2009.

Test and reference products

Desloratadine 5 mg film-coated tablets (Test (A) manufactured by ratiopharm Private Limited, GOA, India for ratiopharm GmbH, Germany (batch number V0350803, manufacturing date: November 2008, expiry date: October 2009, retest date: October 2009) have been compared to Aerius 5 mg film-coated tablets (Reference 1 (B): manufactured by Schering-Plough Canada Inc., Canada (batch number 8STBC20, manufacturing date: not available, expiry date: May 2010) and Aerius 5 mg film-coated tablets (Reference 2 (C): manufactured by Schering-Plough, France (batch number 8048, manufacturing date: not available, expiry date: January 2010).

For the present application, only Reference 2 (c) is relevant and will be reported, as this is a reference product from the EU.

Population studied

Twenty-four (24) adult, male and female white, healthy human subjects, who met the inclusion and exclusion criteria as described in the protocol, were enrolled in study 90044. The mean age, weight, height and BMI of the study subjects was 41 years (range 21 to 55 years), 68.2 kg (range 51.3 to 93.4 kg), 165.7 cm (range 152.5 to 181.5 cm) and 24.6 kg/m² (range 20.0 – 28.7 kg/m²) respectively.

Of the 24 subjects who were dosed, all completed the study. In accordance with the study protocol, data from all subjects who completed at least 2 periods, including one test and one reference products, and for whom the pharmacokinetic profile was adequately characterised were used for pharmacokinetic and statistical analysis.

Analytical methods

Plasma samples were analysed for desloratadine using a validated gas-liquid chromatographic/nitrogen phosphorus detection method with desloratadine-d₅ as internal standard. Automated solid phase extraction (with Oasis MCX 10 mg extraction plates) was used for sample preparation. The method was validated for both desloratadine and 3-hydroxy desloratadine in human plasma and a validation report was provided (Project number 45081GNC (revision 05)). Different partial validations were performed including the transfer of the method to another laboratory, changes in the original calibration range and a change in anticoagulant (EDTA K2 plasma instead of EDTA K3 plasma). The results shown below for accuracy and precision, long-term stability of desloratadine and IS in solution at -20°C and long-term stability of desloratadine in matrix at -20°C and at -80°C are those obtained in EDTA K2 plasma; the other results were obtained in EDTA K3 plasma.

The calibration curve for desloratadine ranged from about 25.00 pg/mL to 5000 pg/mL. A weighted linear regression (1/C²) was performed to determine the concentrations of the samples. Intra-assay and inter-assay precision and accuracy were tested.

The results of the stability investigations were satisfactory. Overall, the bioanalytical method was considered adequately validated.

Pharmacokinetic Variables

The pharmacokinetic variables for Study 90044 were AUC_{0-72h}, AUC_{0-inf}, C_{max}, T_{max}, residual area, T_{1/2el} and K_{el}. The bioanalytical analyte was desloratadine.

The area under the plasma concentration-time curve (AUC_{0-t}) was determined by the linear trapezoidal rule.

Statistical methods

ANOVA was performed on ln-transformed AUC_{0-72h}, AUC_{0-inf}, and C_{max} and untransformed K_{el} and T_{1/2 el}. A non-parametric test (Friedman's test) was carried out to compare the T_{max} between treatments. Ratios of least-squares means (LSM) (A/B and A/C) and 90% geometric confidence intervals were calculated for ln-transformed AUC_{0-72h}, AUC_{0-inf}, and C_{max}, for both uncorrected and potency-corrected data. Inter- and intra-subject CVs were also calculated.

Bioequivalence was to be concluded if the 90% geometric confidence intervals of the ratio of least-squares means for ln-transformed AUC_{0-72h} and C_{max} were within the acceptable range of 80.00% to 125.00%.

All ANOVAs were performed with the SAS General Linear Models Procedure (GLM). The model included sequence, subject within sequence, period and treatment as factors. The sequence effect was tested using subjects within sequence effect as the error term. The treatment and period effects were tested against the residual mean square error.

Results

Summary of the pharmacokinetic results and the statistical analysis:

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

Treatment	AUC _{0-t}	AUC _{0-∞}	C _{max}	t _{max}	T _{1/2}
	µg/ml/h	µg/ml/h	µg/ml	h	h
Test (Desloratadine (A))	46849.39 $\pm$ 22219.86	54613.84 $\pm$ 36916.11	2379.88 $\pm$ 880.26	3.26 (1.00- 12.00)	21.07 $\pm$ 11.65
Reference 2 (Aerius (C))	43784.02 $\pm$ 22615.54	51423.00 $\pm$ 37421.07	2212.70 $\pm$ 826.16	4.50 (1.50- 12.00)	21.40 $\pm$ 11.60
*Ratio (90% CI)	107.49 (103.47- 111.66)	107.48 (103.36- 111.77)	106.92 (100.42- 113.84)	-	-
CV (%)	7.72	7.93	12.98	-	-
AUC _{0-∞} 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

Reference 2(C), Aerius 5 mg film-coated tablets manufactured by Schering-Plough, France

Safety data

All formulations were well tolerated, with no major side effects and no relevant differences in safety profiles were observed between the preparations, particularly with respect to the number and pattern of adverse events.

A total of 9 treatment-emergent adverse events (TEAEs) were reported by 5 of the 24 subjects who received at least one dose of the study medication (safety population). The breakdown by treatment group is as follows: 3 TEAEs reported by 12.5% (n=3) of the 24 subjects who received Treatment A, 2

TEAEs reported by 8.3% (n=2) of the 24 subjects who received Treatment B, and 4 TEAEs reported by 12.5% (n=3) of the 24 subjects who received Treatment C.

The most commonly reported TEAEs were related to procedures (including "Procedural pain", "Post-procedural swelling", and "Post-procedural haematoma") and were reported by 16.7% (n=4) of subjects who constituted the safety population (n=24). In addition, "Erythema" and "Headache" were also reported by 8.3% (n=2), each, of subjects who constituted the safety population. Of the 9 TEAEs reported, all were graded as mild. Of the 9 TEAEs reported, the relationship of 2 was judged as "possible" and 7 as "not related".

No deaths, serious or significant adverse events were reported during this study.

Conclusions

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

2.4.3 Pharmacodynamics

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

2.4.4 Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5 Discussion on Clinical aspects

To support this generic application, one pilot bioavailability study and one pivotal bioequivalence study were performed.

The pilot bioavailability study was performed to assess the variability of the drug and to optimize the study design for the definitive bioequivalence study. This single center, randomised, single-dose, open-label, 3-way crossover study performed to compare the rate and extent of absorption of desloratadine 5 mg tablets from two different batches of desloratadine ratiopharm with Aerius 5 mg tablets. The formulation of Test 1 (A) in the pilot study was identical to the formulation of the test medication in the pivotal study.

The bioequivalence study, which is pivotal for the assessment, was a cross-over, two-period, two-sequence, open-label study. This design was considered adequate. The study was conducted in fasting state, which is generally considered the most discriminatory approach for such immediate release preparations, and desloratadine (i.e. the parent compound) was the analyte for the pharmacokinetic assessment including conclusions on bioequivalence.

The CHMP noted that light smokers (i.e. smoking less than 10 cigarettes per day) were allowed to participate in this study. This was acceptable since desloratadine is not reported to be neither a

substrate nor an inhibitor of CYP 1A2, the enzyme which is known to be induced during cigarettes and cigars smoking.

The calculation of the pharmacokinetic parameters as well as their statistical evaluation is acceptable. Using truncated AUC (0-72h) is deemed appropriate. Relevant for the assessment was the comparison of the test product with the EU reference product.

Overall, the study is in line with the requirements of the applicable Guideline on the Investigation of Bioequivalence.

The 90% confidence interval for the ratio (test/reference) of the geometric least squares means for the log-transformed parameters AUC_{0-72h} and C_{max} were within the range of 80.00% to 125.00%. Bioequivalence between test product Desloratadine ratiopharm 5mg film-coated tablets with the reference product Aeries 5mg film-coated tablets was therefore established.

The Applicant presented comparative dissolution profiles between the test and reference products used for bioequivalence study (biobatches n° V0350803 and n° 8048). Dissolution was found to be pH-independent. The in vitro dissolution tests were carried out using the following analytical method: paddle apparatus, 900 mL, 50 rpm, 37°C, three pHs.

For the test product, more than 85% of the drug substance was dissolved within 15 minutes at each pH; however, this was not true for the reference product (< 85% dissolved at each pH). Mathematical evaluation of the dissolution profiles using the similarity factor f_2 showed a value below 50 at pH 4.5 and 6.8.

The dissolution studies supported that the test and the reference product have similar dissolution profiles.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The CHMP did not require the applicant to submit a risk management plan because the application concerns a medicinal product containing a known active substance for which no safety concern requiring additional risk minimisation activities has been identified.

PSUR submission

The PSUR submission schedule should follow the PSUR schedule for the reference product. The PSUR of the reference medicinal product is on a 2-yearly cycle. The last data lock point for the reference medicinal product was 15.07.2011.

User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a double bridging making reference to Xylometazoline hydrochloride 0.1% nasal spray and Desloratadin Teva 5mg film-coated tablets. The bridging report submitted by the applicant has been found acceptable.

3 Benefit-Risk Balance

This application concerns a generic product. The reference product is indicated for the relief of symptoms associated with allergic rhinitis and urticaria. No non-clinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance. The applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a single centre, randomised, single-dose, blinded, 3-way crossover bioequivalence study. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements.

The products were studied using a crossover design with 24 healthy volunteers being administered an oral dose of 1×5 mg under fasting conditions in each study period. For each subject, there were 3 dosing periods, separated by a washout period of 21 days. Subjects were confined to the clinic at least 10 hours prior to dose and until 24 hours post-dose during each period. Each study period included a single-dose drug administration of either the test or the reference product. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate.

The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Desloratadine ratiopharm met the protocol-defined criteria for bioequivalence when compared with Acrius. The point estimates and their 90% confidence intervals for the parameters AUC_{0-72h} and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4 Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Desloratadine ratiopharm in the treatment of relief of symptoms associated with allergic rhinitis and urticaria is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation***Pharmacovigilance System***

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management System

Not applicable

PSUR cycle

The PSUR cycle for the product will follow PSURs submission schedule for the reference medicinal product.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable.

Obligation to complete post-authorisation measures

Not applicable.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.