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Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Desloratadine Teva

International nonproprietary name: desloratadine

Procedure No. EMEA/H/C/002419

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Table of contents

1 Background information on the procedure 3
1.1 Submission of the dossier 3
1.2 Steps taken for the assessment of the product 4
2 Scientific discussion 5
2.1 Introduction 5
2.2 Quality aspects 5
2.2.1 Introduction 5
2.2.2 Active Substance 5
2.2.3 Finished Medicinal Product 6
2.2.4 Discussion on chemical, and pharmaceutical aspects 8
2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects 8
2.2.6 Recommendation(s) for future quality development 8
2.3 Non- Clinical aspects 8
2.3.1 Introduction 8
2.3.2 Ecotoxicity/environmental risk assessment 9
2.4 Clinical Aspects 9
2.4.1 Introduction 9
2.4.2 Pharmacokinetics 10
2.4.3 Pharmacodynamics 13
2.4.4 Additional data 13
2.4.5 Post marketing experience 13
2.4.6 Discussion and conclusions on Clinical aspects 13
2.5 Pharmacovigilance 14
3 Benefit-Risk Balance 14
4 Recommendation 15

1 Background information on the procedure

1.1 Submission of the dossier

The applicant Teva Pharma B.V. submitted on 24 January 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Desloratadine Teva, 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.

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: Neoclarityn 5mg film-coated tablets
  - Marketing authorisation holder: Schering-Plough Europe
  - Date of authorisation: 15-01-2001
  - Marketing authorisation granted by: Community
  - Community Marketing authorisation number: EU/1/00/161/001-013

- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
  - Product name, strength, pharmaceutical form: Neoclarityn 5mg film-coated tablets

- Marketing authorisation holder: Schering-Plough Europe
- Date of authorisation: 15-01-2001
- Marketing authorisation granted by: Community
- Community Marketing authorisation number: : EU/1/00/161/001-013

■ 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: Aerius 5 mg Film-Coated Tablets
- Marketing authorisation holder: Schering-Plough Europe
- Date of authorisation: 15-01-2001
- Marketing authorisation granted by: Community
- Community Marketing authorisation number(s): EU/1/00/160/001-013, EU/1/00/160/036
- Bioavailability study number(s): 1262

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 János Borvendég.

- The application was received by the EMA on 24 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 23 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 meeting on 19-22 September 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 Teva on 22 September 2011.

2 Scientific discussion

2.1 Introduction

The Marketing Authorization Application of Desloratadine Teva 5 mg film-coated tablet was submitted to the centralised procedure according to regulation (EC) No 726/2004, article 3(3). The legal basis is article 10(1) of Directive 2001/83/EC. The reference product is the centrally authorised medicinal product Neoclarytin 5 mg film-coated tablet. The reference medicinal products Aerius/Neoclarityn 5 mg tablets (MA holder Schering-Plough Europe) were centrally authorized on the 15th January 2001.

The reference medicinal product is indicated for the relief of symptoms associated with allergic rhinitis and urticaria. 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 bioequivalence. No new clinical studies are either required or submitted with this application. The Applicant provided a comprehensive overview of clinical data on desloratadine in clinical use based upon the conclusions of the relevant clinical studies published in the literature.

The relative oral bioavailability of Desloratadine Teva 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.

2.2 Quality aspects

2.2.1 Introduction

Desloratadine 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 film-coated tablet-printed in white ink: "D5" on one side and plain on the other and are stored in polyamide/aluminium/polyvinyl chloride/aluminium foil blisters.

2.2.2 Active Substance

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

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

forms have similar solubility and therefore no difference in the bioavailability and performance of the product are expected.

Manufacture

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, equipments 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.

Specification

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

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.

2.2.3 Finished 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 Teva 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.

Adventitious agents

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

Manufacture of the product

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 Teva 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.

Product Specification

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 the 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.

2.2.4 Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished medicinal 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 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.

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 was submitted. This was justified by the applicant as the introduction of Desloratadine Teva 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.

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 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
Objective(s) of the Study	Compare the bioavailability of 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

2.4.2 Pharmacokinetics

Methods

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 dosingat pre-defined times. Plasma was harvested from these samples and assayed for desloratadine.

Test and reference products

Desloratadine 5 mg film-coated tablets manufactured by Teva Pharmaceutical Works Private Limited Company, Hungary (Lot No. 0190310, manufacturing date 03/2010, exp. date 09/2010) has been compared to Aerius 5 mg film-coated tablets manufactured by Schering-Plough Ltd., Belgium, for Essex Pharma GmbH, Germany (Lot No. 9STBAB2B01, manufacturing date N/A, exp. date 08/2011).

Population studied

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_{0-72h} and C_{max}. Other pharmakokinetic 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_{0-72h} 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_{0-72h} 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_{0-72h} 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.

Conclusions

Based on the presented bioequivalence study Desloratadine 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 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.

2.4.5 Post marketing experience

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

2.4.6 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 (AUC_{0-72h}) 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 AUC_s 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 AUC_{0-72h} and C_{max} were within the range of 80.00% to 125.00%. Bioequivalence between test product Desloratadine Teva 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.

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

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet 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.*

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 nonclinical studies have been provided for this application. An adequate summary of the available nonclinical 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 provided an update of published literature relevant to the product.

The bioequivalence study forms the pivotal basis with a single dose, randomized, open-label, two-period, two-sequence, two-treatment, single- centre, crossover, comparative bioavailability 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 36 healthy 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.

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

The test formulation of Desloratadine Teva met the protocol-defined criteria for bioequivalence when compared with the Aerius. The point estimates and their 90% confidence intervals for the parameters $AUC_{0\text{-}72h}$ 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.

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 Teva in the treatment of relief of symptoms associated with allergic rhinitis and urticaria is favourable and therefore recommends the granting of the marketing authorisation.

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. 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

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

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.