22 September 2011
EMA/895265/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dasselta

International nonproprietary name: desloratadine

Procedure No. EMEA/H/C/002310

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

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1 Background information on the procedure

1.1 Submission of the dossier

The applicant Krka, d.d., Novo mesto submitted on 03 February 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Dasselta, 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 23 March 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 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: 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(s): EU/1/00/160/001
- Bioavailability study number(s): Confidential

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:

Rapporteur: János Borvendég

- The application was received by the EMA on 03 February 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 21 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 19-20 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 Dasselta on 20 September 2011.

2 Scientific discussion

2.1 Introduction

The Marketing Authorization Application of Dasselta 5 mg film-coated tablets is made in the centralised procedure according to regulation (EC) No 726/2004, Article 3(3). It is in compliance with the 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 tablets. The reference medicinal products –

Aerius®/Azomyr®/Neoclarityn® 5 mg tablets (MA holder Schering-Plough Europe) was authorized on 15th January 2001 via centralised procedure in accordance to Article 8 of Directive 2001/83/EC.

Reference medicinal product Aerius is indicated for the relief of symptoms associated with allergic rhinitis and urticaria, like those proposed for Dasselta. 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. Then, new clinical studies are neither required nor submitted. In spite of this general rule the Applicant submitted 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 Dasselta 5 mg film-coated tablets (manufactured by KRKA d.d. Novo mesto, Slovenia) 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.

An additional pack-size of 250 film-coated tablets containing more units than the pack size of the reference product is proposed. It is confirmed that this additional pack size is consistent with the dosage regimen and duration of use.

2.2 Quality aspects

2.2.1 Introduction

Dasselta 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 light blue, round with bevelled edges are stored in polyamide/aluminium/polyvinyl chloride/aluminium foil blisters or a high density polyethylene container and polypropylene closure bottles 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 different polymorphic forms.
The manufacturing processes produce consistently the same form(s) of desloratadine.

Manufacture

The synthesis processes of desloratadine include one chemical step followed by purification.
The quality of the starting material supplied by the different manufacturers is satisfactory supported by either a Certificate of Suitability from EDQM or by an 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 different 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', the Q6A Guideline on Setting Specifications and the impurity discussion.
Limits of specified and unspecified related substances are set in line with ICH Q3A guidelines. The maximum level of total impurities is set at a level which is qualified with regard to safety. The limits for residual solvents are in line with ICHQ3C and Ph. Eur. requirements. The limits for assay are based on general pharmacopeial limits for active substances.
Satisfactory data have been provided regarding PhEur and in-house analytical tests.
Analytical results confirm batch to batch consistency and uniformity of the quality of the substance 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° ± 2°C/ 60 % ± 5 % RH and 40° ± 2°C/ 75 % ± 5 % RH, have been provided to support the proposed re-test period of 24 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

Dasselta 5 mg film-coated tablets are a conventional immediate release pharmaceutical form.
The excipients used are all standard and commonly used in the pharmaceutical industry.

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, Acetate 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.

Adventitious agents

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 (EMEA/410/01 Rev. 2). No excipients derived from human origin have been used.

No novel excipients are used in the manufacturing process of Dasselta.

Manufacture of the product

The manufacturing process is a conventional technology. The manufacturing formula, flow chart and description of the manufacturing process are presented. The main process steps are supervised by suitable in-process controls and their acceptance criteria are specified.
The manufacturing process has been validated on pilot batches.

Product Specification

The specification of the drug product are acceptable. 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.

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. The control tests and specifications of drug product are adequately drawn up. Photostability tests were performed on two batches.
Based on the stability data provided the proposed shelf-life is granted, please see SmPC.

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 was submitted. This was justified by the applicant as the introduction of Dasselta manufactured by KRKA d.d. Novo Mesto, Slovenia 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 Discussion on Non-Clinical aspects

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

2.3.4 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 bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment.

The applicant also provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of desloratadine based on published literature.

The SmPC is in line with the SmPC of the reference product.

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	Study Identifier	Location of Study Report	Objective of the Study	Study Design; Type of Control	Test Product(s); Dosage Regimen; Rout of Administration	No. of Subjects	Healthy Subjects/ Diagnosis Of Patients	Duration of Treatment	Study Status; Type of report
BE	10-282	Section 5.3.1.2.	Assessment of single-dose relative bioavailability of two tablet formulations after administration under fasting conditions	Crossover; Fasting state with a 2-weeks washout period	**Test:** Desloratadine film-coated tablets 5 mg (B.No.: 1252 01 P003 1009) **Reference:** Aerius® film-coated tablets 5 mg (B.No.: 8STBAAFB01)	24	Healthy subjects	Single Dose	Complete; Full

2.4.2 Pharmacokinetics

Methods

Study design

Study 10-282 was a single-dose, randomized, open-label, two-period, two-sequence, two-treatment, single-centre, crossover study designed to evaluate the comparative bioavailability of desloratadine from Dasselta 5 mg Film-Coated Tablets (Manufactured by KRKA, d.d., Novo Mesto, Slovenia) and Aerius 5 mg Film-Coated Tablets (MA holder Schering-Plough Europe) under fasting conditions.

Subjects were randomly assigned to one of the two dosing sequences. Subjects were administered the test or reference medication (as per the randomisation scheme) as a single oral dose of tablet containing 5 mg of desloratadine with 240 mL of water in the morning under fasting conditions and subsequently fasted for a period of at least 5 hours. They were not allowed to lie down or sleep for the first 6 hours after drug administration. At 5 and 10 hours post dose standard meals were served. During each study period, blood samples were taken at 0 (pre-drug administration), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7.5, 9, 12, 24, 36, 48 and 72 hours after dosing. Plasma was harvested from these samples and assayed for desloratadine. The wash-out period was 2 weeks.

The study was conducted at a single study site outside the community. The bioanalytic analyses were performed by contract research organisation outside the community. The pharmacokinetic and statistical analysis was performed at KRKA d.d., R& D, Pharmacokinetics Department.

Study was conducted in accordance to the study protocol (dated 10 February 2010) and under approval by the competent national authorities.

Test and reference products

Dasselta 5 mg film-coated tablets manufactured by KRKA d.d. Novo Mesto, Slovenia (batch No. 1252 01 P003 1009, manufacturing date October 2009; retest date September 2010) has been compared to Aerius 5 mg film-coated tablets (Batch No: 8STBAAFB01, exp. date August 2010).

The batch size of the test product Dasselta 5 mg film-coated tablets was in accordance with the guideline. Composition of the test product was identical to the formulation intended to be marketed.

Population studied

Twenty four (24) healthy male volunteers were included in the study and there were no dropouts.Study population was defined as healthy male volunteers, aged 18-55 years, Caucasian race, non smoker, BMI within 18,5 and 30 kg/m^2. The baseline characteristics are detailed below.

Table 2. Demographic characteristics of subjects in study 10-282

	Age (years)	Height (m)	Weight (kg)	BMI (kg/m2)
MEAN	34	1,81	85	26
SD	10	0,08	11	2
MIN	22	1,69	65	22
MAX	53	1,97	103	28
n	24	24	24	24

There were no protocol violations reported including no substantial difference between the planned and actual sampling times.

Analytical methods

An LC/MS/MS assay for the determination of desloratadine in human plasma was developed and validated by the contract research organisation outside the community. At the study site the plasma samples were frozen at -20°C ± 5°C until assayed at the analytical site. The calibration range for the bioanalytical method was 24.88 – 4976.00 pg/ml. A Re-analysis of part of the samples was conducted during the study, with all results within the predefined acceptance range of ±20.0% of the original value.

The analytical method was developed for simultaneous determination of desloratadine and its 3-OH metabolite. However the protocol of the bioequivalence study required measuring only the desloratadine concentration.

The bioanalytical method is considered adequately validated.

Pharmacokinetic Variables

The main pharmacokinetic parameters in this study were AUC_{0-72h}, and C_{max}. Other pharmakokinetic parameters, such as AUC_{inf}, AUC_t/AUC_{inf}, K_{el}, T_{max} and $T_{1/2}$ were provided for information purpose only.

Calculations of pharmacokinetic parameters were performed in Kinetica Version 5.0 and SAS System for Windows Release 9.1. The individual plasma levels of desloratadine obtained for the two formulations were used for the model-independent determination of pharmacokinetic parameters.

Statistical methods

ANOVA including sequence, subjects nested within sequence, period and treatment was to be performed on the ln-transformed data for AUC_{0-72h} and C_{max} and on the raw data for AUC_{0-72h}, C_{max} and T_{max}. T_{max} were to be analyzed using an additional non-parametric test (Wilcoxon test). The 90% confidence intervals (CI) of the Test/Reference ratios of geometric means for AUC_{0-72h} and C_{max} were to be calculated based on the least square means. The predefined acceptance range for the conclusion on bioequivalence based on AUC_{0-72h} and C_{max} was 80.00-125.00 %.

There were no missing values and no outliers in the study.

Results

The results show that the test product is bioequivalent to the reference product.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, T_{max} median, range)

Treatment	AUC_{0-72} pg/ml/h	AUC_{inf} pg/ml/h	C_{max} pg/ml	T_{max} h	$T_{1/2}$ h
Test	32432.74 ± 7322.33	35337.88 ± 8015.73	2252.40 ± 570.09	2.50 (1.00 – 6.00)	22.21 ± 10.23
Reference	33230.67 ± 6261.88	35707.58 ± 6964.83	2249.60 ± 601.73	2.00 (1.00 – 6.00)	20.85 ± 2.92
*Ratio (90% CI)	96.79% (91.89% - 101.95%)	98.18% (93.02% - 103.64%)	100.39% (93.64% - 107.63%)	-	-
CV (%)	14.4	15.4	19.7	-	-

AUC_{inf} area under the plasma concentration-time curve from time zero to infinity
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration
$T_{1/2}$ half-life

*ln-transformed values

Safety data

There were no adverse events reported in the study 10-282.

Conclusions

Based on the presented bioequivalence study Dasselta 5 mg film-coated tablets are 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 profiles of both the reference and test product were fast and complete in three tested dissolution media: 0.1N Hydrochloric Acid, Acetate Buffer pH 4.5 and Phosphate Buffer pH 6.8. Dissolution profiles are assessed as being similar.

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 on Clinical aspects

The design of the bioequivalence study is in line with the regulatory requirements, in particular *Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1* in its current version. A two-sequence, two-period, cross-over design has been employed. The determination of the pharmacokinetic parameters and their statistical evaluation is acceptable. With regard to the AUC, truncated AUC over 72 h has been used for the evaluation which is generally acceptable for oral immediate release formulations. The study has been conducted according to GCP, and no important issues have been reported regarding the conduct of the study. The pre-defined acceptance criteria of 80.00-125.00 % (for desloratadine AUC_{0-72h} and C_{max}) are in line with regulatory requirements and have been met. Choice of desloratadine as the analyte for establishing bioequivalence is acceptable; the bioanalytical method was adequately validated. Dasselta and the reference product have similar dissolution profiles.

2.4.7 Conclusions on clinical aspects

The bioequivalence of Dasselta 5 mg film-coated tablets to the reference medicinal product Aerius 5 mg film-coated tablets can be regarded as established.

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 of the well established safety profile of the reference product and proved bioequivalence between Dasselta and the reference product.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product. No additional risk minimisation activities were required beyond those included in the product information.

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 July 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 version of desloratadine film-coated tablets. The reference product Aerius is indicated for relief of symptoms associated with allergic rhinitis and urticaria. No nonclinical studies have been provided for this application but 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 on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a single-dose, randomized, open-label, two-period, two-sequence, two-treatment, single-centre, crossover study under fasting conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. 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 Dasselta 5 mg film-coated tablets met the protocol-defined criteria for bioequivalence when compared with the Aerius 5 mg film-coated tablets. The point estimates and their 90% confidence intervals for the parameters AUC_{0-72} 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 Dasselta 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.

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.