22 February 2007
EMA/426692/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment Report

Aerius

International Nonproprietary Name: desloratadine

Procedure No. EMEA/H/C/313/X/33

Note

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

Disclaimer:
The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

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PRODUCT INFORMATION

Name of the medicinal product:	Aerius
Applicant:	Schering-Plough Europe
Active substance:	Desloratadine
International Nonproprietary Name/Common Name:	Desloratadine
Pharmaco-therapeutic group (ATC Code):	R06A X27
Therapeutic indication(s):	Aerius is indicated for the relief of symptoms associated with: - allergic rhinitis (AR) - chronic idiopathic urticaria (CIU)
Pharmaceutical form(s):	Oral solution
Strength(s):	0.5 mg/ml
Route(s) of administration:	Oral use
Packaging:	Bottle (glass) + spoon (plastic)
Package size(s):	30, 50, 60, 100, 120, 150, 225 and 300 ml

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1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Schering Plough Europe submitted on 30 June 2006 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Aerius 0.5 mg/ml oral solution under Annex II, point 2 iv to Commission Regulation (EC) No 1085/2003.

Schering Plough Europe is already the Marketing Authorisation Holder of Aerius 5 mg film coated tablets on 15/01/2001 (EU/1/00/160/001-013), Aerius 5 mg oral lyophilisate on 16/04/2002 (EU/1/00/160/022-034) and of Aerius 0.5 mg/ml syrup on 16/04/2002 (EU/1/00/160/014-021) under Part A of the Annex to Council Regulation No. (EEC) 2309/93 of 22 July 1993, as amended.

Aerius is indicated for the relief of symptoms associated with:
- allergic rhinitis (AR)
- chronic idiopathic urticaria (CIU)

Licensing status:

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

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: Dr. Pieter Neels Co-Rapporteur: Not applicable

CHMP Peer reviewer(s): Not applicable

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 30 June 2006.
- The procedure started on 19 July 2006.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 20 September 2006.
- During the meeting on 13-16 November 2007, 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 16 November 2006.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 December 2006.
- The Rapporteurs circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 26 January 2007.
- During the meeting on 19-22 February 2007, 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 Aerius on 22 February 2007. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 22 February 2007.

2 GENERAL CONDITIONS FOR THE MARKETING AUTHORISATION

2.1 Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

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

Not applicable

2.3 Other conditions

Pharmacovigilance system

The submitted Pharmacovigilance System is in line with the pharmacovigilance work developed so far by the MAH and in compliance with current requirements.

Risk Management plan

The Committee agreed that there was no need to request a Risk Management Plan with respect to these line extensions.

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

Not applicable

3 SCIENTIFIC DISCUSSION

3.1 Introduction

Desloratadine, the major active metabolite of loratadine, is a long-acting tricyclic antihistamine with selective peripheral histamine H1-receptor antagonistic activity. Similar to the parent drug loratadine, desloratadine has been investigated and shown to possess peripheral antihistaminic effects with no sedative or other central nervous system effects at the clinically recommended dose. Desloratadine was developed for its more favourable pharmacokinetic profile than that of loratadine, exhibiting less extensive first-pass metabolism and a longer plasma elimination half-life.

This application is a line extension to the existing desloratadine products. Desloratadine 5-mg film coated tablets have been authorised in 2001. Two line extensions were approved in 2002, namely for the 0.5 mg/ml desloratadine syrup and for a 5-mg oral lyophilisate. The latter has never been marketed.

The proposed formulation is mainly intended for paediatric use. The recommended dose is 1.25 mg (2.5 ml) for children of 1 to 5 years, 2.5 mg (5 ml) for children of 6 to 11 years and 5 mg (10 ml) for patients of 12 years or more.
This application is arising from a post approval obligation of the marketing authorisation for the desloratadine syrup. Schering-Plough committed to reformulate that product to make it more suitable for the recommended patient age and the likely duration of the treatment. More specifically, it was requested

to remove sucrose, sodium benzoate, and the colorant (E 110) from the formulation. Updates of the reformulation program were being presented to the Competent Authority every six months.

Schering-Plough will stop the manufacturing and distribution of the desloratadine syrup in the EU once an authorisation is granted for the desloratadine oral solution.

3.2 Quality aspects

Introduction

Desloratadine oral solution, 0.5 mg/ ml is a clear, colourless oral solution. It is packaged in amber glass bottles closed with child-resistant polypropylene closures. It is presented in fill volumes of 30 ml, 50 ml, 60 ml, 100 ml, 120 ml, 150 ml, 225 ml and 300 ml.

The excipients used in the manufacture of the oral solution are: propylene glycol, sorbitol, hypromellose, sucralose, citric acid, sodium citrate dihydrate, disodium edentate and flavour.

A plastic spoon accompanies each package presentation. The 150-mL pack size might include a plastic syringe alternatively. Both the spoon and syringe are graduated to measure and dispense 2.5 ml and 5 ml doses of the drug product.

Active Substance

The drug substance used in the manufacture of desloratadine oral solution is the same and has identical specifications with the one used in the already approved strengths.

Medicinal Product

- Pharmaceutical Development

The objective of the pharmaceutical development program was to obtain a reformulated oral liquid desloratadine product more suitable for the recommended patient age and the likely duration of the treatment.

Compared to the composition of the desloratadine syrup the following excipients have been removed from the formulation: sucrose, sodium benzoate and colorant E110. Hypromellose and sucralose are newly included in the formulation acting as a thickener and a sweetener respectively. Hypromellose is a widely used excipient in pharmaceutical oral formulations, since it has an acceptable safety profile and it is tasteless. The use of sucralose in foodstuffs has been endorsed in 2000 by the EU Scientific Committee for Food. Directive 94/35/EC on sweeteners for use in foodstuffs permits the use of sucralose in a broad range of foodstuffs at maximum concentrations ranging from 10 to 3000 mg/kg.
Other excipients include propylene glycol, which in the absence of sugar and sodium benzoate and at the selected concentration acts as an antimicrobial preservative.
Most excipients comply with the relevant Ph.Eur. monographs. Sucralose is tested according to the USP/NF taking into account the specific EU criteria of purity concerning sweeteners for use in foodstuffs.

The compatibility of the active substance and the new excipients has been adequately established by appropriate compatibility and long-term stability studies, while the taste acceptability of the reformulated product was confirmed in a study in paediatric subjects.

The manufacturing process developed for the desloratadine oral solution uses conventional mixing, filtering, and packaging equipment. A minor modification in the sequence of raw material addition has eliminated the need for a colorant that has been used in the previous formulation in order to mask the

occasional colour formation. During the manufacturing process development critical parameters such as the pH, the holding times of the intermediate solutions, the fill volumes have been identified and appropriate ranges have been established.

The proposed container closure system for the desloratadine oral solution is identical to that of the original desloratadine syrup. The measuring devices used (spoon, syringe) meet the requirements found in Ph Eur. 5, Monograph 2.9.27. "Uniformity of Mass of Delivered Doses from Multidose Containers".

- Adventitious Agents

The medicinal product contains no adventitious agents

- Manufacture of the Product

The manufacturing process has been sufficiently described and consists of the following main steps: solution compounding, filtration and filling.
All critical process parameters have been identified and controlled by appropriate in process controls.
There were deviations from the ICH on process validation, however this has been found acceptable based on the data provided from three pilot scale and one production scale batches and the fact that the manufacturing method employed is a commonly used, standard and well understood method. In addition the Applicant has undertaken the responsibility to perform validation studies in accordance with ICH requirements as a post authorisation commitment.

- Product Specification

The product specifications include tests for appearance, pH, identification and assay (desloratadine, propyleneglycol and edetate), desloratadine degradation products (in accordance with ICH Q3B) and microbiological quality. The test methods have been appropriately described and validated. Supporting batch analysis data from clinical, primary stability and pilot scale batches have been provided and they demonstrate good compliance with the proposed specifications..

- Stability of the Product

Stability studies were performed on 1 clinical and 3 stability batches according to the ICH requirements. Samples were stored at 25^{o}C/60 % RH and 30^{o}C/65 % for up to 12 months and in 40^{o}C/75 % RH for 6 months.
The parameters tested were the ones included in the proposed specifications. In all cases the stability results presented were satisfactory. No trends were observed during storage and the results were not affected by the fill volume or storage position (upright or inverted). It can be concluded that the data support the proposed shelf life for the commercially packaged product under the conditions specified in the SPC.
Furthermore two batches of the oral solution packed in the proposed amber glass bottles were exposed to photostability studies. No significant change was observed, which confirms the suitability of the bottles to protect the product from light.

Discussion on chemical, pharmaceutical and biological aspects

The applicant has developed a sugar, colorant, preservative free formulation, which is more suitable for administration to children compared to the currently approved desloratadine syrup. The active substance is of the same quality as the one used in the currently approved formulations. Information on development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. The excipients are commonly used in oral pharmaceutical formulations and comply with Ph. Eur. requirements. The packaging material is commonly used and well documented. The manufacturing process of the finished product is a standard process that has been adequately described. There are some deviations from the ICH requirements as far as process validation is concerned, however

the data available provide enough evidence that the process is well understood and controlled and the applicant has committed to perform process validation studies in accordance with the ICH requirements post authorisation within an agreed timeframe.
Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life. In addition representative samples of the first three production scale batches will be placed on long-term and accelerated stability testing.

3.3 Non-clinical aspects

A complete non-clinical development program had previously been submitted to support the current approved oral formulations. These data are considered relevant to the new syrup formulation, thus no additional non-clinical studies were submitted in the present application.

3.4 Clinical aspects

Introduction

The present application concerns a new syrup formulation which has been developed further to the CHMP's request made in April 2002 at the time of the approval of the current syrup formulation.

The MAH stated that in accordance with the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98, July 2001), no new bioavailability (BA)/bioequivalence (BE) studies were conducted.

The clinical development program to support this new syrup formulation consisted of a single clinical study P04128 to evaluate the taste acceptability and the safety of the reformulated, sugar-free desloratadine syrup in paediatric subjects.

GCP

The Clinical trial was performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that the clinical trial conducted outside the community was carried out in accordance with the ethical standards of Directive 2001/20/EC.

Study P04128

Main Objective and design

It is an open- label study, assessing the taste acceptance of reformulated desloratadine syrup.

Each subject tasted a single dose of the reformulated desloratadine syrup and rated acceptability using the smiley- face questionnaire. One hundred and five male and female subjects, between the ages of 6 and 11 years of age, inclusive, were included.
Overall, the taste of the reformulated desloratadine syrup was rated as acceptable (mean= 2.9) based on the scale of 1 for " really bad" and 5 for " really good".

Results

Responses to the taste assessment were fairly evenly distributed across the five possible responses. Nineteen subjects (18.1%) rated the syrup as " really good," 20 subjects (19.0%) rated the syrup as " good," 20 subjects (19.0%) were " not sure," 24 subjects (22.9%) rated the syrup as " bad," and 21 subjects (20.0%) rated the syrup as "really bad." The response from subject number 96 was not recorded.

No adverse events were reported in this study.

Discussion on clinical aspects

Further to the limited clinical development program undertaken by the MAH, the CHMP requested from the MAH additional justification for not providing bioavailability/bioequivalence data to support the extension application for the reformulated DL syrup.

In response to this concern, the MAH referred to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98, July 2001) where it is stated that *'If the product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an oral solution currently approved as a medicinal product, no bioequivalence study is required, provided the excipients contained in it do not affect gastrointestinal transit, absorption or in vivo stability of the active substance'*.

The MAH argued that the replacement of the excipient sucrose by sucralose and hypromellose is not expected to influence the gastrointestinal transit or absorption of desloratadine. The osmotic contribution of sucralose is small, approximately 10 mmolar as compared with an isotonic solution of about 300 mmolar, and would not be expected to meaningfully alter the osmolarity of the gastrointestinal contents. Although modified cellulose polymers such as hypromellose have been reported to have a laxative effect at high doses (generally in the range of multiple grams per day), hypromellose would not be expected to exert any effect on gastrointestinal transit at the level present in this reformulation (maximum dose of 35 mg per day).

The MAH also stated that the approved paediatric dose levels supportive of the current syrup formulation were based on the results of PK studies that established the appropriate age-adjusted dose based on the observation of comparable systemic exposure in children of each age group to that in adults: 5 mg DL (10 mL) for ≥12 year old, 2.5 mg DL (5 mL) for 6 to 11 year old, 1.25 mg DL (2.5 mL) for 1 to 5 year old. Since the new syrup formulation is not expected to alter the gastrointestinal transit time, absorption, or bioavailability of DL, the MAH concluded that similar dosage adjustment could be applied for the new syrup formulation, as compared to the current syrup formulation.

Having considered the above, the CHMP considered that the lack of bioavailability/bioequivalence data for the new syrup formulation was acceptable.

3.5 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 MAH to submit a risk management plan because the application resulted from a commitment to reformulate a syrup to make it more suitable for the recommended patient age and likely duration of treatment.

3.6 Overall conclusions, risk/benefit assessment and recommendation

Quality
The quality of the 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. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

Not applicable

Efficacy and Safety

Based on the available clinical data supportive of the oral approved formulations for desloratadine, the CHMP considered that the lack of bioavailability/bioequivalence data for the new syrup formulation was acceptable.
The CHMP concluded that the efficacy and safety profile of the new syrup formulation was expected to be similar to the other oral approved formulations.

User Consultation

Results of the readability testing have been submitted and two minor corrections have been introduced in the Package Leaflet.

Risk-benefit assessment

The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Aerius 0.5 mg/ml oral solution in the relief of symptoms associated with:
- allergic rhinitis (AR)
- chronic idiopathic urticaria (CIU)

was favourable and therefore recommended the granting of marketing authorisation.