22 February 2007
EMA/426693/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment Report

Aerius

International Nonproprietary Name: desloratadine

Procedure No. EMEA/H/C/313/X/32

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):	Orodispersible tablets
Strength(s):	2.5 mg and 5 mg
Route(s) of administration:	Oral use
Packaging:	blister (PVC/OPA/alu)
Package size(s):	5, 6, 10, 12, 15, 18, 20, 30, 50, 60, 90 and 100 tablets

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1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Schering Plough Europe submitted on 1 June 2006 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Aerius 2.5 and 5 mg orodispersible tablets 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 1 June 2006
- The procedure started on 21 June 2006.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 September 2006.
- During the meeting on 16-18 October 2006, 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 18 October 2006
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 November 2006.
- The Rapporteur circulated the Report on the applicant’s responses to the List of Questions to all CHMP members on 12 January 07.
- During the CHMP meeting on 22-24 January 2007, 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 1 February 2007.
- The Rapporteur circulated the Report on the applicant’s responses to the List of outstanding issues to all CHMP members on 9 February 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 20 February 2007.

2 GENERAL CONDITIONS FOR THE MARKETING AUTHORISATION

2.1 Manufacturing authorisation holder

2.2 Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

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

Not applicable

2.4 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.

2.5 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 an extension to the existing marketing authorisation and it includes the addition 2.5 mg and 5 mg orodispersible tablets in the already approved desloratadine formulations. The 2.5 mg orodispersible tablets are intended for paediatric patients between 6 and 11 years old.

Currently, desloratadine is available in the following formulations: 5 mg film-coated tablets, 0.5 mg/ml syrup and 5 mg oral lyophilisate formulations.

3.2 Quality aspects

Introduction

Desloratadine orodipersible tablets is an additional pharmaceutical form to the currently approved desloratadine formulations. Two strengths of the product have been developed containing 2.5 mg and 5 mg of the active substance respectively.
Other ingredients include mannitol, crospovidone, microcrystalline cellulose, aspartame, flavour, colorant, sodium hydrogen carbonate, citric acid anhydrous, magnesium stearate, colloidal silicon dioxide, pregelatinised starch, sodium starch glycolate, basic butylated methacrylate copolymer.
All excipients used in the product are of non-animal origin and comply with their corresponding European Pharmacopoeia monographs.

Active Substance

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

Medicinal Product

- Pharmaceutical Development

The main objectives of the development were to produce tablets with acceptable taste masking, fast disintegration times and appropriate content uniformity. The appropriate content uniformity is achieved by granulating part of the ingredients and setting in process controls for the particle size distribution of the granules. Finally fast disintegration times are ensured by the careful selection of the excipients used in the final blend and a low tablet hardness target. As a result of the latter, the tablets are relatively friable and require immediate packaging into blisters to avoid physical damage. Both tablet strengths are dose proportional and obtained from a common final blend.

Due to the mildly effervescent properties of the drug product a moisture resistant packaging with a rigid structure has been used to protect the orodispersible tablets during transportation and use. Blister cells are cold-formed from a PVC/Al foil/Polyamide/PCV laminate. Another laminate, consisting of Paper/Polyester/Al foil/Heat Seal Coating, is then used for sealing the blister.

During the manufacturing process development different types of granulation and milling have been investigated in order to select the ones that lead to acceptable granule particle size distribution and thus acceptable content uniformity. In addition different holding times for the intermediates and the final blend have been studied and their acceptability has been confirmed in long-term stability studies.

- Adventitious Agents

No materials that might include adventitious agents are included in this product.

- Manufacture of the Product

The manufacturing process is standard granulation process and consists of the following steps: high shear granulation, partial drying, wet milling, final drying, milling, coating and sieving of the coated granules. Then the granules are blended with the rest of the excipients, compressed into tablets and packaged.

All critical process parameters have been identified and controlled by appropriate in process controls. The validation reports from 3 production scale batches for each strength demonstrate that the process is reproducible and provides a medicinal product that complies with the in-process and finished product specifications.

- Product Specification

The specification for the finished product at release and shelf life includes tests for appearance, identification (TLC and HPLC), assay (HPLC), content uniformity (Ph. Eur.), dissolution, disintergration time, degradation products (HPLC), loss on drying, hardness and microbial quality (Ph. Eur.). All tests included in the specification have been satisfactorily described and validated.

- Stability of the Product

Stability studies were carried out on 3 pilot scale batches for each strength according to the ICH requirements. Samples were stored at 25oC/60 % RH for 24 months and in 40oC/75 % RH for 6 months. In addition, one product-scale batch of both the 2.5-mg and the 5.0-mg strength was monitored for 18 months at 25°C/60%RH and 6 months at 40°C/75%RH. All batches were produced by the proposed manufacturer and packed in the packaging intended for marketing.
The parameters tested were the ones included in the proposed specifications. In all cases the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SPC.
Furthermore one of the 2.5-mg pilot batches has been subjected to photostability testing in accordance with ICH requirements. There were no significant differences observed between the exposed sample and the dark control.

Discussion on chemical, pharmaceutical and biological aspects

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 drug substance and drug product has been presented in a satisfactory manner. The excipients are commonly used in these types of 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. The results of tests carried out indicate satisfactory consistency and uniformity of all the important quality characteristics of the product, and these in turn lead to the conclusion that the it should have a satisfactory and uniform clinical. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow-Up Measures after the opinion, within an agreed timeframe.

3.3 Non-clinical aspects

Introduction

As part of the original marketing authorisation application (MAA), non-clinical studies have been performed in order to characterise pharmacological properties and toxicological profile of desloratadine (DL). Non-clinical data specific to the orodispersible tablet formulation (mucosal irritation studies in hamsters and dogs) and additional toxicology studies to complement the non-clinical development program previously submitted aimed at supporting this line extension application.

The applicant stated that these non-clinical studies are GLP-compliant.

- Local tolerance

Two studies have been performed to evaluate the mucosal irritation of DL 5 mg orodispersible tablets in hamsters and in dogs, respectively.

In hamsters, irritation following application of the tablet was observed starting on day 1. On day 4, the mean score was 1.8 (range : 0-3) on the side of tablet application and 0 on the contralateral side. In the sham control group, the score was 0 at any time for all animals. The histopathological examination revealed ulcers (5/6), inflammation (5/6) and fibroplasia (4/6) on the treated side, with no lesion on contralateral side.

In dogs, the irritation score was 0 for all animals at all times. Inflammatory infiltration was noticed on both cheeks of treated animals necropsied at the end of the dosing period, with necrosis observed on both cheeks of ¼ animals. In the group necropsied two weeks later, ¾ animals displayed inflammation on both cheeks and ¼ on none.

- Carcinogenicity studies

Since previously conducted loratadine carcinogenicity studies on rats and mice adequately assessed the carcinogenic risk for DL, no further studies were conducted at the time of the original MAA. At present, results from a 24 month carcinogenicity study conducted in mice are available and included in this application.

In the 24 month carcinogenicity study conducted in mice, mortality was associated with intestinal abnormalities (impaction, distension, dilation of large bowel). Body weight gain was decreased in the high dose groups, but recovered following discontinuation of DL. These abnormalities could result from the anticholinergic effect displayed by DL when used at high dose. No increase of tumor incidence was observed.

- Other toxicity studies

Other toxicology studies have been performed with DL (SCH 34117) and the known impurities and degradation products (DS1, DS2, SCH11334; SCH 26485, SCH357130, SCH446720 and SCH 446721). Those included 3-month and one month dose ranging studies in 3 different species i.e. mice, rats and monkeys. Additionally, genotoxicity studies have also been performed with DL and the known impurities and degradation products.

Results from these toxicology and genotoxicity studies did not raise any particular concern to the CHMP.

Ecotoxicity/environmental risk assessment

The environmental risk assessment has been performed for DL expected to be used by 2009. Further to updated calculation requested by CHMP, the values were 0.3220; 0.025µg/L and 0.008 µg/L for Fpen, PEC sw-i and PEC sw-r, respectively. The PEC sw-r is below 0.01 µg/L and no action limit is reached. The CHMP considered that no further environmental assessment (phase II) was necessary since no relevant risk to the environment were anticipated under the conditions of the present evaluation.

Discussion on the non-clinical aspects

Toxicological data from the mucosal irritation study performed in hamsters, raised some safety concerns. Although available clinical and post-marketing data (in the US) were limited for the orodispersible tablet

formulation, the analysis of AEs related to mucosal irritation was in overall reassuring. Nevertheless, the CHMP considered that close safety surveillance should be performed to investigate the clinical relevance of this toxicity finding.

As for the other non clinical data provided as complement to the previously submitted non clinical program, the CHMP considered these data to be acceptable and furthermore agreed to reflect the results from the 24-month carcinogenicity study in mice in the SPC.

3.4 Clinical aspects

Introduction

On 15 January 2001, the dose formulation originally authorised was desloratadine 5 mg film-coated tablets. Subsequently, approvals were granted for desloratadine 0.5 mg/ml syrup and desloratadine 5 mg oral lyophilisate on 16 April 2002. The present extension application concerns a new orodispersible formulation to be used in adults and children aged 12 years and over (5mg dose) and in children aged 6 to 11 years old (2.5 mg dose) in the current approved indications, i.e. *"relief of symptoms associated with allergic rhinitis (AR) and chronic idiopathic urticaria (CIU)."*

The MAH referred to the already approved formulations as DL 5 mg tablet and Cardinal Reditabs tablet (or Cardinal oral lyophilisate) for the conventional film-coated tablet and the oral lyophilisate, respectively.

The clinical development program to support this new orodispersible tablet formulation (5mg and 2.5 mg doses), also referred as 'CIMA Reditabs Tablet or CIMA orodispersible tablet' consisted of the following studies e.g:

- one pilot study P02393, single-dose, open-label, randomised, 2-way cross-over design to evaluate the bioequivalence of a prototype formulation (DL 5 mg orodispersible tablet) with the conventional film-coated tablet formulation (DL 5 mg)
- one pivotal study P02721, single dose, open-label, randomised, 3-way cross-over design to evaluate the bioequivalence of the new orodispersible tablet formulation (CIMA DL 5mg Reditabs) with the oral lyophilisate formulation (Cardinal DL 5mg Reditabs)

In addition, a pilot study P02430, multiple dose (14 days), open-label design was conducted to evaluate the buccal irritation of a prototype formulation (DL 5 mg orodispersible tablet).

Previously, a number of studies to investigate the pharmacodynamics, the dose proportionality of DL and the influence of food have been performed and submitted to support the current approved formulations. The MAH referred to those studies to support the pharmacodynamics of the new orodispersible tablet formulation, the dose proportionality of DL over the range of 5mg and 20mg and the lack of food effect on DL bioavailability. Furthermore, the MAH referred to study P01216, previously submitted to support the BE of the oral lyophilisate formulation (Cardinal DL 5mg Reditabs) with both conventional tablet and syrup formulations, currently approved.

In accordance with the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98, July 2001), no further BE study has been performed to support the additional strength (2.5mg orodispersible tablets).

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.

Pharmacokinetics

Methodological aspects

1. Analytical methods

-**study P02393**:the analysis of plasma samples for DL and 3-OH DL was performed using a validated LC-MS/MS method with SPRI as sponsor. The calibration range for both analytes ranged from 0.025 to 10.0 ng/mL.

- **study P02721**: the analysis of the plasma concentrations of DL and 3-hydroxydesloratadine (OH DL) (major metabolite) were performed by the Department of Drug metabolism and Pharmacokinetics of Schering-Plough Research Institute (SPRI) using validated liquid chromatography with tandem mass spectrometric method (LC-MS/MS). The calibration range for both analytes ranged from 0.025 to 10.0 ng/mL.

2. Pharmacokinetic data analysis

In the different bioequivalence studies, statistical analysis including means and coefficients of variation are provided for the concentration-time data and the derived pharmacokinetic parameters. The primary pharmacokinetic variables of interest for the determination of bioavailability/bioequivalence comparisons were log-transformed AUC and Cmax. They were statistically analysed using a cross-over analysis of variance ANOVA.
In the presented tables, the PK characteristics are given as arithmetic means (CV) except for Tmax, which is displayed as median with min,max values. For the PK characteristics of the different treatments, the 90% confidence intervals around the point estimate are presented based on a parametric analysis. The 90% CIs are calculated with the residual error (MSE) and associated degrees of freedom from the ANOVA. Bioequivalence can be concluded when the 90% CI for the ratio of means based on log-transformed data is entirely within the predefined acceptance equivalence range of 80-125% for AUC and Cmax.

Bioequivalence studies

- Study P02393

Primary and secondary objectives
To determine the bioequivalence of the CIMA DL Reditabs (rapidly-disintegrating) 5 mg tablet with the DL 5 mg conventional tablet under fasting conditions.

The secondary objective is to assess the taste and irritation of the CIMA DL Reditabs 5 mg tablet formulation.

Study design

The study has been performed between May 2001 and August 2001.

The study is a randomised, single-dose, open-label, two-way, cross-over study in 20 subjects between 19 and 42 years. 19 subjects (17 Hispanic) completed the study. One subject withdrew for reasons unrelated to the study.

Test product: CIMA DL Reditabs 5 mg tablet (CIMA Labs Inc, MN, USA for Schering Plough Research Institute, New jersey, USA)). Batch n° 78012-057.

Reference product: DL 5 mg oral tablet (Schering Plough Research Institute, New Jersey, USA). Batch n° 76728-054.

Blood samples were collected over 120 hours after each administration. Plasma concentrations of DL and 3-OH DL were determined using a LC-MS-MS method.

Methodology

The PK parameters were calculated based on the concentration versus time data and were analysed statistically using an ANOVA model.

Irritation of the entire oral cavity is assessed at pre-dose and up to 15 minutes post-dose for each administration of CIMA Reditabs. Each subject rated oral sensations and pain/discomfort and the observer evaluates the presence of erythema and ulcers.

Immediately after taking the CIMA Reditabs, questions were asked to each subject about the taste of the medication.

Results

With respect to BE, statistical results are summarised in Tables 1 and 2 below:

Table 1. Mean (%CV) pharmacokinetics parameters of DL and 3-OH DL following single dose administrations of 5mg rapidly-disintegrating tablet (CIMA Reditab®) and DL 5 mg tablet

Treatment	Mean (%CV) Pharmacokinetic Parameters				
	Cmax (ng/mL)	Tmax[a] (hr)	AUC(tf) (ng·hr/mL)	AUC(I) (ng·hr/mL)	t½ (hr)
	DL (n=20)				
A: DL 5 mg CIMA Reditab®	2.58 (36)	4.0 (1.5-8.0)[b]	64.1 (63)	76.2 (99)	28.4 (75)
B: DL 5 mg Tablet[b]	2.89 (55)	2.0 (1.0-8.0)	65.5 (74)	76.7 (102)	28.1 (60)
	3-OH DL (n=20)				
A: DL 5 mg CIMA Reditab®	0.96 (51)	6.0 (1.5-36)[b]	26.1 (33)	28.8 (28)	40.1 (51)
B: DL 5 mg Tablet[b]	1.04 (62)	6.0 (1.5-8)	25.4 (32)	28.9 (21)[c]	35.8 (32)[c]

a: median (range)
b: n=19
c: n=18

Table 2. Point estimate and 90% confidence intervals for AUCinf and Cmax for DL and 3-OH DL following single dose administrations of of 5mg rapidly-disintegrating tablet (CIMA Reditab®) and DL 5 mg tablet

Comparison		Relative Bioavailability (%)	Confidence Interval (%)
	DL		
DL 5 mg CIMA Reditab®/DL 5 mg Tablet	AUC(I)	104	96-112
	Cmax	97.2	89-106
	3-OH DL		
DL 5 mg CIMA Reditab®/DL 5 mg Tablet	AUC(I)	105	99-111
	Cmax	99.3	92-108

The 90% confidence intervals of the ratio of means are well in the acceptance range of 80-125% for AUC and Cmax for DL and 3-OH DL. Bioequivalence can be concluded between DL 5 mg Reditabs tablets and DL 5 mg oral conventional tablets with respect to rate and extent of absorption.

With respect to the taste and irritation assessments, there were no reports of erythema, oral sensation, pain/discomfort or ulcers associated with CIMA DL 5 mg Reditabs and the subjects favored the taste of this new formulation.

- Study P02721

Primary and secondary objectives

To evaluate the bioequivalence of CIMA DL 5 mg orally-disintegrating tablet and the Cardinal DL 5 mg orally disintegrating tablet (oral lyophilisate currently approved) under fasting conditions. The second objective is to evaluate the effect of water on the bioavailability (BA) of the CIMA DL 5 mg orally disintegrating tablet.

Study design

The study is performed between January and March 2004 with Schering Plough Corporation, New Jersey, USA, as sponsor.

The study is carried out according to a randomised, single-dose, open-label, three-way, cross-over design in 24 healthy non-Caucasian volunteers between the age of 18 to 45 years. 22 subjects completed the three periods of the study. Each dose administration is separated by a wash-out period of at least 10 days. Two subjects (n° 6 and n°12) withdrew from the study and their data were not included in the PK analysis.

Based on previous studies (P01419 and P02393), the intra-subject variability in DL and 3-OH DL has been expected to be not more than 20% for AUC and Cmax. A power of at least 90% is expected.

Each subject received a single dose of the CIMA DL 5 mg Reditabs (rapidly disintegrating) tablet with and without water and the Cardinal DL 5 mg Reditabs tablet with water. Each subject received the three treatments in a cross-over manner.

Treatment A: Cardinal DL Reditabs 1 x 5 mg tablet with 240 mL of water. Batch n°2-MCR-12. (batch size : 294 118 tablets)

Treatment B: CIMA DL Reditabs 1 x 5 mg tablet with 240 mL of water (CIMA Labs Inc, MN, USA). Batch n° 78012-122.

Treatment C: CIMA DL Reditabs 1 x 5 mg tablet without water (CIMA Labs Inc, MN, USA). Batch n° 78012-122.

Blood samples were collected pre-dose and up to 120 hours after each administration. Plasma concentrations of DL and 3-OH DL were determined using a liquid chromatographic-tandem mass spectrometric method (LLOQ: 0.025 ng/ml).

Methodology

The PK parameters were calculated based on the concentration versus time data and were analysed statistically using an ANOVA model.

Results

With respect to BE, statistical results are summarised in Tables 3 and 4 below:

Table 3 Mean pharmacokinetic parameters of DL and 3-OH DL in healthy adult subjects following single-dose of 5 mg Cardinal DL Reditabs tablet, CIMA DL Reditabs tablet administered with and without water

Treatment	Parameter		
	Cmax (ng/mL)	Tmax[a] (hr)	AUC(I) (ng·hr/mL)
DL			
A: Cardinal DL REDITABS® With Water[b]	2.83 (47)	3.0 (1.5 – 6.0)	52.8 (51)
B: CIMA DL REDITABS® With Water[b]	2.92 (39)	2.5 (1.5 – 6.0)	54.7 (54)
C: CIMA DL REDITABS® Without Water[b]	2.90 (38)	3.0 (1.0 – 6.0)	51.8 (56)
3-OH DL			
A: Cardinal DL REDITABS® With Water[b]	1.22 (28)	6.0 (2.0 – 8.0)	34.5 (23)
B: CIMA DL REDITABS® With Water[b]	1.26 (20)	6.0 (3.0 – 8.0)	34.9 (23)
C: CIMA DL REDITABS® Without Water[b]	1.29 (27)	6.0 (2.0 – 6.0)	34.3 (24)

a: Median (range)
b: n=22

Table 4 Point estimates and 90% confidence intervals for AUC and Cmax for DL and 3-OH DL following single-dose of 5 mg Cardinal DL Reditabs tablet, CIMA DL Reditabs tablet administered with and without water

Comparison	Parameter	Ratio Estimate (%)	Confidence Interval (%)
DL			
CIMA With Water[a]/Cardinal With Water[a]	AUC(I)	103	98 - 109
	Cmax	106	98 - 114
CIMA Without Water[a]/CIMA With Water[a]	AUC(I)	94	89 - 99
	Cmax	99	92 - 107
3-OH DL			
CIMA With Water[a]/Cardinal With Water[a]	AUC(I)	101	97 - 105
	Cmax	105	99 - 111
CIMA Without Water[a]/CIMA With Water[a]	AUC(I)	98	94 - 102
	Cmax	101	95 - 108

a: n=22

Clinical efficacy

No clinical efficacy studies have been performed with the new DL orodispersible tablet formulation. A complete program of clinical efficacy and safety data had been previously submitted to support the use of DL conventional tablets in the approved indications.

- Discussion on Pharmacokinetics and Clinical Efficacy

In the pivotal study P02721, the 90% confidence intervals were well in the acceptance range of 80-125% for the primary parameters AUC_{0-t}, AUC_{inf} and C_{max} for both desloratadine and 3-OH desloratadine. The median (min,max) Tmax values were similar for the both products. The test product CIMA DL Reditabs was well originated from a batch of at least 100 000 units (biobatch size of 294 118 tablets) which was in accordance with the Note for Guidance on the Investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98, July 2001).

The CHMP concluded that DL 5 mg orodispersible tablet (CIMA Reditabs 5 mg) was bioequivalent to the DL 5mg oral lyophilisate (Cardinal DL Reditabs) and DL 5 mg orodispersible tablet (CIMA Reditabs) administered with water was bioequivalent to DL 5 mg orodispersible tablet (CIMA Reditabs). In this study (24 volunteers with 12 males and 12 females), subgroup analyses by gender showed that relative bioavailability of DL and 3-OH DL was similar for male and female subjects.

In the pilot study P02393, no evidence of oral irritation was found following single-dose administration of the CIMA Reditabs. All subjects found the CIMA Reditabs to have a favorable taste.

The CHMP considered that the lack of clinical efficacy studies with the new DL orodispersible tablet formulation (CIMA DL Reditabs Tablet) is acceptable since BE has been demonstrated with the approved DL 5mg oral lyophilisate (Cardinal DL Reditabs).

In addition, the concern raised by CHMP over the linearity in the dose range of 2.5 to 20 mg has been adequately addressed by the MAH. The CHMP considered that the extrapolation of the results from the pivotal BE study P02721 performed with the 5 mg strength can be made for the 2.5 mg additional strength.

Clinical Safety

The safety analysis is based on the 3 phase-1 clinical studies P02721, P02430 and P02393 performed in healthy subjects and the post-marketing data from the US.

From Clinical Trials

- Patient exposure

Overall, 64 subjects were exposed to at least a single dose of the 5 mg orodispersible desloratadine tablet. Of the 64 subjects, 20 were exposed to the 5 mg orodispersible desloratadine tablet for 14 consecutive days.

- Adverse events

In the single-dose **Study P02721,** 2 of the 24 subjects (8%) reported one treatment-emergent AE each. One of these subjects reported pharyngitis 11 days after receiving the second treatment (orodispersible tablet with water), which was considered by the investigator to be mild. The other subject experienced acute appendicitis 5 days after receiving the first treatment (orodispersible tablet with water), which led to her hospitalization. This event was categorized as a SAE. Both events were considered by the investigator to be non-treatment related.

In the multiple-dose **Study P02430,** 9 of the 20 subjects (45%) reported at least one AE during the study. A total of 15 AEs were reported (13 headaches, 1 musculo-skeletal pain, 1 pharyngitis); all were mild in severity. The report of pharyngitis was from one subject approximately 4½ hours post-dose on Day 9 and resolved on Day 10. This AE was considered unrelated to treatment by the investigator. Thirteen of the fifteen AEs were reported as being treatment-related. No SAEs were reported. There were no reports of buccal erythema, sensation, pain/discomfort, or ulcers. No subject discontinued from the study because of AEs.

In the single-dose **Study P02393,** 1 of the 20 subjects (5%) reported AEs during the study. The subject reported two occurrences of toothache. One of these occurrences was moderate; the other was mild in severity. No treatment-related AEs were reported. No SAEs were reported. There were no reports of buccal erythema, sensation and pain/discomfort, or ulcers associated with the orodispersible 5 mg desloratadine tablet. .

The **most common AE** reported was headache, which was experienced by nine subjects (13 occurrences) in the multiple-dose Study P02430. These events were considered by the investigator to be treatment related. All other AEs were reported once or twice.

- Serious adverse event/deaths/other significant events

No deaths were reported. One SAE was reported in Study P02721. A subject experienced acute appendicitis 5 days after receiving the first treatment (orodispersible tablet with water), which led to her hospitalization. This event was considered by the investigator to be non-treatment related.

- Laboratory findings

There were no clinically significant changes from baseline in any of the laboratory parameters evaluated. Although some sporadic high and low laboratory values were noted in these studies during both pre- and post-treatment, no pattern was evident, and none were considered to be clinically significant.

- Discontinuation due to adverse events

No subject discontinued from the studies because of AEs.

From Post-marketing experience

The orodispersible tablets (DL RediTabs tablets) is currently marketed only in the US. Total patient exposure for patients treated with the DL RediTabs formulations from 26 June 2002 (US approval date) to 15 March 2006 was estimated from unit sales data provided by IMS MIDAS market research database. The estimated DL RediTabs Tablet exposure was 10,533,307 patient-days or 28,839 patient-years.

During this covering period, a total of 32 AEs, including one serious adverse event (SAE) from a clinical trial study, were reported in 16 patients receiving DL RediTabs Tablet. Twenty-six of the 32 AEs were reported in 13 patients 12 years and over, including in patients with unreported age, and the remaining six AEs were reported in three patients less than 12 years of age. A summary of the AEs is provided in Table 5.

Table 5 Summary of Adverse Events for Desloratadine RediTabs in Patients 12 Years and Over, Including in Patients With Unreported Age, and in Patients Less Than 12 Years

Body System and Preferred Term	12 Years and Over, and Unreported Age	Less Than 12 Years
Cardiac Disorders	**1**	**-**
Tachycardia	1	-
Eye Disorders	**1**	**-**
Dry Eye	1	-
Gastrointestinal Disorders	**9**	**1**
Abdominal Pain	1	-
Abdominal Pain Upper	1	-
Diarrhoea	1	1
Dry Mouth	1	-
Dyspepsia	1	-
Mouth Ulceration	1	-
Nausea	2	-
Vomiting	1	-
General Disorders and Administration Site Conditions	**6**	**1**
Asthenia	1	-
Fatigue	1	-
Malaise	1	-
No Adverse Effect	2	1
Nonspecific Reaction	1	-
Infections and Infestations	**1**	**-**
Appendicitis[a]	1	-
Injury, Poisoning, and Procedural Complications	**2**	**3**
Medication Error	2	3
Nervous System Disorders	**5**	**-**
Dizziness	1	-
Dysgeusia	3	-
Memory Impairment	1	-

Respiratory, Thoracic, and Mediastinal Disorders	**-**	**1**
Nasal Congestion	-	1
Skin and Subcutaneous Tissue Disorders	**1**	**-**
Swelling Face	1	-
Total	26	6

a: Appendicitis was reported as a serious adverse event in Study P02721.

The most common AE reported was dysgeusia in patients 12 years and over, including in patients with unreported age, and medication error in patients under 12 years old.

Of the 32 AEs, one was reported as an SAE. This SAE was reported in a 39 year-old healthy female subject in study P02721 who experienced acute appendicitis 5 days after receiving the first treatment (CIMA with water), which led to her hospitalization. This event was considered by the investigator to be non-treatment related .

- Discussion on Clinical Safety

No new safety signals were identified with this orodispersible tablet formulation. The CHMP noted that the safety data related to this new formulation were very limited.

From clinical trials, only 64 subjects were exposed to at least a single dose and only 20 subjects received multiple dose treatment (14 days). The most common AE reported was headache, which was experienced by nine subjects (13 occurrences) in the multiple-dose study P02430.

From postmarketing data, only combined data for the Cardinal oral lyophilisate and the CIMA orodispersible tablet were available.

However, the CHMP acknowledged that extensive safety data of DL are available from the current approved formulations. The safety profile of the DL orodispersible tablets is expected to be similar to the other approved formulations.

Although available clinical and post-marketing data (in the US) were limited for the orodispersible tablet formulation, the analysis of AEs related to mucosal irritation was in overall reassuring. Two cases of pharyngitis were observed. There were no reports of oral erythema, sensation, pain/discomfort, or ulcers. Two post-marketing cases of mouth ulceration and dry mouth were reported.

Nevertheless, the CHMP recommended a close safety surveillance of the related AEs to investigate the clinical relevance of the toxicity finding.

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 this application concerned existing dosage range.

3.5 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

Previously submitted non clinical data for the current approved formulations were considered relevant to the DL 5 mg orodispersible tablets to characterise its pharmacological properties and toxicological profile.

Based on the submitted non clinical data, the CHMP considered that the toxicological profile of DL orodispersible tablet has been adequately addressed. Nevertheless, a concern was raised related to possible mucosal irritation thus the CHMP recommended a close safety surveillance of the related AEs to investigate the clinical relevance of this toxicity finding.

As for the other non clinical data provided as complement to the previously submitted non clinical program, the CHMP considered these data to be acceptable and furthermore agreed to reflect the results from the 24-month carcinogenicity study in the SPC.

Efficacy

The proposed DL 5mg orodispersible tablet has demonstrated bioequivalence (BE) with the approved DL 5mg oral lyophilisate. Based on the BE results and the previously submitted data in support of the clinical efficacy of DL oral formulations already approved, the CHMP considered that a similar efficacy profile is expected with DL orodispersible tablet in the approved indications.

Furthermore, to support the 2.5 mg additional strength for the orodispersible tablet, the extrapolation of the BE results performed with the 5 mg strength was in accordance Note for Guidance on the Investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98, July 2001) and was therefore considered acceptable by the CHMP.

Safety

The safety profile of the DL orodispersible tablets is expected to be similar to the other approved formulations. Nevertheless, the CHMP recommended a close safety surveillance of the related oral AEs to investigate the clinical relevance of the toxicity finding.

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 2.5 and 5 mg orodispersible tablets in the relief of symptoms associated with:

- allergic rhinitis (AR)
- chronic idiopathic urticaria (CIU)

was favourable and therefore recommended the granting of marketing authorisation.