CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Loratadine Sandoz orodispersible tablets 10 mg
Sandoz B.V., the Netherlands

loratadine

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/0693/001/DC
Registration number in the Netherlands: RVG 33303

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Pharmacotherapeutic group:	antihistamines – H_1 antagonist
ATC code:	R06AX13
Route of administration:	oral
Therapeutic indication:	allergic rhinitis; chronic idiopathic urticaria
Prescription status:	non prescription
Date of authorisation in NL:	1 January 2008
Concerned Member States:	Decentralised procedure with CZ, FI, FR, SE, SK and UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the concerned member states have granted a marketing authorisation for Loratadine Sandoz orodispersible tablets 10 mg, from Sandoz B.V. The date of authorisation was on 1 January 2008 in the Netherlands. The product is indicated for symptomatic treatment of allergic rhinitis (AR) and chronic idiopathic urticaria (CIU).

A comprehensive description of the indications and posology is given in the SPC.

Loratadine, the active ingredient in the medicinal product, is a tricyclic antihistamine with selective, peripheral H_1-receptor activity. Loratadine has no clinically significant sedative or anticholinergic properties in the majority of the population and when used at the recommended dosage. Loratadine has no significant H_2-receptor activity. It does not inhibit norepinephrine uptake and has practically no influence on cardiovascular function or on intrinsic cardiac pacemaker activity.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Claritine 10 mg tablets, containing 10 mg loratadine, which has been registered in Belgium by Schering-Plough B.V. since 1987. In the Netherlands, Claritine 10 mg tablets (NL License RVG 13388) and Claritine Reditabs, oral lyophilisate 10 mg (NL License RVG 20868) have been granted marketing authorisation in 1989 and 1998, respectively. In addition, reference is made to Claritine authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, *i.e.* including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the Swedish reference product Clarityn®-S 10 mg orodispersible tablets, registered in Sweden. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new preclinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance and excipients
The active substance is loratadine, an established active substance described in a draft monograph for the European Pharmacopoeia (Ph.Eur.*) that has been published in Pharmeuropa (last updated in nr. 17.1, January 2005). Loratadine is a white or almost white crystalline powder. The active substance specification is considered adequate to control the quality and meets the requirements of this draft monograph (nr. 17.1, January 2005). Batch analytical data demonstrating compliance with this specification have been provided for 3 production scale batches for both manufacturers.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Stability data on the active substance have been provided for one manufacturer for 3 batches in accordance with applicable European guidelines demonstrating the stability of the active substance over 18 months. For another manufacturer, stability data on the active substance have been provided for 9 pilot-scale batches in accordance with applicable European guidelines demonstrating the stability of the active substance over 48 months. Based on the data submitted, a retest period could be granted of 2 years for batches from all manufacturers without further storage conditions.

The excipients are usual for an orodispersible tablet formulation, and the amounts are normal as well. All excipients comply with the requirements laid down in their respective Ph.Eur. monographs, except for sweet orange flavour, maize starch (dried) and microcrystalline cellulose (E460) for which in-house specifications of the active substance manufacturer were provided.

** Ph.Eur is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Loratadine 10 mg orodispersible tablets contain as active substance 10 mg of loratadine, and are white, round, flat tablets.

The tablets are packed in unit dose perforated blisters (Alu/Alu).

The excipients are: sweet orange flavour, aspartame (E951), citric acid anhydrous (E330), silica (colloidal anhydrous (E551)), maize starch (dried), lactose anhydrous, magnesium stearate (E470b), croscarmellose sodium (E468), mannitol (E421), sorbitol (E420), crospovidone, silica (colloidal hydrated (E551)), polysorbate 80 (E433), povidone (E1201), microcrystalline cellulose (E460).

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The objective was to develop a product that would be bioequivalent with the innovator product Claritine.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 4 pilot batches in accordance with the relevant European guidelines. The MAH committed to submit certificates of analysis of the first 3 industrial scale batches, and to use these batches to validate its manufacturing process at this scale.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification of the finished product is based on the monograph for orodispersible tablets in the Ph.Eur. and includes tests for appearance, identification, content uniformity, uniformity of mass, disintegration time, dissolution rate, related substances, assay, water content and microbiological purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided.
Batch analytical data of 4 full-scale batches from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 4 industrial-scale batches in accordance with applicable European guidelines demonstrating the stability of the product over 12 months. On basis of the data submitted, a shelf life was granted of 2 years. The labelled storage conditions are *Store in the original package in order to protect from moisture.*
After finalisation of the procedure additional data were provided, based on which the shelf life was extended to 3 years (see table on page 10 of this report: variation NL/H/0693/001/IB/007).

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non-clinical aspects

This product is a generic formulation of Claritine, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of loratadine released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Loratadine is a well-known active substance with established efficacy and tolerability.

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Claritine marketed by Schering-Plough B.V.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product, Loratadine Sandoz orodispersible 10 mg tablets (Sandoz B.V.)

is compared with the pharmacokinetic profile of the Swedish reference product Clarityn-S 10 mg orodispersible tablets (Schering-Plough AB). Both the parent loratadine and the active metabolite descarboethoxy loratadine were evaluated in this study.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states. Orodispersible tablets are considered to be equivalent to normal tablets in this application, since (1) both dosage forms are authorised in the EU and (2) it is safe to assume that the bioavailablity of the orodispersible form will not be less than the bioavailability of the regular form. Therefore, the MAH's approach to show essential similarity was considered acceptable.

However, during the procedure, a potential serious risk to public health was raised by France regarding the bioequivalence between conventional uncoated tablets, which is the reference product formulation in France, and the applied orodispersible tablets. France maintained their major objection until the end of the procedure, and therefore the MAH made three commitments:

1) The MAH committed to perform a bioequivalence study between Loratadine 10 mg, orodispersible tablets, and a Clarityn 10 mg formulation, identical to the French reference product.
2) The MAH committed to not launch the Loratadine 10 mg orodispersible tablets in France until the results of the new bioequivalence study are disclosed.
3) The MAH committed to withdraw its marketing authorisation in France in case the results of the new bioequivalence study are negative.

A single-centre, single-dose, open-label, randomised, 3-way cross-over, bioequivalence study was carried out under fasted conditions in 52 healthy male subjects, aged 19-45 years. Each subject received a single dose (as 4x10 mg) of one of the 2 loratadine formulations after 10 hours fasting. For each subject there were 3 dosing periods, separated by washout periods of 14 days. The two sequences were Test-Ref-Test or Ref-Test-Ref. Therefore, half of the study population received two times the Test formulation (and one time Reference), and half of the population received two times the Reference formulation (and one time Test).
Drug administration: After moistening the mouth with 30 ml of water, one orally dispersible tablet was placed on the tongue and let dissolved. After the first orally dispersible tablet was dissolved, each of the remaining three orally dispersible tablets was placed on the tongue and also let dissolved. Following the last dissolution of the fourth orally dispersible tablet, 210 ml of water was taken. This sequence was performed within 5 minutes.
Blood samples were collected at pre-dose and at 0.33, 0.67, 0.75, 0.83, 1.0, 1.25, 1.5, 1.75, 2.0, 2.33, 2.67, 3.0, 3.5, 4.0, 6.0, 8.0, 12, 24, 36, 48, and 72 hours after administration in each period. Three subjects did not complete the study. One subject was withdrawn from the study after drug administration in period 2 due to spilling of the study drug, and two subjects withdrew for personal reasons. Forty-nine subjects were eligible for pharmacokinetic analysis. Forty-nine subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of loratadine under fasted conditions.

Treatment N = 49	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	57.2 ± 82.3	60.4 ± 89.5	19.8 ± 21.7	1.0 (0.67-2.0)	13.1 ± 9.7
Reference	60.4 ± 96.8	63.6 ± 104.7	19.5 ± 18.3	1.0 (0.67-3.5)	13.0 ± 10.3
***Ratio(90% CI)**	0.98 (0.90-1.06)	0.98 (0.91-1.07)	1.01 (0.89-1.11)	--	--
CV (%)	24.5	24.7	34.3	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life

**ANOVA using ln-transformed values from first administration of test and reference only*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of descarboethoxy loratadine under fasted conditions.

Treatment N = 49	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	160.2 ± 67.3	178.8 ± 117.7	14.0 ± 4.9	1.5 (0.75-3.5)	20.5 ± 7.3
Reference	165.6 ± 61.2	186.0 ± 127.1	15.0 ± 5.4	1.5 (1.0-8.0)	20.4 ± 8.7
***Ratio(90% CI)**	0.95 (0.92-0.99)	0.95 (0.92-0.99)	0.94 (0.88-0.98)	--	--
CV (%)	10.1	10.4	15.9	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life

**ANOVA using ln-transformed values from first administration of test and reference only*

Loratadine should be taken once daily without reference to food intake. From the literature it is known that food does not interact with the absorption of loratadine. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement are within the bioequivalence acceptance range of 0.80-1.25. The statistical analysis of the pharmacokinetic data was adequate. Based on the pharmacokinetic parameters of loratadine and the active metabolite descarboethoxy loratadine under fasted conditions, it can be concluded that Loratadine Sandoz 10 mg tablets and the Clarityn-S 10 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk Management Plan

Loratadine was first approved in 1987, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of loratadine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation, which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Loratadine Sandoz 10 mg orodispersible tablets have a proven chemical-pharmaceutical quality and are generic forms of Claritine, a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents. However, during the procedure, a potential serious risk to public health was raised by France regarding pharmacokinetics between conventional uncoated tablets, which is the reference product formulation in France, and the application for orodispersible tablets. France maintained their major objection until the end of the procedure, and therefore the MAH made three commitments (see below).

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other loratadine containing products.

The Board followed the advice of the assessors. Loratadine Sandoz 10 mg orodispersible tablets are authorised in the Netherlands on 1 January 2008. The concerned member states with the exception of France, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Loratadine 10 mg orodispersible tablets with the reference product, and have therefore granted a marketing authorisation.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The decentralised procedure was finished on 23 November 2006.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from November 2006 till November 2009.

The date for the first renewal will be: 23 November 2011.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to submit certificates of analysis of the first 3 industrial scale batches, and to use these batches to validate its manufacturing process at this scale.

Clinical aspects

- The MAH committed to perform a bioequivalence study between Loratadine 10 mg, orodispersible tablets, and Clarityn 10 mg (identical to the French reference product).
- The MAH committed to not launch the Loratadine 10 mg orodispersible tablets in France until the results of the new bioequivalence study are disclosed.
- The MAH committed to withdraw its marketing authorisation in France in case the results of the new bioequivalence study are negative.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change to comply with Ph.Eur. or with the national pharmacopoeia of a Member State. Change of specification(s) of a former non-European pharmacopoeial substance to comply with Ph.Eur. or with the national pharmacopoeia of a Member State. Active substance.	NL/H/0693/ 001/IB/001	IB	21-8-2007	20-9-2007	Approval	N
Update to DMF.	NL/H/0693/ 001/II/002	II	24-10-2008	3-6-2009	Approval	N
Update to DMF.	NL/H/0693/ 001/II/003	II	24-10-2008	3-6-2009	Approval	N
Change in the name of the medicinal product in CZ only.	NL/H/0693/ 001/IB/004	IB	27-7-2009	26-8-2009	Approval	N
Submission of a new or updated CEP from a manufacturer currently approved.	NL/H/0693/ 001/IA/005	IA	3-12-2009	17-12-2009	Approval	N
Submission of a new or updated CEP from a manufacturer currently approved.	NL/H/0693/ 001/IA/006	IA	3-12-2009	17-12-2009	Approval	N
Change in shelf-life of the finished product: 2 years -> 3 years.	NL/H/0693/ 001/IB/007	IB	15-12-2009	14-1-2010	Approval	N
Implementation of change(s) requested by the EMEA/National Competent Authority following the assessment of an Urgent Safety Restriction, class labelling, a Periodic Safety Update report, Risk Management Plan, Follow Up Measure/Specific Obligation, data submitted under Article 45/46 of Regulation (EC) No 1901/2006, or amendments to reflect a competent authority Core SPC; implementation of agreed wording.	NL/H/0693/ 001/IB/008	IB	27-9-2010	10-12-2010	Approval	N
Grouped IA changes.	NL/H/0693/ 001/IA/009/ G	IA/G	28-9-2010	29-10-2010	Approval	N
Grouped IA changes.	NL/H/0693/ 001/IA/010/ G	IA/G	13-11-2010	13-12-2010	Approval	N