CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Loratadine Sandoz 10, 10 mg tablets 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 during the evaluation process and provides a summary of the grounds for suspension of the marketing authorisation in the Netherlands, which was granted on 12 July 2001.
Some knowledge of medicines and diseases is expected as the language in this report may be difficult for laymen to understand.

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 applicant has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/317/001/E/001
Registration number in the Netherlands: RVG 25765

15 April 2010

Pharmacotherapeutic group:	Other antihistamines for systemic use
ATC code:	R06AX13
Route of administration:	oral
Therapeutic indication:	symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria
Prescription status:	non prescription
Date of first authorisation in NL:	12 July 2001
Suspension of MA in NL:	24 September 2009
Concerned Member States:	Repeat use procedure with BG, CZ, EE, FR, HU, IT, LT, LV, PL, RO, SI, SK
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 data on quality, safety and efficacy, the member states considered that the application for Loratadine Sandoz 10, 10 mg tablets for the indications:

symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria

was not approvable, since a potential serious risk to public health was identified. The details of this potential serious risk to public health are provided in the report below. No marketing authorisation has been granted in the concerned member states. As this concerns a repeat use procedure, the marketing authorisations granted during the initial mutual recognition procedure will be suspended. The initial mutual recognition procedure NL/H/317/001/MR is discussed briefly in Annex I.

CMD(h) referral
The potential serious risk for public health, for which a CMD(h) referral was started, pertained to the following principal deficiencies:

- retrospective widening of the confidence interval is not accepted according to the current guidance documents.
- bioequivalence between Loratadine Sandoz 10 and the reference product was not demonstrated for the parent compound.

Therefore, the benefit-risk profile of the generic Loratadine Sandoz 10 is considered to be negative.
As the CMD(h) could not reach agreement, the procedure was referred to the CHMP on 31 July 2008.

CHMP referral
Bioequivalence with regard to the parent compound was not demonstrated, although bioequivalence between Loratadine Sandoz 10 and the reference product was shown for the active metabolite. According to the currently applicable guidance, outlined in the *Questions & Answers on the Bioavailability and Bioequivalence Guideline*, bioequivalence must be demonstrated for the parent compound for generic products. Therefore, the products cannot be considered bioequivalent and the CHMP concluded that the benefit-risk profile of Loratadine Sandoz 10 is negative. The CHMP recommended the suspension of the granted Marketing Authorisations. The existing marketing authorisation in the Netherlands, granted on 12 July 2001 was therefore suspended.
The conditions for lifting the suspension require the applicant to submit the results of a correctly planned study that demonstrates the bioequivalence between the two products in accordance with the current guidance. Any widening of the confidence intervals should be agreed prospectively in the study design.

Loratadine, the active ingredient in Loratadine Sandoz 10, is a tricyclic antihistamine with selective, peripheral Hl-receptor activity. Loratadine has no clinically significant sedative or anticholinergic properties in the majority of the population and when used at the recommended dosage.
During long-term treatment there were no clinically significant changes in vital signs, laboratory test values, physical examinations or electrocardiograms.
Loratadine has no significant H2-receptor activity. It does not inhibit norepinephrine uptake and has practically no influence on cardiovascular function or on intrinsic cardiac pacemaker activity.

This repeat use procedure concerns a generic application claiming essential similarity with the innovator product Claritine 10 mg tablets (NL RVG 13388) which has been registered in the Netherlands by Schering-Plough Nederland B.V. since 1989. In addition, reference is made to Claritine 10 mg authorisations in the individual member states (reference product).

The application is made 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 reference product Lisino 10 mg tablets, registered in Germany. 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.

No new pre-clinical 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, and no paediatric development programme has been submitted, as this is not required for generic medicinal 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
The active substance is loratadine, an established active substance described in the European Pharmacopoeia (*Ph.Eur.**) Loratadine is a white to off-white powder not soluble in water, but very soluble in acetone, alcohol and chloroform.

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.

Specification
The applicant has submitted a full list of the specifications for loratadine raw material. The purification method and the quality have been laid down unambiguously; the quality by additional characterizations. The purity of the resulting reference standard is satisfactory; the standard complies with Ph. Eur. The analytical methods have been described in sufficient detail. Batch analytical data demonstrating compliance with this specification have been provided for 2 batches.

Stability
Real time and accelerated stability data on the active substance have been provided in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 2 years when stored below 25°C in the proposed packaging.

** 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 Sandoz 10 contains as active substance 10 mg of loratadine, and is a white, round tablet.

The tablets are packed in PVC/Al, PVC/PE/PVDC/Al blister packs and PP securitainer packages.

The excipients are: lactose monohydrate, magnesium stearate, maize starch, microcrystalline cellulose.

Pharmaceutical development

The development was based on various products marketed by the innovator in the various EU countries. The use of lactose and varying blending times were tested in relation to the flow of the material. The excipients are all well-known, pharmacopoeial substances, are usual for tablet formulations, and are safe for the proposed concentrations. The additional specifications laid down for lactose monohydrate conform to the Ph. Eur. monograph, and are specific for particle size and density.
The tablet at issue has been compared with the brand leader tablets from different countries with respect to appearance, average weight, disintegration time, related substances, dissolution profile and assay. Most tablet characteristics are similar except for the appearance of the tablet since these tablets are round having no score or inscription. Most reference products marketed are oval. The development process has been sufficiently described.
The MAH has presented a comparison of the dissolution profiles of the originator products marketed in the various countries and the product at issue. It can be concluded that all dissolution profiles of the reference product and the generic product at issue are quite similar and fast with >85% in 15 minutes. The specification for dissolution is based on the result of dissolution of the biobatch.

Manufacturing process

The tablets are produced by standard processes. The manufacturing process is described in detail and comprises procedures of sieving, mixing and compression of the mixture to tablets. Sieve sizes are presented. A flow-chart is included. The critical steps of the different stages of the manufacturing process and the corresponding parameters to test these steps have been described.
The manufacturing process has been validated for one full-scale batch. Considering the simplicity of the manufacturing process, the validation report is acceptable. The applicant committed to validate two more full-scale batches.

Product specification

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, uniformity of mass, identity, assay, related substances, dissolution and microbiological quality. The methods of analysis include Ph.Eur., HPLC and USP standards. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 3 pilot-scale batches and 1 production-scale batch from the proposed production sites have been provided, demonstrating compliance with the specification. The applicant committed to submit batch analysis results of 2 additional full-scale batches.

Stability tests on the finished product

Stability data on the product have been provided for 3 pilot-scale batches from one manufacturer (stored at 25°C ± 2/60%RH ± 5, 30°C ± 2/60%RH ± 5, and 30°C ± 2/70%RH ± 5, and 1 full-scale batch (stored at 40°C ± 2/75%RH ± 5) from another manufacturer. The appearance of the tablets packaged in PVC/Al and in PVC/PVDC/Al blisters does not comply with the specification when stored at 40°C/75%RH, as it changes into slightly off-white. When stored for 24 months at 30°C/70%RH, it complies with the specifications. The tablets packaged in PVC/PE/PVDC/Al blisters comply with the specifications of the appearance during 6 months at 40°C/75%RH, and at the other conditions.
The dissolution time shows a value of about 100% initially, which does not essentially change during the study. The content of loratadine remains unchanged. All known and unknown individual impurities and the total impurities remain within the specified limits.
The submitted stability results support a shelf-life of 3 years for the PVC/Alu blister and PVC/PVDC/Alu blister packagings, and 18 months for the PVC/PE/PVDC/Alu blister packagings, all when stored not above 25°C. The applicant is required to submit post-approval stability data of production-scale batches in PVC/PVDC/Al blisters and additional stability data of the initiated studies with pilot-scale batches in PVC/PE/PVDC/Al packaging.

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 10 mg tablets, 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.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Loratadine Sandoz 10 mg tablets (Sandoz B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Lisino 10 mg tablets (Essex Pharma, Germany).

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

Design
A single-centre, single-dose, open, randomised, two-way, two-period, two-sequence, crossover bioequivalence study was carried out in 36 healthy subjects (20 male/16 female), aged 19-44 years. Each subject received three 10 mg tablets of one of the 2 loratadine formulations. There were 2 dosing periods, separated by a washout period of 21 days.
According to the SPC, the tablet should preferably be taken before meals. In light of the increased bioavailability of loratadine under fed conditions, a fed bioequivalence study for this substance was considered appropriate. The products were administered 6 minutes after a standardised high-fat high-calorie breakfast (2 slices of toast with butter, 2 eggs fried in butter, 2 strips of bacon, 113 g mashed potatoes with 10 g butter and 240 mL milk).
After administration of the products blood was collected over a period of 168 h (20 sampling points).

Analytical/statistical methods
In plasma unchanged loratadine and the main metabolite descarboethoxyloratadine (des-loratadine) were determined with a validated LC-MS/MS assay. The pharmacokinetic parameters were estimated by standard non-compartmental methods. The methods of analysis are acceptable.

Results
All 36 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of active metabolite des-loratadine.

Treatment	$AUC_{0\text{-}168h}$	$AUC_{0\text{-}\infty}$	C_{max}	t_{max}	$t_{1/2}$

N=36	ng.h/ml	ng.h/ml	ng/ml	h	h
Test	150 ± 98	160 ± 130	10.4 ± 4.6	3.4 ± 5.6	30.0 ± 17.1
Reference	169 ± 110	181 ± 153	11.4 ± 4.6	3.3 ± 5.7	29.4 ± 15.5
***Ratio (90% CI)**	-	0.90 (0.84-0.96)	0.90 (0.82-0.99)	-	-
CV (%)	-	16.2	23.1	-	-

$AUC_{0-\infty}$ 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

**ln-transformed values*

The 90% confidence intervals calculated for $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80-1.25. Based on the pharmacokinetic parameters of des-loratadine under fed conditions, it can be concluded that Loratadine Sandoz 10, 10 mg tablets and Lisino 10 mg tablets are bioequivalent with respect to rate and extent of absorption.

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).

Discussion on bioequivalence
During the repeat use procedure, two of the CMSs, CZ and PL, argued that according to the relevant guidance documents (see *Questions & Answers on the Bioavailability and Bioequivalence Guideline* CHMP/EWP/40326/06), bioequivalence for loratadine tablets should be based also on data for the parent drug. Although it is acknowledged that plasma levels of descarboethoxyloratadine are approximately 4-fold higher than those of the parent, and activity is approximately 4-fold higher, analysis of loratadine in plasma samples, and thus assessment of bioequivalence based on loratadine plasma levels is possible, and should be the primary endpoint of a bioequivalence study for loratadine tablets. The 90% CI's for $AUC_{0-t,}$ $AUC_{0-\infty}$ and C_{max} were calculated and the results are presented in the table below.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of loratadine.

Treatment N=36	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	43.7 ± 37.1	46.5 ± 39.2	12.6 ± 12.0	1.8 ± 0.7	14.6 ± 16.6
Reference	48.6 ± 42.8	51.6 ± 44.5	14.0 ± 15.6	1.8 ± 0.8	16.8 ± 16.0
***Ratio (90% CI)**	0.79-0.96	0.78-0.95	0.79 -1.09	-	-
CV (%)	-	-	-	-	-

$AUC_{0-\infty}$ 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

**ln-transformed values*

The results indicate that the 90% CI's for Cmax and AUC's are outside of the standard acceptance criteria, when considering the parametric analysis of logarithmically transformed data. On the other hand the nonparametric determination of the 90% confidence intervals using data without logarithmic transformation shows bioequivalence of all three parameters, since the 90% CI's are within the limits of 0.80-1.20.
These results indicate that there is a justifiable chance to prove the bioequivalence of the two formulations even by comparing the parent compound. However, this issue could not be resolved during the procedure, and the matter was referred to the CMD(h) as a potential serious risk for public health.

CMD(h) referral
At the CMD(h) meeting of 22 July 2008 the RMS presented its view and the applicant's written response was discussed. There was a concern with regard to the demonstration of bioequivalence. Bioequivalence was demonstrated for the metabolite; the 90% confidence intervals for C_{max} and AUC for the parent compound were outside the 80-125% limits. No agreement was reached at the meeting, and therefore an art 29(4) referral to the CHMP was initiated on 31 July 2008.

CHMP referral
The applicant was requested to provide the CHMP with the parent compound data from the submitted bioequivalence study or to provide satisfactory justifications for the absence of these data. The applicant decided to perform a new BE study. The design and results of this study are discussed below.

Bioequivalence study - design
A single-centre, randomised, single-dose, open-label, laboratory blinded 2-way crossover bioequivalence study was carried out under fasting conditions in 80 healthy subjects (34 male/46 female), aged 18-55 years. The rate and extent of absorption of Loratadine Sandoz 10 was compared to the reference Clarityne Allergy tablets marketed in the Netherlands by Schering-Plough Ltd.
Prior to study commencement, subjects were randomly assigned to a treatment in accordance with the randomization scheme used. Subjects were confined to the clinical research facility from at least 10 hours prior to drug administration until after the 36-hour post-dose blood draw in each period. The treatment phases were separated by a washout period of 21 days. Subjects were administered a single oral dose (10 mg) of either the test or reference study medication and were served meals approximately 4 hours following study drug administration. Blood samples were collected prior to dosing (0) and at 0.333, 0.667, 1, 1.333, 1.667, 2, 2.333, 2.667, 3, 4, 8, 12, 24, 36, 48, 72 hours post-dose in each period.

Analytical/statistical methods
Loratadine and descarboethoxyloratadine concentrations in plasma were determined using a LC-MS/MS-assay. The method was fully validated and quality control was made according to established GLP principles as well as the international regulatory recommendations and guidelines. The CHMP noted the statement on GLP compliance in bio-analysis and considered that the analytical methods are acceptable and validated appropriately, and seem adequate to accurately determine the concentration of loratadine and descarboethoxyloratadine in plasma.
The basic statistical parameter analysis of $AUC_{0-t,}$ $AUC_{0-\infty}$ and C_{max} of loratadine and descarboethoxyloratadine was performed using the SAS System. Following the logarithmic transformation, both AUCs and C_{max} values were subjected to analysis of variance (ANOVA). The CHMP considered that the statistic analysis was described adequately, and that the methods for statistical assessment of this bioequivalence study were acceptable.

Bioequivalence study - results
Out of the 80 participants, 77 completed the study. Two subjects withdrew for personal reasons, and one prior to period 2 due to testing positive for benzodiazepines.
The applicant provided the pharmacokinetic parameters for both loratadine and descarboethoxyloratadine.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of active metabolite descarboethoxyloratadine.

Treatment N=77	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	33.2 ± 17.2	38.7 ± 29.4	2.26 ± 1.05	1.3 (1.0-12.0)	22.1 ± 7.9
Reference	34.4 ± 17.9	40.3 ± 31.5	2.48 ± 1.16	1.3 (0.6-12.0)	22.1 ± 8.7
***Ratio (90% CI)**	0.97 (0.94-1.00)	0.97 (0.94-1.00)	0.92 (0.86-0.97)	-	-
CV (%)	11.6	11.0	21.8	-	-

$AUC_{0-\infty}$ 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

**ln-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of loratadine.

Treatment N=77	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	12.7 ± 14.7	13.5 ± 16.0	3.92 ± 4.04	1.0 (0.6-4.0)	19.9 ± 13.5
Reference	13.5 ± 15.7	14.5 ± 17.5	4.30 ± 4.43	1.0 (0.6-2.3)	21.0 ± 13.9
***Ratio (90% CI)**	0.89 (0.83-0.95)	0.89 (0.83-0.96)	0.84 (0.75-0.94)	-	-
CV (%)	32	32	46	-	-

$AUC_{0-\infty}$ 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

**ln-transformed values*

In conclusion, the applicant considered that the newly submitted study demonstrated bioequivalence of the test product Loratadine Sandoz 10 mg tablets with reference product Clarityne Allergy 10 mg tablets for AUC_{0-t} and $AUC_{0-\infty}$ of loratadine. However, for the C_{max} parameter of loratadine, bioequivalence failed.

Bioequivalence – discussion
The applicant considered that due to the large intra-subject variability of loratadine (CV% - 46,4) the use of a wider CI (i.e. 0.75 – 1.33) is justified, which would allow the acceptance of the results of the study. Furthermore, the applicant stated that the differences in C_{max} do not have a major clinical effect on the use of this product in humans. Additionally, results of this BE study for $AUC_{0-t,}$ $AUC_{0-\infty}$ and C_{max} of descarboethoxyloratadine demonstrated bioequivalence of the test product Loratadine Sandoz 10 mg tablets with reference product Clarityne Allergy 10 mg tablets.
The applicant concluded that in light of the above discussions, supported by published information (CPMP 2004, Bruin *et al* 2001, Ronald *et al* 2000, Claritin prescribing information) and taking into account the available pharmacovigilance data showing no serious safety or efficacy concerns with loratadine that

could warrant its discontinuance from the market, Loratadine Sandoz 10 should be considered to be an efficacious and safe product.

CHMP opinion

The CHMP noted that data on both loratadine and its major active metabolite, descarboethoxyloratadine were presented in the clinical study report. According to the current guidance as outlined in the *Questions & Answers on the Bioavailability and Bioequivalence Guideline* (CHMP/EWP/40326/06), bioequivalence should preferably be based on data for the parent drug, loratadine. This has been confirmed in the most recent draft guideline on bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1).

The data showed that the 90% confidence intervals for the ln-transformed $AUC_{0-t,}$ $AUC_{0-\infty}$ and C_{max} of descarboethoxyloratadine are within the acceptance range of 0.80-1.25. However, for loratadine, the 90% confidence interval for the ln-transformed C_{max} is outside the predefined acceptance range of 0.80-1.25 (although the 90% confidence intervals for the ln-transformed $AUC_{0-t,}$ $AUC_{0-\infty}$ were respected). The CHMP considers that the widening of the acceptance range to 75-135% was not predefined in the study protocol and is as such not acceptable. Therefore, the CHMP concluded that bioequivalence between Loratadine Sandoz 10 and the reference product was not sufficiently demonstrated.

In conclusion, the applicant provided a new bioequivalence study during this referral procedure, but obtained results in line with the previous study: although the 90% confidence intervals for the metabolite are well within the 0.80-1.25 acceptance range, the C_{max} of the parent compound is still outside this criterion. According to the Q & A document, a wider interval may be acceptable, but only if prospectively defined and justified, addressing in particular any safety or efficacy concerns for patients switched between formulations. A *post hoc* justification of an acceptance range wider than defined in the protocol cannot be accepted as was done for this study, where a widened interval of 0.75-1.33 was introduced. Therefore, bioequivalence of the 10 mg loratadine test and reference formulations is not demonstrated and the CHMP considered that the positive benefit-risk profile of Loratadine Sandoz 10 could not be concluded.

The applicant proposed the assumption that the parent compound is inactive. This was rejected, as the absolute activity should be taken into account, rather than the ratio of activity compared to the metabolite. In order to consider the parent compound as inactive, a significantly lower level of activity would have been required. The data available shows that the parent compound is sufficiently measurable, and therefore must be measured, in order to assess bioequivalence.

CHMP conclusion

The results of the new study show that the same conclusions can be drawn as from the initial study: although the 90% confidence intervals for the metabolite are well within the 0.80-1.25 acceptance range, the C_{max} of the parent compound is still outside this criterion. According to the currently applicable guidance, bioequivalence must be demonstrated for the parent compound for generic products. Therefore, the products cannot be considered bioequivalent and the CHMP concluded that the benefit-risk profile of Loratadine Sandoz 10 is negative. The CHMP recommended the suspension of the granted Marketing Authorisations. The conditions for lifting the suspension require the applicant to submit the results of a correctly planned study that demonstrates the bioequivalence between the two products in accordance with the current guidelines. Any widening of the confidence intervals should be agreed prospectively in the study design. See also EMA Doc. Ref. EMA/321803/2009.

Procedures NL/H/317-319/001/MR

The Committee noted that this product was previously authorised during the initial Mutual Recognition Procedure in a number of other Member States on the basis of the same data. These countries are AT, BE, LU, DE, DK, EL, ES, FI, NO, PT, SE and UK. The CHMP recommended that the authorisations in these countries should also be suspended.

Moreover, for procedures NL/H/318/001/MR and NL/H/319/001/MR the same data were submitted. Therefore, the CHMP conclusion also applies to the products registered through these procedures: Loratadine 10 mg, tablets (NL License RVG 25766) and Otrivin neusallergie loratadine 10 mg tablet (NL License RVG 25767), respectively.

Procedure NL/H/318/001 involved DE, BE, FR, IT, AT, EE, ES, HU, IE, LT and LV. Through procedure NL/H/319/001 the product was registered in the following CMSs: AT, BE, DE, DK, EL, ES, FI, IE, LU, NO, PT, SE and UK. The Marketing Authorisations granted for these procedures have been suspended.

Risk management plan

Loratadine was first approved in October 1991, 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.

Product information

Readability test

The package leaflet has not been evaluated via a user consultation study, as this was not considered necessary at the time of the initial mutual recognition procedure. The PIL is of sufficient quality.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The CHMP, on the basis of the data submitted during the repeat use procedure, considered that Loratadine Sandoz 10, 10 mg tablets have not demonstrated a satisfactory risk/benefit profile during the repeat use procedure, CMD(h) and CHMP referrals (see also discussion below). Loratadine Sandoz 10 cannot be considered an appropriate generic version of the reference product Claritine 10 mg tablets. Therefore, no marketing authorisations were granted and the existing marketing authorisations were suspended.

Although bioequivalence has been shown for the active metabolite, the applicant was requested to demonstrate bioequivalence for the parent compound as well. The parent compound results of bioequivalence testing for the initial mutual recognition procedure were not within the 0.80-1.20 acceptance range. Therefore, CMSs CZ and PL raised a potential serious risk to human health and referred the procedure to the CMD(h).

In the CMD(h) meeting of 22 July 2008, the RMS presented its view and the applicant's written response was discussed. No agreement was reached at the meeting, and therefore an art 29(4) referral to the CHMP was initiated.

During the CHMP referral, results of a newly performed bioequivalence study were presented. Although the 90% confidence intervals of the metabolite proved well within the 0.80-1.25 acceptance range, the C_{max} of the parent compound was still outside this criterion. Following these results, the applicant suggested widening of the confidence intervals. This was found unacceptable, as according to the *Q & A on the Bioavailability and Bioequivalence Guideline*, a wider interval may be acceptable, but only if prospectively defined and justified.
In the meeting in May 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, was of the opinion that the objections that triggered the Article 29(4) Referral prevent the granting of a Marketing Authorisation for Loratadine Sandoz 10 and associated names. A negative opinion was therefore adopted on 29 May 2009.

In conclusion, the benefit-risk balance of Loratadine Sandoz 10, 10 mg tablets is negative. The applicant failed to demonstrate bioequivalence based on parent compound data, in accordance with current European guidelines. No marketing authorisations could be granted, and marketing authorisations granted previously will be suspended.
In addition, the marketing authorisations granted during procedures NL/H/318/001/MR and NL/H/319/001/MR have been suspended. In the Netherlands, the MAs for Loratadine Sandoz 10, Loratadine 10 mg, tablets and Otrivin neusallergie loratadine 10 mg tablet were suspended on 24 September 2009.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BE	Bioequivalence
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
HPLC	High Performance Liquid Chromatography
ICH	International Conference of Harmonisation
LC/MS/MS	Liquid chromatography−Tandem Mass Spectrometry
MA	Marketing Authorisaton
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
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
Q & A	Questions and Answers
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 PRIOR TO THE REPEAT USE 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
Mutual Recognition Procedure	NL/H/317/001/MR	MR	31-10-2001	29-1-2002	Approval	Y, Annex I
Change of the manufacturing site(s) for part or all of the manufacturing process of the medicinal product. Addition of packager.	NL/H/317/001/V/001	V	7-6-2002	5-7-2002	Approval	N
Change of the manufacturing site(s) for part or all of the manufacturing process of the medicinal product. Addition of packager.	NL/H/317/001/V/002	V	7-6-2002	5-7-2002	Approval	N
Name and/or address of the marketing authorization holder (see Art 4a of Directive 65/65/EEC or Art. 5a of Directive 81/851/EEC) in Luxembourg.	NL/H/317/001/V/003	V	7-6-2002	5-7-2002	Approval	N
Addition of securitainer stability	NL/H/317/001/W/004	W	11-9-2002	24-2-2003	Approval	N
Update DMF	NL/H/317/001/W/005	W	20-6-2003	19-8-2003	Approval	N
Updated related substances method of the finished product	NL/H/317/001/W/006	W	20-6-2003	19-8-2003	Approval	N
Replacement of an excipient with a comparable excipient (excluding adjuvants for vaccines and biologically derived excipients). Replacement of ruminant sourced magnesium stearate with vegetable source	NL/H/317/001/V/007	V	30-6-2003	30-7-2003	Approval	N
Change in the name and/or address of the marketing authorisation holder	NL/H/317/001/IA/008	IA	10-10-2003	24-10-2003	Approval	N
Change in the name of the medicinal product	NL/H/317/001/IB/009	IB	16-10-2003	17-11-2003	Approval	N
Change in the name and/or address of a manufacturer of the finished product	NL/H/317/001/IA/010	IA	10-10-2003	24-10-2003	Approval	N
Change to batch release arrangements and quality control testing of the finished product; replacement or addition of a manufacturer responsible for batch release; not including batch control/testing	NL/H/317/001/IA/011	IA	10-10-2003	24-10-2003	Approval	N
Change in the name of the medicinal product	NL/H/317/001/IB/012	IB	16-2-2004	9-3-2004	Approval	N
Change in the name and/or address of a manufacturer of the finished product	NL/H/317/001/IA/013	IA	29-11-2004	13-12-2004	Approval	N
Addition of API source by means of DMF	NL/H/317/001/II/014	II	23-5-2005	16-11-2005	Approval	N
Change in the name and/or address of the marketing authorisation holder	NL/H/317/001/IA/015	IA	7-6-2005	21-6-2005	Approval	N
Change to batch release arrangements and quality control testing of the finished product; replacement or addition of a manufacturer responsible for batch release; including batch control/testing	NL/H/317/001/IA/016	IA	21-5-2007	4-6-2007	Approval	N
Change to batch release arrangements and quality control	NL/H/317/001/IA/017	IA	21-5-2007	4-6-2007	Approval	N

testing of the finished product; replacement or addition of a manufacturer responsible for batch release; including batch control/testing						
Renewal	NL/H/317/001/R/001	R	15-9-2006	19-8-2007	Approval	N
Change to batch release arrangements and quality control testing of the finished product; replacement or addition of a manufacturer responsible for batch release; not including batch control/testing	NL/H/317/001/IA/018	IA	21-5-2007	4-6-2007	Approval	N
Change to batch release arrangements and quality control testing of the finished product; replacement or addition of a site where batch control/testing takes place	NL/H/317/001/IA/019	IA	21-5-2007	4-6-2007	Approval	N
Change in the name and/or address of a manufacturer of the finished product	NL/H/317/001/IA/020	IA	21-5-2007	4-6-2007	Approval	N
Deletion of any manufacturing site (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place).	NL/H/317/001/IA/021	IA	21-5-2007	4-6-2007	Approval	N
Deletion of any manufacturing site (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place).	NL/H/317/001/IA/022	IA	21-5-2007	4-6-2007	Approval	N
Deletion of any manufacturing site (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place).	NL/H/317/001/IA/023	IA	21-5-2007	4-6-2007	Approval	N
Deletion of any manufacturing site (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place).	NL/H/317/001/IA/024	IA	21-5-2007	4-6-2007	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; primary packaging site; solid pharmaceutical forms, e.g. tablets and capsules.	NL/H/317/001/IA/025	IA	21-5-2007	4-6-2007	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; primary packaging site; solid pharmaceutical forms, e.g. tablets and capsules.	NL/H/317/001/IA/026	IA	21-5-2007	4-6-2007	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; primary packaging site; solid	NL/H/317/001/IA/027	IA	21-5-2007	4-6-2007	Approval	N

pharmaceutical forms, e.g. tablets and capsules.						
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; secondary packaging site for all types of pharmaceutical forms.	NL/H/317/001/IA /028	IA	21-5-2007	4-6-2007	Approval	N

ANNEX I – Mutual Recognition Procedure (NL/H/317/001/MR)

The mutual recognition procedure started on 31 October 2001, following first registration of the product in the Netherlands on 12 July 2001. The application was made according to Directive 65/65 article 4.8 iii) first paragraph, abridged application. The procedure started on 31 October 2001 with concerned member states AT, BE, LU, DE, DK, EL, ES, FI, NO, PT, SE and UK.

By day 50, most of the concerned member states expressed objections and/or points for consideration regarding the SPC, quality and the bioequivalence study.
By day 90, the answers of the MAH could solve all major objections and points for consideration and the marketing authorisation was mutually recognised by all Concerned Member States, except BE. The reference product in Belgium is not indicated for chronic urticaria in children younger than 12 years of age. Concerning this indication, no data are available in relation to the body weight. Therefore, BE raised a major objection regarding section 4.1 of the SPC, which could not be solved before day 90. It was decided to withdraw the application in BE.

The procedure ended positively on 29 January 2002.

The following post-approval commitments were made during the procedure:

Quality - active substance
- The MAH committed to provide data showing the lowest amount of each solvent which can be detected by the GC method under consideration and revised data for 5 batches showing actually found residual levels of solvents.

Quality- medicinal product
- The MAH committed to present a revised related substances method for the finished product.
- The MAH committed to submit stability results of two additional full-scale batches.