PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Cetirizine diHCL Losan compressed lozenge 10 mg
Losan Pharma GmbH, Germany

cetirizine dihydrochloride

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/1021/01/MR
Registration number in the Netherlands: RVG 33642

19 January 2010

Pharmacotherapeutic group: antihistamines for systemic use, piperazine derivatives
ATC code: R06AE07
Route of administration: oromucosal
Therapeutic indication: Children 6-12 years: symptomatic treatment of allergic rhinitis (seasonal and perennial) and chronic idiopathic urticaria. Adults and adolescents above 12 year: Symptomatic treatment of allergic rhinitis (seasonal and perennial), associated allergic conjunctivitis and chronic idiopathic urticaria.

Prescription status: non-prescription
Date of first authorisation in NL: 31 August 2006
Concerned Member States: Mutual recognition procedure with IT
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 member states have granted a marketing authorisation for Cetirizine diHCL Losan compressed lozenge 10 mg, from Losan Pharma GmbH. The date of authorisation was on 31 August 2006 in the Netherlands. The product is indicated for symptomatic treatment of allergic rhinitis (seasonal and perennial), associated allergic conjunctivitis and chronic idiopathic urticaria in adults and adolescents above 12 years. In children aged 6 to 12 years, the product is indicated for symptomatic treatment of allergic rhinitis (seasonal and perennial) and chronic idiopathic urticaria.

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

Cetirizine dihydrochloride is a racemate and an antiallergic with specific histamine H1-receptor blocking characteristics. Cetirizine inhibits cutaneous reactions in allergic individuals by VIP (Vasoactive Intestinal Polypeptide) and the P substance, neuropeptides that are considered involved in the allergic reaction. The onset of the effect is within 2 hours; peak efficacy is reached after 4 hours and the effect remains during at least 24 hours. In allergic individuals cetirizine inhibits the recruitment of eosinophils after stimulation with an allergen and nonselective histamine liberator, by a mechanism that is not primarily be explained by the H1-receptor blocking characteristics of the product.

Purpose of the new product

It was mentioned by the MAH that before this application was done only film-coated tablets, oral liquids and drops with cetirizine (dihydrochloride) as drug substance were available. With already registered dosage forms, patient’s compliance, especially for children, could be negatively influenced by the bitter flavour of the drug substance, even after sweetening of the liquid formulation.

Conventional tablets have the disadvantage that they can only be administered with liquid, which may be inconvenient in case of a suddenly occurring allergic attack e.g. during a walk. The intention was to develop a dosage form that can be administered without water and has a good taste and additionally, the dimensions of the product and packaging should be as small as possible so that even in children it can be administered without any problems. Furthermore, the dose should be variable and, if possible, the product should be packed individually. Therefore, a small lozenge with a scoring line was developed.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Zyrtec 10 mg tablets (NL License RVG 13010) from UCB Pharma B.V., which has been registered in the Netherlands since 1988. In addition, reference is made to the Zyrtec 10 mg tablets authorisation in Italy (reference product). The abridged application for Cetirizine diHCl Biofarm is considered appropriate, in view of the following text in the Notice to Applicants: “... all oral solid pharmaceutical forms for immediate release must be regarded as the same pharmaceutical form for the purpose of essential similarity...”.

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 reference product Zyrtec 10 mg comprimés tablets, registered in France. 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 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.

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 cetirizine dihydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). A Ph. Eur. Certificate of suitability (CEP) has been submitted for the drug substance manufacturer.

The drug substance is a white or almost white powder with a weak odour and bitter taste. The substance contains a chiral centre, and the racemate form is used. Polymorphism is not an issue.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Manufacture
The substance is micronised to an acceptable particle size. An acceptable specification for this aspect is present, based on the particle size of the drug substance in the biobatch.

Specification
The active substance specification is considered adequate to control the quality and is in compliance with the Ph. Eur. monograph with additional specifications for residual solvents and particle size. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability
The stability studies have been performed with substance packed in the proposed packaging. Stability data on the active substance have been provided for 3 pilot scale batches (stored at 40°C/75%RH) in accordance with applicable European guidelines demonstrating the stability of the active substance over 24 months. In addition, 3 other development batches were stored during 60 months, 60 months and 48 months at 25°C/60%RH. The results of these batches are considered supportive to the primary batches. Based on the data submitted, a retest period could be granted of 2 years without specific storage conditions.

The MAH has committed to submit the certificates of analysis performed on three commercial scale batches and stability results of production batches post approval.

* Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.
Medicinal Product

Composition
Cetirizine diHCL Losan compressed lozenges contain as active substance 10 mg of cetirizine dihydrochloride, and are round, white to almost white with a break-mark on both sides. The compressed lozenges can be divided into equal halves.

The excipients are: Betadex (E459), Povidone K-25, Sodium cyclamate (E952), Powdered cellulose (E460), Monosodium citrate (E331), Microcrystalline cellulose (E460), Magnesium stearate (E470B), and Apple flavour. Betadex, cyclodextrin, has been chosen as filling agent for it’s good taste masking characteristic, "complex" formation between this excipient and cetirizine is possible.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. Container/closure is: Al/Al blister in cardboard box (15 tablets per pack), HDPE (30 ml) tablet container (for 30 tablets) with LD polypropylene (twist-off) cap with PE desiccant capsule containing 2 g white silica gel. Appropriate requirements have been laid down for these packagings.

The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs except for monosodium and apple flavour. Monosodium conforms a.o. to an in-house monograph, which is based on the Ph. Eur. Monograph of sodium citrate. Apple flavour conforms to Directive 88/388/EC.

The MAH has provided comparative dissolution profiles with the innovator products of the following countries: Greece, Poland, Germany, France, Spain and Italy as a support, compared with test product and bio reference product. The profiles can be considered similar; after 15 minutes for all products at least 85% was dissolved; the results were also within the specification limits. The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and composition.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 pilot scale batches from two manufacturing sites in accordance with the relevant European guidelines. The MAH has committed to perform process validation on the first three production batches from both manufacturing sites. The MAH committed to forward certificates of analysis performed on the first consecutive three commercial scale batches of drug product manufactured at one of the manufacturing sites.

Product specification
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification is based on specific monographs in the Ph.Eur. and USP and includes tests for appearance, diameter, height, odour, friability, hardness, average mass, uniformity of mass, loss on drying, identification, assay, HPLC purity, microbiological purity, LOD desiccant, and dissolution rate. Efforts have been made to produce a lozenge which has a dissolution rate according to a normal conventional tablet. 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 analysis results have been submitted of the same six (2x3) batches as mentioned above at "manufacturing process". Results are in accordance with the release specifications. The MAH has committed to submit release of full scale production batches as soon as available, of all parameters, of both sites (three batches per site).

Stability tests on the finished product
Stability data on the product have been provided for 6 batches (stored at 25ºC/60%RH and 40ºC/75%RH) batches in accordance with applicable European guidelines demonstrating the stability of the product over 36 months. Also photostability studies were performed with this product in both packagings, according to
the NfG ICH Q 1B, which indicated that the product is light stable. On basis of the data submitted, a shelf life was granted of 3 years, without a special storage temperature. The labelled storage condition is: "Store in the original packaging in order to protect from moisture". The MAH has committed to put the first three commercial batches of the drug product on stability, and to test them according to the proposed stability protocol additionally completed about the test “Uniformity of mass of subdivided parts”.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

It is indicated that of all substances only Betadex is of animal origin. The MAH declares that this excipient conforms to the NfG CPMP/BWP/ guideline of 28-2-2001.

II.2 Non clinical aspects

This product is a generic formulation of Zyrtec, 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 cetirizine dihydrochloride 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

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

In order to provide proof for essential similarity, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Cetirizine 10 mg Lozenges is compared with the pharmacokinetic profile of the French reference product Zyrtec 10 mg film-coated tablets.

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

Design:

A single center, open, randomized, two-way, two-sequence, cross-over bioequivalence study was carried out under fasted conditions in 24 healthy caucasian males (n=13) and females (n=11), aged 18 to 45 years. Each subject received a single dose (10 mg) of one of the 2 cetirizine dihydrochloride formulations. After an overnight fast, the lozenge was placed in the subject’s mouth and the subject actively sucked the lozenge. Following complete disintegration of the lozenge the subject rinsed his/her mouth three times with 80 ml water. The water was to be swallowed completely by the subject. The reference tablets were administered with 240 ml of water after fasting overnight. The washout period between the two administrations was at least 6 days (mean elimination half-life of cetirizine is 8 h).

Blood samples were collected predose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 4, 6, 8, 12, 16, 24 and 30 after administration of the products. All 24 subjects were eligible for pharmacokinetic analysis.

Cetirizine dihydrochloride may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of cetirizine dihydrochloride. 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.
Results:
Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, \( t_{\text{max}} \) (median, range)) of cetirizine under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_{0-t} ) (μg.h/ml)</th>
<th>( \text{AUC}_{0-\infty} ) (μg.h/ml)</th>
<th>( C_{\text{max}} ) (μg/ml)</th>
<th>( t_{\text{max}} ) (h)</th>
<th>( t_{1/2} ) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>2.05 ± 0.31</td>
<td>2.22 ± 0.32</td>
<td>0.29 ± 0.06</td>
<td>0.75 (0.5 – 2.67)</td>
<td>8.2 ± 2.1</td>
</tr>
<tr>
<td>Reference</td>
<td>2.11 ± 0.32</td>
<td>2.28 ± 0.31</td>
<td>0.28 ± 0.06</td>
<td>0.75 (0.5 – 3)</td>
<td>8.3 ± 1.9</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>0.97 (0.94 – 1.01)</td>
<td>0.97 (0.94 – 1.01)</td>
<td>1.02 (0.96 – 1.09)</td>
<td>---</td>
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</tr>
<tr>
<td>CV (%)</td>
<td>7.6</td>
<td>7.9</td>
<td>12.7</td>
<td>---</td>
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</tr>
</tbody>
</table>

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

*ln-transformed values

Conclusions:
The 90% confidence intervals calculated for \( \text{AUC}_{0-t} \), \( \text{AUC}_{0-\infty} \) and \( C_{\text{max}} \) 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 cetirizine under fasted conditions, it can be concluded that test Cetirizine diHCL Losan lozenges and reference Zyrtec comprimés are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The intention of the MAH was to develop a pharmaceutical form of cetirizine hydrochloride that can be administered without water and has a good taste. As the cetirizine lozenge is intended for administration without water, this should ideally have been the condition tested in the bioequivalence study. Furthermore, administration without water represents a potential worst-case scenario in case the lozenge was not completely dissolved in saliva and particles of the lozenge hang back in the mouth cavity. By three times rinsing the mouth with water, potential in the mouth remaining particles are swallowed and thereby favour the chance for bioequivalence. Still, the test tablets are allowed to be taken regardless of water.

Note, that although cetirizine hydrochloride exhibits uncomplicated pharmacokinetic behaviour according to the BCS classification system it is a Class III substance (high solubility / low permeability, Wu and Benet, Pharm. Res., 2005). Dissolution of the lozenge is relatively fast and the solubility of cetirizine is high and fast. As the current bioequivalence study shows bioequivalence for the cetirizine lozenges with Zyrtec tablets well within the 90% confidence interval and because of the fast dissolution of the lozenges and high solubility of cetirizine it is expected that potentially remaining particles will be dissolved so fast that rinsing or not rinsing the mouth with water will not significantly affect the outcome of the bioequivalence study. Based on these arguments, rinsing the mouth with water in the bioequivalence study after applying the cetirizine compressed lozenges is considered acceptable.

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
Cetirizine was first approved in 1986, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of cetirizine dihydrochloride can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation 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

SPC
The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Zyrtec marketed by UCB Pharma SA, except for the sections regarding the dosage form.

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.

Remarkable in the set-up of the test is that the interviewer indicated the section in the PIL where the answer can be found, if a participant could not find the answer. In this way the score for comprehensibility and applicability is higher than it would have been without the help of the interviewer. The MAH states that in this way the interviewer has a conversation why the information could not be found and that it is still possible to determine whether the information itself is understandable.

A first test was performed with 10 participants. This lead to the following major results: For almost all items at least 80% scored well on the diagnostic questions. For three items, issues were identified and changes were made. The section 'Do not take Cetirizine' was found to be problematic. Four respondents could not easily find this section or could not find it at all. Since the heading is conform the template, no changes were made.

The second test with the adapted text performed with 10 participants led to the following major results: Results of the second round of testing confirmed the results of the first test round. At least 80% of the respondents scored well on almost all of the diagnostic questions. The corrections made to the leaflet that has been used in the second test round are deemed appropriate. Spontaneous remarks made by the respondents indicate that the leaflet does, however, contain too much medical terms. The PIL has not been adapted after the second test.

There were sufficient questions about the critical sections. The conclusions are clear, concise and clearly presented. 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

Cetirizine diHCL Losan compressed lozenges 10 mg have a proven chemical-pharmaceutical quality and are a generic form of Zyrtec. Zyrtec film-coated tablets are 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.

The SPC is consistent with that of the reference product, except for the sections regarding the dosage form. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other cetirizine containing products.

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

The Board followed the advice of the assessors. Cetirizine diHCL Losan was authorised in the Netherlands on 31 August 2006.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Cetirizine diHCL Losan with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 5 June 2007.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from June 2007 to June 2010.

The date for the first renewal will be 5 June 2012.

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

Quality – active substance
- The MAH has committed to submit the certificates of analysis performed on three commercial scale batches and stability results of production batches post approval.

Quality - drug substance
- The MAH has committed to submit the stability results of production batches of the drug substance.

Quality - medicinal product
- The MAH committed to perform process validation on the first consecutive three commercial scale batches of the drug product manufactured from both manufacturing sites.
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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\textsubscript{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
PIL   Package Leaflet
PSUR  Periodic Safety Update Report
SD    Standard Deviation
SPC   Summary of Product Characteristics
\textit{t}_{\frac{1}{2}} Half-life
\textit{t}_{\text{max}} Time for maximum concentration
TSE   Transmissible Spongiform Encephalopathy
USP   Pharmacopoeia in the United States
VIP   Vasoactive Intestinal Polypeptide
### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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