PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Cetirizine diHCl Losan 10 mg, compressed lozenges
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/1286/001/MR
Registration number in the Netherlands: RVG 35064

26 August 2009

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

Prescription status: Pharmacist only
Date of authorisation in NL: 8 March 2007
Concerned Member States: Mutual recognition procedure with FI and SE
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 10 mg, compressed lozenges from Losan Pharma GmbH. The date of authorisation was on 8 March 2007 in the Netherlands.

The product is indicated for:

Adults and adolescents above 12 year
Symptomatic treatment of allergic rhinitis (seasonal and perennial), associated allergic conjunctivitis and chronic idiopathic urticaria.

Children 6-12 years
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. Cetirizine dihydrochloride is marketed in various European countries as film-coated tablet containing 10 mg cetirizine dihydrochloride, as oral solution containing cetirizine dihydrochloride 1 mg/ml and as oral drops containing cetirizine dihydrochloride 10 mg/ml.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Zyrtec 10 mg film-coated 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 Zyrtec 10 mg film-coated tablets authorisations in the individual member states (reference product). The abridged application for Cetirizine diHCl Losan 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 film-coated 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.
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.*). 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 active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional specifications for residual solvents and particle size. Batch analytical data of 3 pilot-scale batches were provided demonstrating compliance with this specification. The MAH committed to submit batch analytical data of production batches post-approval.

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.

Stability data on the active substance have been provided for three pilot batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 24 months. Based on the data submitted, a retest period could be granted of two years in the proposed packaging without storage conditions. Three other, older, development batches were stored during 60 months and 48 months at 25°C/60%rh. The results of these batches are considered supportive to the primary batches. The MAH committed to submit the stability results of production batches post-approval.

* Ph.Eur., USP and 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 are round, white to almost white compressed lozenges with a break-mark on both sides, and contain as active substance 10 mg of cetirizine dihydrochloride.

The compressed lozenges are packed in aluminium blisters with different pack sizes.

The excipients are:
Betadex (E459),
Povidone K-25,
Sodium cyclamate (E952),
Powdered cellulose (E460),
Monosodium citrate (E331),
Microcrystalline cellulose (E460),
Magnesium stearate (E470B),
Synthetic apple flavour.
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 citrate and synthetic apple flavour, for which in-house specifications apply.

**Pharmaceutical development**

The development is adequately described in accordance with the relevant European guidelines. The packaging is usual and suitable for the products at issue.

The background for the development is as follows: With the registered dosage forms, the patient compliance, especially for children, is negatively influenced by the bitter flavour of the drug substance, which even after intense sweetening of the liquid formulation has a bad taste and furthermore a large bottle packing is inconvenient. Conventional tablets have the disadvantage that they can only be administered with liquid, which is unfavourable in case of a suddenly occurring allergic attack e.g. during a walk. Due to these reasons, 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 with essential similarity to the innovator product Zyrtex 10 mg film-coated tablets.

**Manufacturing process and quality control of the medicinal product**

The manufacturing process has been validated according to relevant European/ICH guidelines. The process is a standard wet granulation process. Process validation data on the product have been presented for six batches in accordance with the relevant European guidelines. The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for amount of granulating liquid, mixing times, drying time, LOD, sieve mesh sizes, tableting rate, tablet hardness, uniformity of mass and content uniformity. 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 batches as at process validation. Results are in accordance with the release specifications. The MAH committed to submit the release results of full scale production batches of both drug product manufacturers.

**Stability tests on the finished product**

Stability data on the product have been provided for six batches in accordance with applicable European guidelines demonstrating the stability of the product for 36 months. On basis of the data submitted, a shelf life was granted of 3 years. The labelled storage conditions are: “Store in the original packaging in order to protect from moisture”.

**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

Good Laboratory Practice
This product is a generic formulation of Zyrtec 10 mg film-coated 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 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.

The content of the SPC approved during the mutual recognition procedure is in accordance with the SPC approved during NL/H/1011/001/MR for another cetirizine generic.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Cetirizine diHCl Losan is compared with the pharmacokinetic profile of the reference product Zyrtec 10 mg comprimés, registered in France.

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.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy subjects (13 male and 11 female), aged 18-45 years. For each subject there were 2 dosing periods, separated by a washout period of at least 6 days. 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. Blood samples were taken 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 hours after administration of the products. There were no drop-outs and pharmacokinetic parameters were evaluated for all 24 subjects.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t\(_{\text{max}}\) (median, range)) of cetirizine dihydrochloride under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=24</th>
<th>AUC(_{0-t}) µg.h/ml</th>
<th>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>
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<tr>
<td>Test</td>
<td></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></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></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>
<td>-</td>
</tr>
<tr>
<td>CV (%)</td>
<td></td>
<td>7.6</td>
<td>7.9</td>
<td>12.7</td>
<td>-</td>
<td>-</td>
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</table>

AUC\(_{0-t}\) area under the plasma concentration-time curve from time zero to infinity
AUC\(_{0-\infty}\) 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

*In-transformed values
Cetirizine dihydrochloride can 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.

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 Cetirizine diHCl Losan and the Zyrtec 10 mg comprimés are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

As the current bioequivalence study shows bioequivalence for the Cetirizine diHCl Losan with Zyrtec tablets 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 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 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**

Cetirizine dihydrochloride 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**

**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 two rounds with 10 participants each. 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 taking into account the results of the tests.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Cetirizine diHCl Losan 10 mg, compressed lozenges have a proven chemical-pharmaceutical quality and are a generic form of Zyrtec 10 mg film-coated tablets. Zyrtec is 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 SPC approved for the mutual recognition procedure NL/H/1101/001/MR. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other cetirizine dihydrochloride 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 10 mg was authorised in the Netherlands on 8 March 2007.

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 10 mg with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 27 February 2008.

A European harmonised birth date has been allocated (6-11-1986) and subsequently the first data lock point for cetirizine is November 2009. The first PSUR will cover the period from March 2007 till November 2009, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 27 February 2013.

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

**Quality – active substance**
- The MAH committed to submit batch analytical data of three production batches.
- The MAH committed to submit the stability results of production batches.

**Quality – drug product**
- Process validation will be performed on the first consecutive 3 commercial scale batches of one of the drug product manufacturers.
- The MAH committed to perform certificates of analysis performed on the first consecutive 3 commercial scale batches of both drug product manufacturers.
- The first three commercial batches of the drug product will be put on stability and tested according to the proposed stability protocol, additionally completed about the test “Uniformity of mass of subdivided parts”.
- The MAH committed to take into consideration the possibility to tighten the release and the shelf life specification limits for the Impurity A content after acquisition of data for the first five production batches.

**Product information – SPC and PL**
- The MAH committed to adapt the SPC and PL, after the ongoing referral for the innovator product Zyrtec is finished.
### List of abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
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<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
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<td>AUC</td>
<td>Area Under the Curve</td>
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<td>BP</td>
<td>British Pharmacopoeia</td>
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<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>$C_{\text{max}}$</td>
<td>Maximum plasma concentration</td>
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<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<td>CV</td>
<td>Coefficient of Variation</td>
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<td>EDMF</td>
<td>European Drug Master File</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EU</td>
<td>European Union</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GLP</td>
<td>Good Laboratory Practice</td>
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<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
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<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
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<td>PAR</td>
<td>Public Assessment Report</td>
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<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PIL</td>
<td>Package Leaflet</td>
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<td>PSUR</td>
<td>Periodic Safety Update Report</td>
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<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>$t_{\frac{1}{2}}$</td>
<td>Half-life</td>
</tr>
<tr>
<td>$t_{\text{max}}$</td>
<td>Time for maximum concentration</td>
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<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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<td>USP</td>
<td>Pharmacopoeia in the United States</td>
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### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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<th>Scope</th>
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<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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