COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Loratadine Accord 10 mg tablets (loratadine)

# NL/H/5191/001/DC

# Date: 31 January 2022

**This module reflects the scientific discussion for the approval of Loratadine Accord 10 mg tablets. The procedure was finalised on 20 October 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.**

# List of abbreviations

| | |
|---|---|
| ASMF | Active Substance Master File |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CHMP | Committee for Medicinal Products for Human Use |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CMS | Concerned Member State |
| EDMF | European Drug Master File |
| EDQM | European Directorate for the Quality of Medicines |
| EEA | European Economic Area |
| ERA | Environmental Risk Assessment |
| ERP | European Reference Product |
| ICH | International Conference of Harmonisation |
| MAH | Marketing Authorisation Holder |
| Ph.Eur. | European Pharmacopoeia |
| PL | Package Leaflet |
| RH | Relative Humidity |
| RMP | Risk Management Plan |
| SmPC | Summary of Product Characteristics |
| TSE | Transmissible Spongiform Encephalopathy |

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Loratadine Accord 10 mg tablets, from Accord Healthcare B.V.

The product is indicated for the symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria.

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

This decentralised procedure concerns a generic application claiming essential similarity with the European Reference Product (ERP) Clarityn 10 mg tablets, which has been registered in Belgium by Bayer B.V. since 30 July 2007 (original product). In the Netherlands, Clarityn is currently not available on the market.

The concerned member states (CMS) involved in this procedure were Bulgaria, Germany, Estonia, Finland, Ireland, Lithuania, Latvia, Norway and Sweden.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

# II. QUALITY ASPECTS

## II.1 Introduction

Loratadine Accord are white or almost white, flat uncoated tablets debossed with “KH” on one side and a score line on the reverse. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The tablet contains as active substance 10 mg of loratadine.

The tablets are packed in clear polyvinylchloride (PVC)-aluminium blister packs in cardboard outer box.

The excipients are: lactose monohydrate, microcrystalline cellulose (E460), maize starch and magnesium stearate (E470b).

## II.2 Drug Substance

The active substance is loratadine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white

crystalline powder and is practically insoluble in water, freely soluble in acetone and methanol. Loratadine shows polymorphism. Polymorph form 1 is consistently produced.

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 general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is in line with the Ph.Eur. monograph for loratadine and the CEP, with additional requirements for particle size distribution and residual solvents. The specification is considered acceptable in view of the European guidelines.

Batch analytical data demonstrating compliance with the drug substance specification have been provided on two drug substance batches.

Stability of drug substance

As the retest period of the drug substance is not covered by the CEP, the MAH proposed its own retest period and storage temperature, supported by stability data. Stability data on the active substance have been provided for 14 production scaled batches stored at 25°C/60% RH (three to 60 months) and 40°C/75% RH (six months). The batches were stored in a double polyethylene bag (outer black) placed in either a fibre drum or a polyethylene drum.

For all batches at all storage conditions no clear changes in any of the tested parameters were observed over time. The proposed retest period of five years and storage condition “preserve in well closed containers, and store between 2-30°C” for the micronised drug substance are justified and accepted.

## II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. The development was based on the characteristics of the reference product Clarityn, experience of the manufacturer with comparable drug products and the manufacturing process, and excipients and drug substance characteristics. Compatibility of the loratadine drug substance with the excipients

has been adequately studied. The excipients are comparable to the reference product, but cellulose, microcrystalline was additionally added to provide hardness to the tablets. The Quality Control dissolution method has been adequately established and the discriminatory nature was demonstrated. A multimedia dissolution study at 3 pH's was performed on the bioequivalence study-test and -reference batches. Only the study performed at pH 1.2 (QC medium) showed comparable dissolution profiles since for both products more than 85% of the drug was dissolved within 15 minutes and the relative standard deviation values were less than 10%. Although the dissolution profiles at pH 4.5 and at pH 6.8 did not reflect similarity it was justified that this will have no impact on mouth taste, oesophagus passage, and gastro-intestinal tract degradation.

Manufacturing process

A standard manufacturing process is used which consists of raw material sifting, granulation, sizing, lubrication, blending, compression, and packing. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product has been provided for three full scaled batches.

Control of excipients

The excipients comply with Ph. Eur. requirements. These specifications are acceptable.

Microbiological attributes

The product complies with microbiological requirements of non-sterile dosage forms for oral administration according to Ph. Eur. 5.1.4, at release and during shelf-life.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, average weight, identification of loratadine, loss on drying, resistance to crushing, friability, dissolution, related substances, uniformity of dosage units, assay, and microbial enumeration. The release and shelf life acceptance criteria are identical. 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. The risk evaluation concerning the presence of nitrosamine impurities is considered complete and adequate. Based on the parameters assessed, no risks have been identified

Batch analytical data from three exhibit batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided on three exhibit batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC-aluminium blister packaging proposed for marketing. Stability data for the bulk packaging of tablets used for transport and storage, i.e. triple laminated aluminium bags were provided as well, stored at 25°C/60% RH (12 months) and 40°C/75% RH (six months). There were no

clear positive or negative trends for the tested parameters in any of the tested batches at both accelerated and long term storage conditions, and the results were all well within the proposed acceptance criteria. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

On basis of the data submitted, a shelf life was granted of two years. The labelled storage conditions are: "This medicinal product does not require any special storage conditions."

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The excipient lactose monohydrate is of ruminant animal origin. 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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Loratadine Accord has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

## III. NON-CLINICAL ASPECTS

### III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Loratadine Accord is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

### III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Clarityn which is available on the European market. Reference is made to the preclinical data obtained with the ERP. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

# IV. CLINICAL ASPECTS

## IV.1 Introduction

Loratadine is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required. For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

## IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Loratadine Accord 10 mg tablets (Accord Healthcare B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Clarityn tablets 10 mg (Bayer Hellas SA, Greece).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the test and reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence studies

*Design*

A single-dose, randomised, two-treatment, two-sequence, four period, fully replicate, comparative crossover bioequivalence study was carried out under fasted conditions in 60 healthy male subjects, aged 21 – 43 years. Each subject received a single dose (10 mg) of one of the two loratadine formulations twice. The tablet was orally administered with 240 ml water after a fasting period. There were four dosing periods, separated by a washout period of 14 days. Blood samples were collected pre-dose and at 0.167, 0.33, 0.50, 0.75, 1.00, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0 and 96.0 hours after administration of the products.

The design of the study is acceptable. Loratadine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of loratadine. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with the *Guideline on the investigation of bioequivalence*.

*Analytical/statistical methods*

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. Subjects receiving at least a test and reference treatment were included in the analysis. Subjects receiving at least two reference treatments were included in the estimation of the intra-subject variability for the maximum plasma

concentration ($C_{max}$). The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

*Results*
51 subjects completed all study periods. Three subjects were withdrawn on medical grounds, two subjects were withdrawn for protocol non-compliance and four subjects discontinued on their own accord. 58 subjects were eligible for pharmacokinetic analysis.

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

| Treatment N=58 | $AUC_{0-t}$ (µg.h/ml) | $AUC_{0-\infty}$ (µg.h/ml) | $C_{max}$ (µg/ml) | $t_{max}$ (h) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|
| **Test** | 22.4 ± 29.0 | 24.0 ± 34.9 | 6.4 ± 5.8 | 1.25 (0.75 – 3.0) | 17.4 ± 16.1 |
| **Reference** | 24.1 ± 34.1 | 25.8 ± 40.1 | 6.8 ± 5.8 | 1.25 (0.75 – 6.0) | 19.5 ± 19.2 |
| ***Ratio (90% CI)** | 0.95 (0.89 – 1.01) | - | 0.94 (0.87 – 1.02) | - | - |
| **CV (%)** | 32.6 | - | 37.0 | - | - |

**$AUC_{0-\infty}$** 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
**CV** coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for $AUC_{0-t}$ and $C_{max}$ are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Loratadine Accord is considered bioequivalent with Clarityn.

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).

## IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Loratadine Accord.

**Table 2. Summary table of safety concerns as approved in RMP**

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|---|---|
| Important identified risks | • Hypersensitivity (including anaphylaxis, angioedema, dyspnoea, pruritus, rash and urticaria)<br>• Abnormal hepatic function (including hepatitis and elevated hepatic enzymes and bilirubin)<br>• Convulsion<br>• Supraventricular tachyarrhythmia |
| Important potential risks | • Movement disorder (including psychomotor hyperactivity and restlessness)<br>• Hallucinations<br>• Abnormal behaviour in paediatric patients (including anger, agitation and aggression)<br>• Ocular dryness<br>• Skin disorders including Stevens-Johnson syndrome/toxic epidermal necrolysis<br>• Interaction with CYP3A4/CYP2D6 inhibitors |
| Missing information | • Use in children less than 2 years of age<br>• Use in lactation |

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

### IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the reference product Clarityn. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

## V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to two other drug products. For bridging the content, a comparison was provided with Loratadine 10 mg tablets (National United Kingdom (UK) license PL 25298/0019). The PL of the national UK license has been user tested while UK was part of the EU. For bridging the design and lay-out, reference was made to Solifenacin succinate Accord (DK/H/2339/001-002/DC).

The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

# VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Loratadine Accord 10 mg tablets has a proven chemical-pharmaceutical quality and is a generic form of Clarityn 10 mg tablets. Clarityn 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 Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Loratadine Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 October 2021.

## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Procedure number* | Scope | Product Information affected | Date of end of procedure | Approval/ non approval | Summary/ Justification for refuse |
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