LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Loratadin NET
loratadine

Asp no: 2020-1363

This module reflects the scientific discussion for the approval of Loratadin NET. The procedure was finalised on 2021-11-09. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Loratadin NET, 10 mg, tablet.

The active substance is loratadine. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Loratadin NET, 10 mg, tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Evolan Pharma AB, applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Clarityn, 10 mg, tablet, authorised in SE since 1989, with Bayer AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Clarityn, 10 mg, tablet, from UK, with Bayer as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of loratadine are well known. As loratadine is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Loratadin NET is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Loratadin NET from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Loratadine with the reference product Clarityn.

Pharmacokinetic properties of the active substance
Absorption: After oral administration, loratadine is rapidly and well absorbed. Concomitant ingestion of food can delay slightly the absorption of loratadine. There are no restrictions with respect to food in the SmPC of the originator.

Loratadine undergoes an extensive first pass metabolism, mainly by CYP3A4 and CYP2D6. The major metabolite – desloratadine – is pharmacologically active. Loratadine and desloratadine achieve maximum plasma concentrations (t_{max}) between 1-1.5 hours and 1.5-3.7 hours after administration, respectively.

Elimination: In healthy subjects, mean elimination half-lives in healthy adult subjects were 8.4 hours (range = 3 to 20 hours) for loratadine and 28 hours (range = 8.8 to 92 hours) for the major active metabolite. The bioavailability parameters of loratadine and of the active metabolite are dose proportional.

Study 17-VIN-0255
Methods
This was a randomised, single-dose, two-treatment, four-period, two-sequence, crossover, fully replicated, bioequivalence study conducted in 44 healthy volunteers, comparing Loratadine, 10 mg, tablet with Clarityn Allergy, 10 mg, tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of loratadine were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 22 Sep 2017 and 26 Oct 2017.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

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

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test (n=83)	**19.730 ± 25.8681**	**6.316 ± 4.6155**	**1.000 (0.67-2.67)**
Reference (n=87)	**21.039 ± 25.9765**	**7.117 ± 5.6658**	**1.000 (0.67-3.00)**
***Ratio (90% CI)**	**96.23 (89.49-103.48)**	**94.67 (85.95-104.28)**	**-**
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 plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study, Loratadin NET is considered bioequivalent with Clarityn.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Loratadin NET. Following the first round of assessment the applicant has updated the RMP in line with Rev2 of GVP V.

Safety specification

There are no items listed in the summary of safety specification which is appropriate considering that the safety profile of the product is well established and that only routine pharmacovigilance activities and risk minimisation measures apply.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan, version 0.1 signed 01 June 2021 is approved.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Loratadin Sandoz in procedure NL/H/0693/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Loratadin NET, is found adequate. There are no objections to approval of Loratadin NET, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

Loratadin NET, 10 mg, Tablet was approved in the national procedure on 2021-11-09.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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