IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Loratadine 10 mg Tablets
Loratadine
PA22871/008/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Loratadine 10 mg Tablet from Azure Pharmaceuticals Ltd on 23rd April 2021 for the symptomatic treatment of allergic rhinitis and chronic idiopathic urticarial.
This application for a marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC, referred to as application generic application and via the decentralised procedure. The Reference Member State for this procedure was transferred from the UK to Ireland (IE) at D120. There were no other Concerned Member States.

The European Reference Product is Clarityn Allergy 10mg Tablets from Bayer plc. (Date of marketing authorisation in the UK: 20 Sep 2011; marketing authorisation number PL PL 00010/0662).

Loratadine 10 mg Tablets are not subject to medical prescription, and subject to supply through pharmacies only.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website www.hpra.ie.

Name of the product	Loratadine 10 mg Tablet
Name(s) of the active substance(s) (INN)	Loratadine
Pharmacotherapeutic classification (ATC code)	R06AX13
Pharmaceutical form and strength(s)	10 mg Tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA22871/008/001
Marketing Authorisation Holder	Azure Pharmaceuticals Ltd
MRP/DCP No.	IE/H/1124/001/DC
Reference Member State	IE
Concerned Member State	UK

II. QUALITY ASPECTS

II.1. Introduction

This application is for Loratadine 10 mg Tablets

II.2 Drug substance

The active substance is loratadine, an established active substance not described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to European guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Loratadine 10 mg Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Clarityn (loratadine) 10 mg Tablets on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. The overview provided based on literature review is thus appropriate. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment

The applicant has not provided a full environmental risk assessment (ERA) in accordance with the guideline (CHMP/SWP/4447/00). Instead justification for the absence of a full ERA is supplied. Since Loratadine 10 mg Tablet 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.6 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of loratadine are well known. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. As loratadine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product.

For this generic application, the applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the test product loratadine 10 mg tablets is compared with the pharmacokinetic profile of the reference product Clarityn 10mg tablets.

A single-dose, randomised, two-period, two-treatment, four-period, two-sequence, cross-over bioequivalence study was carried out. Loratadine 10 mg tablets manufactured by the applicant and Clarityn Allergy 10 mg Tablets marketed by Bayer plc. Based on the pharmacokinetic parameters of active substance loratadine, the reference tablet Clarityn Allergy marketed by Bayer plc and test tablet Loratadine 10 mg Tablets are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Absorption
Loratadine is rapidly and well-absorbed. Concomitant ingestion of food can delay slightly the absorption of Loratadine but without influencing the clinical effect. The bioavailability parameters of Loratadine and of the active metabolite are dose proportional.

Distribution
Loratadine is highly bound (97% to 99%) and its active major metabolite desLoratadine (DL) moderately bound (73% to 76%) to plasma proteins. In healthy subjects, plasma distribution half-lives of Loratadine and its active metabolite are approximately 1 and 2 hours, respectively.

Biotransformation
After oral administration, Loratadine is rapidly and well absorbed and undergoes an extensive first pass metabolism, mainly by CYP3A4 and CYP2D6. The major metabolite-desLoratadine (DL)- is pharmacologically active and responsible for a large part of the clinical effect. Loratadine and DL achieve maximum plasma concentrations (Tmax) between 1–1.5 hours and 1.5–3.7 hours after administration, respectively.

Elimination
Approximately 40% of the dose is excreted in the urine and 42% in the faeces over a 10 day period and mainly in the form of conjugated metabolites. Approximately 27% of the dose is eliminated in the urine during the first 24 hours. Less than 1% of the active substance is excreted unchanged in active form, as Loratadine or DL. The 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.

Renal impairment
In patients with chronic renal impairment, both the AUC and peak plasma levels (Cmax) increased for Loratadine and its active metabolite as compared to the AUCs and peak plasma levels (Cmax) of patients with normal renal function. The mean elimination half-lives of Loratadine and its active metabolite were not significantly different from that observed in normal\ subjects. Haemodialysis does not have an effect on the pharmacokinetics of Loratadine or its active metabolite in subjects with chronic renal impairment.

Hepatic impairment
In patients with chronic alcoholic liver disease, the AUC and peak plasma levels (Cmax) of Loratadine were double while the pharmacokinetic profile of the active metabolite was not significantly changed from that in patients with normal liver function. The elimination half-lives for Loratadine and its active metabolite were 24 hours and 37 hours, respectively, and increased with increasing severity of liver disease.

Elderly
The pharmacokinetic profile of Loratadine and its active metabolite is comparable in healthy volunteers and in healthy geriatric volunteers.

IV.3 Pharmacodynamics

Pharmacotherapeutic group: antihistamines – H1 antagonist, ATC code R06AX13

Mechanism of action
Loratadine, the active ingredient in Loratadine 10 mg Tablets is a tricyclic antihistamine with selective, peripheral H1- receptor activity.

Pharmacodynamic effects
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 of electrocardiograms. Loratadine has no significant H2-receptor activity. It does not inhibit noradrenaline uptake and has practically no influence on cardiovascular function or on intrinsic cardiac pacemaker activity. Human histamine skin wheal studies following a single 10 mg dose has shown that the antihistamine effects are seen within 1-3 hours reaching a peak at 8-12 hours and lasting in excess of 24 hours. There was no evidence of tolerance to this effect after 28 days of dosing with Loratadine.

IV.4 Clinical Efficacy

The efficacy of loratadine in the proposed indications is established in clinical use. No new clinical efficacy studies are provided and none are required.

IV.5 Clinical Safety

The overall safety profile of loratadine is established and generally known. No new safety studies are provided and none are required.

The safety information in the SmPC and Package Leaflet are in line with those of the reference product.

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. Routine pharmacovigilance activities and routine risk minimisation activities are considered sufficient.

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:
- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV.6 Discussion on the clinical aspects

As this is a generic application under Article 10(1) of Directive 2001/83/EC, additional non clinical and clinical studies to demonstrate efficacy and safety are not required. The applicant has submitted the results of a suitable bioequivalence study, which has demonstrated the similarity of the test product for Loratadine 10 mg Tablet manufactured by the applicant against the reference product Clarityn 10mg Tablets marketed by Bayer plc., in accordance with the relevant guidance. The applicant has also submitted a clinical overview and summary of the evidence demonstrating the efficacy and safety of this product in clinical practice.

V. OVERALL CONCLUSIONS

Loratadine 10 mg Tablet manufactured by the applicant is a generic form of Clarityn Allergy 10mg (loratadine) Tablets marketed by Bayer plc. Loratadine is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

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

The HPRA, on the basis of the data submitted considered that Loratadine 10 mg Tablet demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

28.02.2026