IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Alimemazine tartrate 10 mg film-coated tablets
ALIMEMAZINE TARTRATE
PA0343/013/001

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 Alimemazine tartrate 10 mg film-coated tablets, from Key Pharmaceuticals Ltd on 18th December 2020 for second-line treatment in the symptomatic relief of urticaria and pruritus in adults.

This application for a marketing authorisation was submitted under Article 10(1) of Directive 2001/83/EC as amended and via the decentralised procedure with Ireland (IE) as the Reference Member State and the UK as sole Concerned Member State.

The European Reference Product is Vallergan 10mg Tablets from Winthorp Pharmaceutical Ltd t/a Zentiva. (Date of marketing authorisation in the UK: 01-03-1998; marketing authorisation number PL 17780/0464).

Alimemazine tartrate 10 mg film-coated tablets are subject to prescription which may be renewed.

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

Name of the product	Alimemazine 10 mg film-coated tablets
Name(s) of the active substance(s) (INN)	Alimemazine Tartrate
Pharmacotherapeutic classification (ATC code)	R06AD01
Pharmaceutical form and strength(s)	10 mg film-coated tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA0343/013/001
Marketing Authorisation Holder	Key Pharmaceuticals Ltd
MRP/DCP No.	IE/H/0888/001/DC
Reference Member State	IE
Concerned Member State	UK

II. QUALITY ASPECTS

II.1. Introduction

This application is for Alimemazine 10 mg film-coated tablets.

II.2 Drug substance

The active substance is alimemazine tartrate, an established active substance 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 and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each film-coated tablet contains 10 mg of alimemazine tartrate.

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 an 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 relevant European/ICH 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 the 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 Alimemazine 10 mg film-coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Alimemazine 10 mg film-coated tablets is a generic formulation of Vallergan 10 mg Tablets with the same active substance, alimemazine tartrate. No new preclinical data have been submitted.

Pharmacodynamic, pharmacokinetic and toxicological properties of alimemazine tartrate are well known. As alimemazine tartrate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment

Since Alimemazine 10 mg Film-coated Tablet is a generic product, it 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 non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. As alimenazine tartrate 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

This is a generic application submitted under article 10(1) of Directive 2001/83/EC.
Alimemazine tartrate is a well-known active substance with established efficacy and tolerability.
The content of the SmPCs approved during the decentralised procedure is in accordance with that accepted for the reference product.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Alimemazine Tartrate 10mg Film Coated Tablets (Lyrus life sciences Pvt. Ltd., Bangalore, India) is compared with the pharmacokinetic profile of the reference product Alimemazine Tartrate 10 mg Film Coated Tablets (Zentiva, One Onslow Street, Guildford, Surrey, GU1 4YS, UK).

The bioequivalence study was an open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study. Based on the pharmacokinetic parameters of the active substance alimemazine tartrate, the reference tablet and the test tablet are bioequivalent with regard to the rate and extent of absorption and fulfil the bioequivalence requirements as outlined in the CHMP Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr).

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

IV.2 Pharmacokinetics

Alimemazine Tartrate is well absorbed in the digestive tract. There is little information about blood levels, distribution and excretion in humans. The rate of metabolism and excretion of phenothiazines decreases in old age. Alimemazine and its metabolites are eliminated in urine as well as faeces.

IV.3 Pharmacodynamics

Alimemazine tartrate is a propyl-amino phenothiazine derivative with reduced central effects and enhanced antihistaminic and antipruritic effects.

IV.4 Clinical Efficacy

The clinical efficacy of alimemazine tartrate is well established. No additional efficacy clinical studies to demonstrate efficacy have been included in the application. This is appropriate for this type of application.

IV.5 Clinical Safety

The clinical safety of alimemazine tartrate is well established. No additional safety clinical studies to demonstrate safety have been included in the application. This is appropriate for this type of application.

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

Risk Management Plan

The applicant 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 Alimemazine 10mg film-coated tablets.
The revised RMP (version 04, dated 20/10/2020) is acceptable. Routine pharmacovigilance and routine risk minimisation activities are considered sufficient.
The applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Summary of Safety Concerns	
Important identified risks	Neuroleptic malignant syndrome
	Leukopenia and agranulocytosis
	Extrapyramidal side effects
	Use in patients with hepatic or renal dysfunction

	Seizures
	Cardiac arrhythmias
	Use in children < 3 years
	Postural hypotension in children, elderly or volume depleted patients
Important potential risks	Use in pregnancy and lactation
	Failure of thermoregulation
Missing Information	None

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.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5/11/2025.

IV.6 Discussion on the clinical aspects

The Applicant has submitted the results of a suitable bioequivalence study which has demonstrated the similarity of the test product Alimemazine Tartrate 10mg Film Coated Tablets (Lyrus life sciences Pvt. Ltd., Bangalore, India) to the reference product Alimemazine Tartrate 10 mg Film Coated Tablets (Zentiva, One Onslow Street, Guildford, Surrey, GU1 4YS, UK), in accordance with the relevant guidance. 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 also submitted a Clinical Overview and summary of the evidence demonstrating the efficacy and safety of this product in clinical practice.

V. OVERALL CONCLUSIONS

Alimemazine Tartrate 10mg Film Coated Tablets (Lyrus life sciences Pvt. Ltd., Bangalore, India) is a generic form of the reference product Alimemazine Tartrate 10 mg Film Coated Tablets (Zentiva, One Onslow Street, Guildford, Surrey, GU1 4YS, UK) which 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 Alimemazine Tartrate 10mg Film Coated Tablets (Lyrus life sciences Pvt. Ltd., Bangalore, India) demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

April 2021

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
MAH transfer	CRN00C5HM	SmPC section 7, 8, 10 Package Leaflet New MA Holder: Lexon Pharmaceuticals (Ireland) Limited New PA number: PA23176/009/001	N/A	16/04/2021