IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Trazodone Hydrochloride Azure 50 mg Hard Capsules
TRAZADONE HYDROCHLORIDE
PA22871/018/001

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.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Trazodone Hydrochloride Azure 50 mg & 100 mg Hard Capsules, from Azure Pharmaceuticals Ltd on 30th September 2022 for the treatment of anxiety, depression, and mixed anxiety & depression.

IE was the RMS for this procedure, with MT as CMS. The product is subject to medical prescription.

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

Name of the product	Trazodone Hydrochloride Azure 50 mg Hard Capsules
Name(s) of the active substance(s) (INN)	Trazodone Hydrochloride
Pharmacotherapeutic classification (ATC code)	N06AX05
Pharmaceutical form and strength(s)	50 mg Hard Capsules
Marketing Authorisation Number(s) in Ireland (PA)	PA22871/018/001
Marketing Authorisation Holder	Azure Pharmaceuticals Ltd
MRP/DCP No.	IE/H/1108/001/DC
Reference Member State	IE
Concerned Member State	MT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Trazodone Hydrochloride Azure 50 mg & 100 mg Hard Capsules.

II.2 Drug substance

The active substance is trazodone Hydrochloride, an established active substance described in the European Pharmacopoeia.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

The active substance is trazodone Hydrochloride is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The drug substance specification is considered adequate to control the quality in view of the route of synthesis and the various European guidelines.

Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition
50 mg capsules
Hard gelatin capsule shells of size '3' with violet opaque cap marked 'THC' with black colour and green opaque body marked '50' with black colour containing white to off white powder.

100 mg capsules

Hard gelatin capsule shells of size '2' with violet opaque cap marked 'THC' with black colour and fawn opaque body marked '100' with black colour containing white to off white powder.

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.
Compatibility between the active substance and the excipients is supported by stability studies. The packaging materials have shown to be suitable by acceptable stability studies.
The aim of the product development was to formulate essentially similar and bioequivalent generic formulation of the reference product Molipaxin capsules.
Bioequivalence studies were performed for demonstration of bioequivalence between the generic product and the reference product Molipaxin capsules. Comparative dissolution profiles between the generic Biobatch and the reference product used in BE studies are provided and demonstrate comparability for each dissolution medium proposed by the BE-Guideline. Based on the dissolution profiles of the Bio-batches an acceptable dissolution specification has been derived.

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.

Batch formulae have been provided for the manufacture of the product. In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation data on the product have been presented for three full-scale batches in accordance with the relevant European guidelines. The manufacturing 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 adequate to control the relevant parameters for the dosage form and they are and in line with ICH Q6A and Ph Eur requirements for tablets.

The tests and control limits in the specifications have been adequately justified and are considered appropriate for adequate quality control of the product. The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data 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 relevant Ph. Eur requirements and EU legislation on plastic materials and articles intended to come into contact with food.

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.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by EDQM have been provided for gelatine and compliance with the Note For Guidance on Minimising the Risk if Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products has been satisfactorily demonstrated

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 Trazodone Hydrochloride Azure 50 mg and 100 mg Hard Capsules.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is the same as that present in Molipaxin Capsules on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

Pharmacodynamic, pharmacokinetic and toxicological properties of trazodone are well known.

III.2 Ecotoxicity/environmental risk assessment

Since Trazodone Hydrochloride 50 mg and 100 mg Capsules 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.3 Discussion on the non-clinical aspects

As trazodone is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. The Overview provided by the applicant is therefore based on literature review. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

The content of the SmPC approved during the 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 is compared with the pharmacokinetic profile of the reference product.

The study was an open label, balanced, randomized, two treatment, two sequence, two period, cross-over, single-dose oral bioequivalence study of Trazodone Hydrochloride 100 mg Capsules (Test) of Medreich Limited, India and Trazodone hydrochloride 100 mg capsules (Reference) of Zentiva, One Onslow Street, Guildford, Surrey, GU1 4YS, UK in normal healthy, adult, human subjects under fed conditions.

Based on the pharmacokinetic parameters of active substance, the test and reference products 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 products are dose proportional. The pharmacokinetics of the active substance are linear in the therapeutic range. The results of the bioequivalence study performed therefore apply to the other strength.

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

IV.2 Pharmacokinetics

No new information has been provided, which is appropriate for applications of this type.

IV.3 Pharmacodynamics

No new information has been provided, which is appropriate for applications of this type.

IV.4 Clinical Efficacy

No new information has been provided, which is appropriate for applications of this type.

IV.5 Clinical Safety

No new information has been provided, which is appropriate for applications of this type.

Risk Management Plan (RMP)

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 Trazodone Hydrochloride 50 mg & 100 mg hard capsules.
The revised RMP (version 0.2 signed 09 May 2022) 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	• None
Important potential risks	• None
Missing information	• Use during pregnancy and lactation

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

The benefit-risk profile of this product is positive.

V. OVERALL CONCLUSIONS

Trazadone 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 trazadone demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

30.06.2027