IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Dosulepin Hydrochloride Azure 75 mg Coated Tablets
Dosulepin hydrochloride
PA22871/025/001

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 Dosulepin Hydrochloride Azure 75 mg Tablet, from Azure Pharmaceuticals Ltd on 14th April 2023 for the management of depression and associated anxiety.

This marketing authorization application for Dosulepin Hydrochloride Azure 75mg Tablets is being submitted as a generic application under Article 10.1 of Directive 2001/83/EC as amended.

This decentralised application concerns a generic version of Dosulepin Hydrochloride, under trade name Dosulepin Hydrochloride Azure 75 mg Coated Tablets.

The bioequivalence study was performed on Dosulepin Hydrochloride 75 mg Tablets and the reference product Prothiaden 75mg Coated Tablets. The originator product is Prothiaden 75mg Coated Tablets by Teofarma S.r.l., registered since January 1977 (PA1235/005/002).

With Ireland as the Reference Member State in this Decentralized Procedure, Azure Pharmaceuticals Ltd is applying for the Marketing Authorisations for Dosulepin Hydrochloride Azure 75mg Tablets in IE and MT.

No Scientific Advice was given as part of this submission.

The product will be subject to medical prescription that may not 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	Dosulepin Hydrochloride Azure 75 mg Tablet
Name(s) of the active substance(s) (INN)	DOSULEPIN HYDROCHLORIDE
Pharmacotherapeutic classification (ATC code)	N06AA16
Pharmaceutical form and strength(s)	75 mg Tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA 22871/025/001
Marketing Authorisation Holder	Azure Pharmaceuticals Ltd
MRP/DCP No.	IE/H/1183/001/DC
Reference Member State	IE
Concerned Member State	MT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Dosulepin Hydrochloride Azure 75 mg Tablet.

II.2 Drug substance

The active substance is dosulepin hydrochloride, a 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

Dosulepin Hydrochloride Azure 75mg Tablet contains 75mg of the active substance dosulepin hydrochloride.

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)

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 dosage form, 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 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 Dosulepin Hydrochloride Azure 75mg Tablet.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Prothiaden 75mg Coated Tablets 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.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since Dosulepin Hydrochloride Azure 75 mg tablets is a generic product, it will not lead to an increased exposure to the environment. A justification for the absence of environmental risk assessment studies is therefore acceptable.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Dosulepin Hydrochloride are well known. As Dosulepin Hydrochloride is a widely used, well-known active substance, the applicant has not provided additional nonclinical studies and further studies are not required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Dosulepin Hydrochloride 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 Prothiaden 75mg Coated Tablets marketed by MAH Teofarma S.r.l.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Dosulepin 75 mg Tablets is compared with the pharmacokinetic profile of the reference product Prothiaden 75mg Coated Tablets.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Dosulepin 75 mg Tablet of Medreich Limited., India, was compared to the reference product Prothiaden Tablet 75 mg of Teofarma S.r.l., Italy.

Bioequivalence has been shown in accordance with the Bioequivalence Guideline CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **. The 90% confidence interval for the ratio of the test and reference products are contained within the acceptance interval of ≥80.00% and ≤125.00% for the parameters: C_{max} 99.07 (90.21%-108.80%) and AUC_{0-72} 99.38 (92.42%-106.87%).

Treatment	**AUC_{0-72}** **(hr*ng/mL)**	**C_{max}** **ng/ml**	**t_{max}** **h**
Test	925.591 ± 563.0390 (60.83%)	51.198 ± 27.5470 (53.81%)	4.250 (2.50 - 8.00)
Reference	932.862 ± 605.9812 (64.96%)	51.481 ± 29.7906 (57.87%)	4.500 (1.50 - 8.00)
***Ratio (90% CI)**	99.38 (92.42%-106.87%)	99.07 (90.21%-108.80%)	-
AUC_{0-72} Area under the plasma concentration curve at 72 h. **C_{max}** Maximum plasma concentration **t_{max}** Time until Cmax is reached			

Based on the pharmacokinetic parameters of active substance, the reference tablet Prothiaden Tablet 75 mg marketed by Teofarma S.r.l., Italy and test tablet Dosulepin 75 mg Tablet 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 content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Prothiaden Tablet 75 mg marketed by Teofarma S.r.l., Italy.

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

IV.2 Pharmacokinetics

No additional studies investigating the pharmacokinetic effects of Dosulepin Hydrochloride Azure 75mg Tablets were conducted which is acceptable for this generic application.

Dosulepin is readily absorbed from the gastrointestinal tract and extensively metabolised in the liver. Metabolites include northiaden, dosulepin-S-oxide and northiaden-S-oxide. Dosulepin is excreted in the urine, mainly in the form of metabolites; appreciable amounts are also excreted in the faeces. A half-life of about 50 hours has been reported for dosulepin and its metabolites.

IV.3 Pharmacodynamics

No additional studies investigating the pharmacodynamic effects of Dosulepin Hydrochloride Azure 75mg Tablets were conducted which is acceptable for this generic application.

For further information see the SmPCs Section 5.1.

IV.4 Clinical Efficacy

No new Applicant-generated efficacy studies or bibliographical data were submitted in this application.

IV.5 Clinical Safety

No new Applicant-generated safety studies or bibliographical data were submitted in this application.

The reference product for this application, Prothiaden Tablet 75 mg has been on the market in IE since January 1977. Therefore, dosulepin hydrochloride has an established clinical safety profile.

During the pivotal bioequivalence study, both the test and reference products were well tolerated by the subjects. Six adverse events occurred during the study. Four subjects reported an adverse event after administration of test product and two subjects with the reference product. All AEs were reported as mild in severity, requiring no treatment or follow-up. No serious adverse event occurred during conduct of the study. No additional safety data was generated during the BE study that contributes/alters the known safety profile of dolsulepin.

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 Dosulepin Hydrochloride 75 mg Coated Tablets.

Safety specification

Important Identified Risk	• None
Important Potential Risk	• None
Missing Information	• None

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 0.3 signed 21st July 2022 is considered acceptable.

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 proposed renewal date is five years after end of procedure.

IV.6 Discussion on the clinical aspects

This marketing authorization application for Dosulepin Hydrochloride Azure 75mg Tablets is being submitted as a generic application under Article 10.1 of Directive 2001/83/EC as amended.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Dosulepin 75 mg Tablets is compared with the pharmacokinetic profile of the reference product Prothiaden 75mg Coated Tablets.

The 90% confidence interval for the ratio of the test and reference products were reported within the acceptance interval of ≥80.00% and ≤125.00% for the parameters: Cmax 99.07 (90.21%-108.80%) and AUC0-72 99.38 (92.42%-106.87%).

Based on the pharmacokinetic parameters of active substance, the reference tablet Prothiaden Tablet 75 mg marketed by Teofarma S.r.l., Italy and test tablet Dosulepin 75 mg Tablet are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Dosulepin Hydrochloride is a well-known active substance with established efficacy and tolerability. Dosulepin Hydrochloride was first used clinically in 1962 and has been marketed for several decades. The reference product for this application, Prothiaden Tablet 75 mg has been on the market in IE since 1977. The safety results reported in the bioequivalence study were found to be consistent with the known safety profile of Dosulepin Hydrochloride and no other safety studies were submitted in support of this study which is acceptable.

V. OVERALL CONCLUSIONS

Dosulepin Hydrochloride Azure 75mg Tablets is a generic form of Prothiaden 75mg Coated Tablets. Prothiaden 75mg Coated Tablets 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 Dosulepin Hydrochloride Azure 75mg Tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

The proposed renewal date is five years after end of procedure.