**IPAR**

**Public Assessment Report for a**
**Medicinal Product for Human Use**

Scientific Discussion

Dosulepin Hydrochloride 25 mg Hard Capsules
Dosulepin hydrochloride
PA22871/013/001

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 Dosulepin Hydrochloride 25 mg Capsule, hard, from Azure Pharmaceuticals Ltd on 5th August 2022 for the management of depression and associated anxiety.

This is a generic product and the legal basis for this application is article 10 (1) of Directive 2001/83/EC as amended.

HPRA was RMS in this decentralised procedure and Malta was a CMS.

This medicinal product is subject to prescription, which may not be renewed.

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

| | |
|---|---|
| Name of the product | Dosulepin Hydrochloride 25 mg Capsule, hard |
| Name(s) of the active substance(s) (INN) | Dosulepin hydrochloride |
| Pharmacotherapeutic classification (ATC code) | N06AA16 |
| Pharmaceutical form and strength(s) | 25 mg Capsule, hard |
| Marketing Authorisation Number(s) in Ireland (PA) | PA22871/013/001 |
| Marketing Authorisation Holder | Azure Pharmaceuticals Ltd |
| MRP/DCP No. | IE/H/1154/001/DC |
| Reference Member State | IE |
| Concerned Member State | MT |

## II. QUALITY ASPECTS

### II.1. Introduction

This application is for Dosulepin Hydrochloride 25 mg Capsule, hard.

### II.2 Drug substance

The active substance is dosulepin hydrochloride, 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 capsule contains 25mg of 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 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 capsules, 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.7 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.8 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.

Certificates of suitability issued by EDQM have been provided for dosulepin hydrochloride and compliance with the Note For Guidance on Minimising the Risk of 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 Dosulepin Hydrochloride 25 mg Capsule, hard.

## III. NON-CLINICAL ASPECTS

**III.1 Introduction**

This active substance is a generic formulation of Prothiaden 25 mg capsule on the European market. No new preclinical data have been submitted. 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 25 mg Capsule is a generic product, it will not lead to an increased exposure to the environment. Additional studies on environmental risk assessment are therefore not deemed necessary.

**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. A nonclinical overview based on literature review was provided and is acceptable for this type of generic application. Nonclinical sections of the SmPC are in line with the originator, which is acceptable.

## IV. CLINICAL ASPECTS

**IV.1 Introduction**

Dosulepin 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 25 mg hard capsules marketed by 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 Hydrochloride 25 mg Capsule, hard, is compared with the pharmacokinetic profile of the reference product Prothiaden 25 mg hard capsules.
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasting conditions. Dosulepin Hydrochloride 25 mg Capsule, hard, Azure Pharmaceuticals Ltd , was compared to the reference product Prothiaden Capsule 25 mg of Teofarma S.R.L.,
Based on the pharmacokinetic parameters of active substance, the reference Prothiaden Capsule 25 mg and test product Dosulepin Hydrochloride 25 mg hard capsule 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**

The pharmacokinetic profile of dosulepin is well characterised.

*Absorption:* 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.

Bioavailability is in the order of 30% after first - pass hepatic metabolism.

$T_{max}$ occurs with 2 to 4 hours.

*Elimination:* The elimination half -life is biphasic with the first phase being about 15 -18 hours. A mean whole body elimination half-life of about 50 hours has been reported for dosulepin and its metabolites.

**IV.3 Pharmacodynamics**

Dosulepin is a tricyclic antidepressant which acts by inhibiting the re-uptake of monoamine neurotransmitters into presynaptic neurone at central nervous system, so producing a clinical antidepressant effect.

Dosulepin, in common with other tricyclics, inhibits the reuptake of noradrenaline and 5- hydroxytryptamine, with a significantly greater action on the uptake of noradrenaline. In addition, dosulepin inhibits the neuronal uptake of dopamine.
As a consequence of its effects on monoamine levels, dosulepin appears to produce adaptive changes in the brain.

Similarly to other tricyclic antidepressants, it has anticholinergic, antihistaminic and anti-α1 adrenergic effects.

**IV.4 Clinical Efficacy**

No clinical efficacy data are provided as this is a generic application.

**IV.5 Clinical Safety**

Safety review of the bioequivalence study provided did not raise any new or significant safety concerns.
As this is a generic application, no other clinical safety data are required.

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

**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 Dosulepin Hydrochloride 25 mg Hard Capsules.

Routine risk minimization 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 table of safety concerns as approved in RMP

| | |
|---|---|
| Important identified risks | • None |
| Important potential risks | • None |
| 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.

**IV.6 Discussion on the clinical aspects**

As this approval concerns a generic application, there are no new efficacy or safety studies required, as the applicant can refer to the data of the reference medical products. . Instead, the demonstration of bioequivalence is pivotal to the assessment and has already been described.

**V. OVERALL CONCLUSIONS**

Dosulepin Hydrochloride 25 mg Capsule, hard is a generic form of Prothiaden Capsule 25 mg (Teofarma S.R.L.), 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 Dosulepin Hydrochloride 25 mg Capsule, hard demonstrated bioequivalence with the reference product, as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

**VI. REVISION DATE**

01.06.2027