IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Torasemide 5 mg Tablets
Torasemide
PA22871/014/002

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 application for Torasemide 5mg Tablets from Azure Pharmaceuticals Ltd on 11th October 2024.

Torasemide 5mg Tablets have the following indications:
Oedema due to congestive heart failure; hepatic, pulmonary or renal oedema.

The application was submitted via decentralised procedure under Article 10(1) of Directive 2001/83/EC, with IE as RMS and MT as CMS.

The legal status of the product is prescription only.

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

Proposed name of the medicinal product in the RMS	Torasemide 5mg Tablets
Name of the drug substance (INN name):	Torasemide
Pharmaco-therapeutic group (ATC Code):	C03CA04 Torasemide
Pharmaceutical form(s) and strength(s):	5mg
Reference Number(s) for the Decentralised Procedure	IE/H/1155/002/DC
Reference Member State:	IE
Concerned Member States:	MT
Legal basis of application:	Article 10 (1) Generic

II. QUALITY ASPECTS

II.1. Introduction
This application is for Torasemide 5mg and 10mg Tablets.

II.2 Drug substance
The active substance is torasemide, 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

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(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 Torasamide 5mg and 10mg Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Torem tablets on the European market. No new preclinical data have been submitted.

III.2 Ecotoxicity/environmental risk assessment

Since Torasemide 5 mg and 10 mg Tablets 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

Pharmacodynamic, pharmacokinetic and toxicological properties of torasemide are well known. As torasemide is a widely used, well-known active substance, the applicant has not provided additional studies. This is acceptable for this type of application. Overview based on literature review is, thus, appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Torasemide 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, Torem tablets of Meda Pharmaceuticals Ltd. This product was originally authorised in Sweden in 1999 and so is an appropriate reference product for this application.

For this generic application, the applicant has submitted a bioequivalence study in which the pharmacokinetic profiles of the Torasemide 20 mg tablets of Medreich Limited., India and Torem® 10 mg (2 × 10 mg) tablets of Meda Pharmaceuticals Ltd. were compared in normal healthy, adult, human subjects under fasting conditions.

Based on the pharmacokinetic parameters of the test and reference products, Torasemide 20 mg tablets are bioequivalent to Torem 10 mg (2x10 mg) tablets with regard to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the CHMP Guideline on the Investigation of Bioequivalence.

A biowaiver for an *in vivo* bioequivalence study was requested for the 5 mg and 10 mg tablet strengths. Torasemide 5 mg, and 10 mg tablets are dose proportional with the 20 mg tablets. The pharmacokinetics of the active substance are linear in the range from 2.5mg to 200 mg. The drug products are manufactured by the same process and appropriate *in vitro* dissolution data have been provided. The applicant's justification for a strength based biowaiver exemption for *in vivo* bioequivalence studies for the 5mg and 10 mg tablets meets the criteria detailed in CHMP Guideline on the Investigation of Bioequivalence and is accepted. The results of the bioequivalence study performed with the 20mg strength therefore apply to the 5mg and 10 mg strengths..

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

IV.2 Pharmacokinetics

Introduction

The pharmacokinetic profile of torasemide is well characterised and is summarised below.

Absorption
Torasemide is absorbed rapidly and almost completely after oral administration, and peak serum levels are reached after one to two hours.

Serum protein binding
More than 99% of torasemide is bound to plasma proteins.

Distribution
The apparent distribution volume is 16 litres.

Metabolism
Torasemide is metabolised to three metabolites, M1, M3 and M5 by stepwise oxidation, hydroxylation or ring hydroxylation. Further metabolites (M2 and M4) have been found in animal experiments, but not in humans.

Elimination
The terminal half-life of torasemide and its metabolites is three to four hours in healthy subjects. Total clearance of torasemide is 40ml/min and renal clearance about 10ml/min. About 80% of the dose administered is excreted as torasemide and metabolites into the renal tubule - torasemide 24%, M1 12%, M3 3%, M5 41%.

In patients with congestive heart failure and disorders of liver function, the elimination half-lives of torasemide and metabolite M5 are only slightly increased compared with those in healthy volunteers. The amounts of torasemide and metabolites excreted in the urine are similar to those in healthy subjects; therefore no accumulation is to be expected.

In the presence of renal failure, elimination half-life of torasemide is unchanged.

IV.3 Pharmacodynamics

Torasemide is a loop diuretic which acts on the thick ascending limb of the loop of Henle to promote rapid and marked excretion of water, sodium and chloride. Its major site of action is from the luminal side of the cell. Torasemide has a long duration of action, allowing once daily administration. Torasemide appears to promote excretion of potassium and calcium to a lesser extent than other similar loop diuretics.

IV.4 Clinical Efficacy

The clinical efficacy of torasemide is well established. No additional clinical studies to demonstrate efficacy have been included in the application and none are required for a generic application.

IV.5 Clinical Safety

The clinical safety of torasemide is well established. No additional clinical studies to demonstrate safety have been included in the application and none are required for a generic application. The safety information in the Summary of Product Characteristics 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 relating to Torasemide 5mg and Torasemide 10mg Tablets.

Safety specification

Important Identified Risks	None
Important Potential Risks	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.

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 is 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

Acceptable.

V. OVERALL CONCLUSIONS

Torasemide 5mg Tablets and Torasemide 10 mg Tablets are generic forms of the reference medicineal product Torem tablets of Meda Pharmaceuticals Ltd., authorised in Sweden. Torem 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 HPRA, on the basis of the data submitted considered that Torasemide 5mg Tablets and Torasemide 10 mg Tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

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

VI. REVISION DATE

19th July 2029