LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Torasemid Zentiva
(torasemide (anhydrous))

SE/H/2278/01-04/DC

This module reflects the scientific discussion for the approval of Torasemid Zentiva. The procedure was finalised on 2023-09-12. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Torasemid Zentiva, 2,5 mg, 5 mg, 10 mg, 20 mg, tablet.

The active substance is torasemide (anhydrous). A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The applications for Torasemid Zentiva, 2,5 mg, 5 mg and 10 mg, Tablet, are generic applications submitted according to Article 10(1) of Directive 2001/83/EC, while the application for Torasemid Zentiva, 20 mg, Tablet, is a hybrid application submitted according to Article 10(3) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and with the following concerned member states (CMS):

Torasemid Zentiva, 2,5 mg	PL
Torasemid Zentiva, 5 mg	BG, EE, LT, LV, PL
Torasemid Zentiva, 10 mg	BG, EE, IT, LT, LV, PL
Torasemid Zentiva, 20 mg	BG, PL

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Torem, 5 mg, tablet, authorised in Sweden since 1993, with Meda AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Dilutol, 10 mg, tablet, from Spain with Meda Pharma S.L. as marketing authorisation holder.

European Reference Product (ERP)

A European Reference Product is used in CMS EE, LT, LV and PL:

Torasemid Zentiva, 2,5 mg	Torem, 2,5 mg, tablet, authorised 1993, Roche AB*
Torasemid Zentiva, 5 mg	Torem, 5 mg, tablet, authorised 1993, Meda AB
Torasemid Zentiva, 10 mg	Torem, 10 mg, tablet, authorised 1995, Meda AB
Torasemid Zentiva, 20 mg	Torem, 10 mg, tablet, authorised 1995, Meda AB

* This MA was deregistered by Roche AB in 2007, Meda AB subsequently acquired the remaining Torem MAs in 2008.

The justification to use these products is based on the RMS's own files.

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of torasemide are well known. As torasemide is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Torasemid Zentiva is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Torasemid Zentiva from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted a bioequivalence study comparing Torasemid Zentiva 20 mg, tablet with the reference product Dilutol 10 mg, tablet.

<u>Pharmacokinetic properties of the active substance</u>
Absorption: Systemic bioavailability after oral administration is 80-90%. Torasemide is rapidly and almost completely absorbed after oral administration, and peak serum levels are reached after 1-2 hours. There are no restrictions with respect to food in the SmPC of the originator.

Linearity: The pharmacokinetics of torasemide are linear (or possibly slightly more than dose-proportional) within the dose range 2.5 – 40 mg.

Elimination: Torasemide is eliminated mainly by hepatic metabolism, with only around 25 % of torasemide being excreted unchanged into the urine. The terminal half-life is 3-4 hours in healthy subjects.

Bioequivalence study 2021-5077

Methods

This was a single-dose, two-way crossover study conducted in 30 healthy volunteers (of whom 28 completed the study) under fasting conditions. One tablet of Torasemid Zentiva 20 mg was compared with two tablets of Dilutol 10 mg (by MEDA Pharma S.L., purchased from the Spanish market). Blood samples for concentration analysis were collected pre-dose and up to 24 hours after drug administration. Plasma concentrations of torasemide were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 11 November 2021 and 08 January 2022.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for torasemide, n=28.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**8087.0 ± 1944.8**	**3903.9 ± 831.5**	**0.75 (0.50-1.75)**
Reference	**8057.8 ± 2034.0**	**3738.9 ± 902.8**	**0.75 (0.50-1.25)**
***Ratio (90% CI)**	**100.51 (98.31-102.77)**	**104.75 (99.32-110.47)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver is sought for the additional tablet strengths of 2.5 mg, 5 mg and 10 mg.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation are in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). The bioanalytical method has been adequately validated.

Based on the submitted bioequivalence study, Torasemid Zentiva 20 mg tablet is considered bioequivalent with two tablets of Dilutol 10 mg.

From a pharmacokinetic perspective, absence of studies with the additional strengths of 2.5, 5 and 10 mg is acceptable, as plasma AUC of torasemide increases in a dose-proportional (or slightly more than dose-proportional) manner within the dose range 2.5 - 40 mg.
For quality aspects of biowaiver, see Quality section above.

Pharmacodynamics/Clinical efficacy/Clinical safety

The applications for Torasemid Zentiva, 2,5 mg, 5 mg and 10 mg are generic applications while the application for Torasemid Zentiva, 20 mg, is a hybrid application.

A clinical overview written by Tomáš Hauser April 2022 was provided. The scientific literature has been reviewed up to 2021.
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted.

Pharmacodynamics
The pharmacodynamic properties of torasemide were adequately described in the clinical overview.

Clinical efficacy
Since bioequivalence with the originator product is demonstrated, additional data is not necessary for Torasemid Zentiva, 2,5 mg, 5 mg and 10 mg for the treatment of essential hypertension (2.5 mg and 5 mg strength), congestive heart failure (5-10 mg); hepatic or renal oedema (10 mg), applied according to article 10(1), i.e, generics.

Marketing authorisation for Torasemid Zentiva 20 mg was applied according to article 10(3), i.e., a hybride application, as the reference product is not approved in this strength. Nevertheless, the posology of the reference product includes dose recommendations up to, and over, 20 mg. Bioequivalence is shown between Torasemid Zentiva 20 mg and Dilutol (reference product for bioequivalence studies) 2 x 10 mg allowing for bridging to data for the reference product. Furthermore, the Applicant has provided bibliographic support for the use of torasemide 20 mg in the treatment of congestive heart failure, hepatic oedema and renal oedema. This is considered sufficient and no additional studies are considered warranted.

Clinical safety
The Applicant has provided a summary of safety for short- and long-term use of doses up to, and over, 20 mg daily for different indications. No new and unexpected safety issue were reported for doses over 10 mg. i.e., the hybrid part of the application. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary

There are no objections to approval of Torasemid Zentiva concerning efficacy and safety.

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 Torasemid Zentiva.

Safety specification
No RMP is in place for Torem. The safety concerns initially proposed for Torasemide Zentiva are either already reflected in the SmPC or well-known adverse events of loop diuretics. Therefore, the Summary of safety concerns is left empty.

Table 2: Summary of safety concerns RMP version 0.2 (8 December 2022)

Summary of safety concerns	
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.

Summary of the RMP
The submitted Risk Management Plan, version 0.2 signed 8 December 2022 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The applications for Torasemid Zentiva, 2,5 mg, 5 mg and 10 mg, tablet, are generic applications submitted according to Article 10(1) of Directive 2001/83/EC, while the application for Torasemid Zentiva, 20 mg, tablet, is a hybrid application submitted according to Article 10(3) of Directive 2001/83/EC.

The reference product for the 20 mg strength has been deregistered. Nevertheless, the posology of the reference product includes dose recommendations up to, and over, 20 mg.
The Applicant has provided a summary of safety for short- and long-term use of doses up to, and over, 20 mg daily for different indications. No new and unexpected safety issue were reported for doses over 10 mg. i.e., the hybrid part of the application.

The quality of the generic product, Torasemid Zentiva, is found adequate. There are no objections to approval of Torasemid Zentiva, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Torasemid Zentiva, 2,5 mg, 5 mg, 10 mg, 20 mg, tablet was positively finalised on 2023-09-12.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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