LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Bendozid
(bendroflumethiazide)

This module reflects the scientific discussion for the approval of Bendozid. The procedure was finalised at 2025-09-11. 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, the Member States have agreed to grant a marketing authorisation for Bendozid, 2,5 mg, 5 mg, Tablet.

The active substance is bendroflumethiazide. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Bendroflumethiazide is a thiazide diuretic which reduces the reabsorption of electrolytes from the renal tubules, thereby increasing the excretion of sodium and chloride ions, and consequently, of water. This mechanism results in reduced blood volume and pressure, making bendroflumethiazide useful for the treatment of hypertension and oedema.

In addition, thiazides have a long-term hypotensive effect, most likely due to a reduction in peripheral resistance of the blood vessels. For the treatment of hypertonia, bendroflumethiazide may be used either alone or in combination, as it enhances the effects of other antihypertensive agents.

The excretion of potassium and bicarbonate ions are less affected than that of sodium and chloride, while the excretion of calcium in urine is significantly reduced. Through their effect on calcium excretion, thiazides inhibit the formation of calcium oxalate and phosphate crystals as well as their aggregation and stone growth.

The claimed indications are:
- Treatment of oedema, associated with heart failure or of other origin;
- Prophylactic treatment of recurrent idiopathic nephrolithiasis;
- Treatment of hypertension

in adult patients.

II.2 General comments on the submitted dossier

The application for Bendozid, 2.5 mg, 5 mg, tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Salures, 5 mg, tablet, authorised in Sweden since 1961, with Pfizer AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Salures, 5 mg, tablet, from Sweden with Pfizer AB as marketing authorisation holder.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The MPA has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the European Community, the MPA has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP aspects
A statement on the application of appropriate GCP standards in the submitted study has been provided. No issues regarding GCP have been identified. The clinical facility was inspected by the Austrian authority (BASG) in 2011, without any critical findings. The clinical study site had a valid certification to conduct clinical studies 2016-2019 by the Hungarian authority (OGYÉI). The analytical facility was inspected by the German authority (BfArM) in 2017, without any critical findings. No inspection of the submitted bioequivalence study is needed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

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.

Drug 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.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of the active substance bendroflumethiazide are well known. As bendroflumethiazide is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
The applicant was asked to provide an ERA document in line with current version of the guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*).

The applicant was not able to identify any pre-existing ERA or any usable literature data for Bendroflumethiazide and an updated Phase II ERA should be submitted within two years after end of the current procedure. A commitment letter stating that the applicant commits to submitting an updated ERA in line with the new ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*) within two years after end of this procedure has been submitted.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Bendozid (bendroflumethiazide) with the reference product Salures.

Pharmacokinetic properties of the active substance
Absorption: Bendroflumethiazide has been reported to be completely absorbed. Following an oral dose of bendroflumethiazide maximal plasma concentrations occur at approximately 2 hours.

The pharmacokinetics of bendroflumetiazide is not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator.

Linearity: The pharmacokinetics of bendroflumethiazide is linear within the dose range 2.5-5 mg (Schäfer-Korting and Mutschler, 1982).

Elimination: The terminal half-life is 9 hours.

Study 553B16
Methods
This was a single-dose, two-way crossover study conducted in 24 healthy volunteers, comparing Bendozid, 5 mg, tablet with Salures, 5 mg, tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of bendroflumethiazide were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2017-02-03 and 2017-02-17.

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 bendroflumethiazide, n=24.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**317.495 ± 74.9796**	**53.555 ± 15.7371**	**1.50 (1.00-4.00)**
Reference	**305.567 ± 55.9456**	**49.774 ± 10.3528**	**1.88 (1.00-5.00)**
***Ratio (90% CI)**	**102.70 (96.37-109.44)**	**105.19 (96.44-114.74)**	**-**

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 was sought for the additional strength of 2.5 mg.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were 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 was adequately validated.

Based on the submitted bioequivalence study, Bendozid is considered bioequivalent with Salures.

Absence of studies with the additional strength of 2.5 mg is acceptable, as all conditions for biowaiver for additional strength(s), as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr) are fulfilled and since the pharmacokinetics of bendroflumethiazide is linear between 2.5 mg and 5 mg.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system
Proposed MAH: ExtractumPharma Co. Ltd.
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the MPA considers the Summary acceptable.

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 Bendozid.

Bendozid tablets of the MAA are generic versions of the Salures tablets. Hence, the safety concerns are essentially the same as those of the reference product Salures. However, in this case the reference product has been on the market since the sixties and there is no RMP available for the reference product.

Part II Safety specification
No safety concerns are presented by the applicant; neither is any condition of missing information identified. This is endorsed.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed, which is endorsed.

Part VI Summary of the RMP
The applicant has adequately summarised the RMP.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.1 signed 30.09.2024, is found 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.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

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.

Renewal date
The renewal date will be 5 years after approval date.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Bendozid, is found adequate. There are no objections to approval of Bendozid, 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 ratio is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments

Description	Due date
An updated ERA in line with the new ERA guideline *(EMEA/CHMP/SWP/4447/00 Rev. 1-Corr.*)* should be submitted post-approval.	Within 2 years following end of current procedure.

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available on the Swedish MPA website.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved SmPC is available on the Swedish MPA website.

V.4.2 Assessment of User Testing

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Bendroflumetiazid Alternova 2.5 mg, 5 mg tablets (SE national procedure 5.4.1-2013-33084) for the content, and to Amitriptyline Expharma 25 mg film-coated tablets (NL License RVG: 117611) for the design/layout/forma.

The bridging report submitted by the applicant has been found acceptable.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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