IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Bendroflumethiazide 2.5mg Tablets
Bendroflumethiazide
PA22749/021/001

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.

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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 for Bendroflumethiazide 2.5 mg & 5 mg Tablets, from Bristol Laboratories Limited on 23rd of November 2018.

For the treatment of oedema and hypertension. Bendroflumethiazide may also be used to suppress lactation.

This application for a national marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a generic application. Bendroflumethiazide 2.5 mg & 5 mg Tablets are generic versions of Aprinox 2.5mg and 5mg tablets of Waymade PLC.

Bendroflumethiazide 2.5 mg & 5 mg Tablets are prescription only, for supply through pharmacy and for promotion to healthcare professionals only.

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	Bendroflumethiazide
Name(s) of the active substance(s) (INN)	BENDROFLUMETHIAZIDE
Pharmacotherapeutic classification (ATC code)	C03AA01
Pharmaceutical form and strength(s)	2.5 mg & 5 mg
Marketing Authorisation Number(s) in Ireland (PA)	PA1240/028/001-002
Marketing Authorisation Holder	Bristol Laboratories Limited

II. QUALITY ASPECTS

II.1. Introduction

This application is for Bendroflumethiazide 2.5 mg and 5 mg tablets.

II.2 Drug substance

The active substance is Bendroflumethiazide, 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 tablet contains either 2.5 mg Bendroflumethiazide or 5 mg Bendroflumethiazide.
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 guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with respective Ph. Eur. monographs.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets, 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 Bendroflumethiazide 2.5mg and 5mg tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Aprinox 2.5mg and 5mg 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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

III.5 Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment has not been performed as this product is intended for generic substitution and therefore will not result in an increase of risk to the environment during use, storage and disposal.

IV. CLINICAL ASPECTS

IV.1 Introduction

Bendroflumethiazide is a well-known active substance with established efficacy and tolerability.

The content of the SmPCs approved during the national procedure is in accordance with that accepted for the reference products Aprinox 2.5mg and 5mg tablets of Waymade PLC (previously Boots PLC). The reference products have been authorised in the UK since September 1986 and so the 10-year period of data exclusivity has expired.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Bendroflumethiazide 2.5mg is compared with the pharmacokinetic profile of the reference product Aprinox 2.5mg.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Bendroflumethiazide 2.5mg tablet, Bristol Laboratories Ltd, was compared to the reference product Aprinox 2.5mg tablet, Waymade PLC. Based on the pharmacokinetic parameters of the active substance bendroflumethiazide, the reference tablet Aprinox 2.5mg tablet marketed by Waymade PLC and test tablet Bendroflumethiazide 2.5mg are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the CHMP Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr).

The 5mg tablets are dose proportional with the 2.5mg tablets. The pharmacokinetics of the active substance bendroflumethiazide are linear in the range 2.5mg-5mg range. The applicant has provided justification for a biowaiver for the 5mg strength and therefore the results of the bioequivalence study performed with the 2.5mg tablet also apply to the 5mg strength.

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

IV.2 Pharmacokinetics

Absorption: Bendroflumethiazide has been reported to be completely absorbed from the gastrointestinal tract and it is fairly extensively metabolised.

Distribution: Bendroflumethiazide is more than 90% bound to plasma proteins.

Metabolism: There are indications that it is fairly extensively metabolised. Peak plasma levels are reached in 2 hours and a plasma half- life of between 3 and 8.5 hours on average.

Elimination: About 30% is excreted unchanged in the urine with the remainder excreted as uncharacterized metabolites.

IV.3 Pharmacodynamics

Bendroflumethiazide is a thiazide diuretic which reduces the absorption of electrolytes from the renal tubules, thereby increasing the excretion of sodium and chloride ions, and consequently of water. The excretion of other electrolytes, notably potassium and magnesium, is also increased.

Thiazides also have a hypotensive effect, due to a reduction in peripheral resistance and enhance the effects of other antihypertensive agents.

IV.4 Clinical Efficacy

The clinical efficacy of bendroflumethiazide is well established. No additional efficacy clinical studies to demonstrate efficacy have been included in the application. This is appropriate for this type of application.

IV.5 Clinical Safety

The clinical safety of bendroflumethiazide is well established. No additional efficacy clinical studies to demonstrate efficacy have been included in the application. This is appropriate for this type of application.

Pharmacovigilance System
The marketing authorisation holder (MAH) submitted a summary of the Pharmacovigilance System, including confirmation of the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

Risk Management Plan

The risk management plan proposed by the applicant, including the proposed pharmacovigilance activities and risk minimisation measures, is considered acceptable. The approved summary of safety concerns is outlined in the table below:

Table 1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Electrolyte disturbances (including hypokalaemia, hyponatraemia, hypomagnesaemia and hypercalcaemia) especially in patients with renal or hepatic impairment • Hyperuricaemia and exacerbation of gout • Use in patients with Addison's disease • Hyperglycaemia and aggravation of diabetes mellitus • Ventricular arrhythmias with concomitant use of pimozide, thioridazine or terfenadine • Hypomagnesaemia in patients with alcoholic cirrhosis • Exacerbation/activation of systemic lupus erythematosus
Important potential risks	• Foetal toxicity • Maternal toxicity
Missing information	None

Routine pharmacovigilance activities and routine risk minimisation measures have been proposed by the applicant and this is considered acceptable.

The applicant should follow the PSUR submission cycle as adopted in the final version of the European Union Reference Dates (EURD) list.

IV.6 Discussion on the clinical aspects

Sufficient clinical information has been submitted by the applicant to support authorisation of this medicinal product.

The benefit/risk profile of the product is considered to be positive.

V. OVERALL CONCLUSIONS

Bendroflumethiazide 2.5 mg & 5 mg Tablets are generic forms of Aprinox 2.5mg and 5mg tablets of Waymade PLC. Aprinox 2.5mg and 5mg tablets of Waymade PLC are well-known medicinal products 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 SmPCs are consistent with those of the reference products.

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 Bendroflumethiazide 2.5 mg & 5 mg Tablets demonstrated bioequivalence with the reference products as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE