LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Bendroflumetiazid Alternova 2.5 mg and 5 mg, Tablet

This module reflects the scientific discussion for the approval of Bendroflumetiazid Alternova. The procedure was finalised at 2013-10-24. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Bendroflumetiazid Alternova 5 mg and 10 mg are a generic applications made according to Article 10(1) of Directive 2001/83/EC. The applicant, Alternova A/S applies through the national procedure to register the products in Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

Bendroflumetiazid Alternova is presented in the form of tablets containing 2.5 mg and 5 mg of bendroflumethiazide. The excipients are anhydrous lactose, pregelatinised maize starch, talc and stearic acid. The tablets are packed in plastic containers.

II.2 Drug Substance

Bendroflumethiazide has a monograph in the Ph Eur.

Bendroflumethiazide is a white or almost white, crystalline powder which is practically insoluble in water, freely soluble in acetone, soluble in ethanol (96 per cent). The structure of bendroflumethiazide has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Bendroflumetiazide Alternova tablet is formulated using excipients described in the current Ph Eur. All raw materials used in the product has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as poor aqueous solubility.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

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 SPC of the originator. The pharmacokinetics of bendroflumethiazide is linear within the dose range 2.5-5 mg (Schäfer et al 1982). The terminal half-life is 9 hours.

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 24 healthy volunteers, comparing Bendroflumethiazide, 5 mg, tablets, with Salures, 5 mg, tablets, by Pfizer AB under fasting conditions. The study was conducted at GVK Biosciences Pvt. Ltd, Ameerpet, Hyderabad, India between 17th and 27th January 2013. Blood samples were collected pre-dose and up to 48 hours post-dose. The study design is considered acceptable. Plasma concentrations of bendroflumethiazide were determined with an achiral validated LC/MS/MS method. The use of an achiral analytical method is considered acceptable in this case, although the pharmacokinetics and pharmacodynamics for the individual enantiomers of bendroflumethiazide has not been studied in the literature, since the active substance has a wide therapeutic index, the confidence intervals for AUC and C_{max} for the racemate are narrow and not close to the acceptance limits in the current study and the T_{max} values for the racemate are also similar between test and reference product, indicating no difference in rate of absorption between formulations. Therefore it is not considered likely that the results for the individual enantiomers would differ from the results for the racemate in a clinically relevant way. 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%. From a pharmacokinetic point of view, absence of studies with the additional strength 2.5 mg is acceptable, as the pharmacokinetics of bendroflumethiazide is linear between 2.5 mg and 5 mg.

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

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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 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.

The results of the conducted bioequivalence study can be extrapolated to other strengths since the criteria for biowaiver for additional strengths are fulfilled according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence.

The risk/benefit ratio is considered positive and Bendroflumetiazid Alternova 2,5 mg and 5 mg tablets are recommended for approval.

VI. APPROVAL

Bendroflumetiazid Alternova 2,5 mg and 5 mg tablets was approved in the national procedure on 2013-10-24

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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