LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Valsartan/Hydrochlorothiazide ratiopharm

(valsartan/hydrochlorothiazide)

SE/H/750/001-003/DC

This module reflects the scientific discussion for the approval of Valsartan/ Hydrochlorothiazide ratiopharm. The procedure was finalised at 2009-11-27. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Ratiopharm GmbH has applied for a marketing authorisation for Valsartan/Hydrochlorothiazide ratiopharm, film-coated tablets 80/12.5 mg, 160/12.5 mg and 160/25 mg claiming essential similarity to Co-Diovan (Diovan Comp), film-coated tablet, 80/12.5 mg, 160/12.5 mg and 160/25 mg marketed in the EU by Novartis. The product contains valsartan and hydrochlorothiazideas active substances. For approved indications see the Summary of Product Characteristics. The products used in the bioequivalence studies are Co- Diovan forte 160/25 mg film-coated tablets and Co-Diovan 160/12.5 film-coated tablets manufactured by Novartis Pharma, Germany.

II. QUALITY ASPECTS

II.1 Introduction

Valsartan/Hydrochlorothiazide ratiopharm, film coated tablets containing 80 of valsartan and 12.5 mg of hydrochlorothiazide or 160 mg of valsartan and 12.5 hydrochlorothiazide or 160 mg of valsartan and 25 hydrochlorothiazide . The excipients are silicified microcrystalline cellulose (microcrystalline cellulose and colloidal anhydrous silica), crospovidone and magnesium stearate in the tablet core. The 80/12.5 mg strength is a pink tablet coated with Opadry light orange (hydroxypropyl methylcellulose, titanium dioxide, macrogol, iron oxide yellow and iron oxide red). The 160/12.5 mg strength is a brick red tablet coated with Opadry red (hydroxypropyl methylcellulose, titanium dioxide, macrogol and iron oxide red). The 160/25 mg strength is a light-brown tablet coated with Opadry brown (hydroxypropyl methylcellulose, titanium dioxide, macrogol, iron oxide yellow, iron oxide red and iron oxide black). The tablets are packed in PVC/PE/PVDC/Al blister or in HDPE bottles.

II.2 Drug Substance

Both drug substances, valsartan and hydrochlorothiazide, have a monograph published in Ph Eur.

Valsartan is a white to almost white hygroscopic powder which is practically insoluble in water. The structure of valsartan has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism and stereochemistry is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Regarding hydrochlorothiazide it is referred to the Ph. Eur. Certificate of Suitability (CoS). Specification provided for the hydrochlorothiazide by the applicant complies with the monograph in the Ph. Eur. and also includes additional tests in compliance with the CoS.

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

The re-test period of hydrochlorothiazide is confirmed by the CoS.

II.3 Medicinal Product

Valsartan/Hydrochlorothiazide ratiopharm, film-coated tablets 80/12.5 mg, 160/12.5 mg and 160/25 mg are formulated using excipients described in the current Ph Eur, except for silicified microcrystalline cellulose which is controlled according to USP/NF and iron oxides which are controlled according to NF. All raw materials used in the product are of vegetable origin.

The product development has taken into consideration the physico-chemical characteristics of the active substances.

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, when stored below 25ºC

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

Two bioequivalence studies (including bioanalysis) were performed at Anapharm, Montreal, Canada between the 10th of February and 22nd of March 2007 (study 60702) and between the 1st and 23rd of May 2007 (study 60703) respectively. Study 60702 was a randomised, open-label, single-dose, 2-way crossover bioequivalence study with the tablet strength 160 mg/25 mg. Study 60703 was a randomised, open-label, single-dose, 3-way crossover bioequivalence study comparing the tablet strength 160 mg/12.5 mg and 120 mg/12.5 mg (additional strength not included in the application) of the test product with the 160 mg/12.5 mg of the reference product. Valsartan and hydrochlorothiazide in plasma were determined with a validated LC-MS-MS method. Bioequivalence was demonstrated regarding C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for valsartan and hydrochlorothiazide using the acceptance range 80-125%. The absence of a study with the 80 mg/12.5 mg strength is considered acceptable from a pharmacokinetic point as the pharmacokinetics of both valsartan and hydrochlorothiazide is linear in the therapeutic dose range.

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 testing of the package leaflet has been performed and is acceptable.

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 Valsartan/Hydrochlorothiazide ratiopharm, film coated tablets 80/12.5 mg, 160/12.5 mg and 160/25 mg are recommended for approval.

VI. APPROVAL

The Decentralised procedure for Valsartan/Hydrochlorothiazide ratiopharm, film coated tablets 80/12.5 mg, 160/12.5 mg and 160/25 mg was successfully finalised on 2009-11-27.

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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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