LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Valsartan/Hydrochlorothiazide ratiopharm

(valsartan/hydrochlorothiazide)

SE/H/994/01-02/DC

This module reflects the scientific discussion for the approval of Valsartan/Hydrochlorothiazide ratiopharm. The procedure was finalised at 2010-12-21. 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 claiming essential similarity to Diovan comp marketed in Sweden/ the EU by Novartis. The product contains valsartan hydrochlortiazide as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Co Diovan Forte tablets marketed by Novartis Pharma GmbH in Germany

II. QUALITY ASPECTS

II.1 Introduction

Valsartan/Hydrochlorothiazide ratiopharm, film-coated tablets containing 320 of valsartan and 12.5 mg of hydrochlorothiazide or 320 of valsartan and 25 mg of hydrochlorothiazide . The excipients are microcrystalline, croscarmellose sodium, povidone and magnesium stearate in the tablet core. The 320 mg/ 12.5 mg tablets are pink, modified capsule-shaped, film-coated tablet with Opadry containing: polyvinyl alcohol, titanium dioxide, macrogol, talc, iron oxide yellow and iron oxide red.
The 320 mg/25 mg tablets are yellow, modified capsule-shaped, scored film-coated tablet with opadry containing: polyvinyl alcohol, titanium dioxide, macrogol, talc and iron oxide yellow.
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 320/12.5 mg and 320/25 mg are formulated using excipients described in the current Ph Eur except for the iron oxides which are controlled according to the other relevant pharmacopoeia (JPE or USP- National Formulary). 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 and the precautions for storage claimed in the SPC.

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

To support the application, one single-dose bioequivalence study with the strength 320 mg/25 mg under fasting conditions was submitted.

The study was a single centre, randomised, single-dose, open-label, 4-way crossover replicate bioequivalence study in 30 healthy volunteers. A 4-period crossover replicate design study was chosen to estimate within-subject variability for C_{max} of the reference compound, in order to justify a widening of the acceptance range for C_{max}. Plasma concentrations of valsartan and hydrochlorothiazide were determined with a validated HPLC/MS/MS method. Bioequivalence was demonstrated for AUC and C_{max} for both valsartan and hydrochlorothiazide.

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.

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
User testing of the package leaflet has not been performed. The proposed PL is harmonised with the referral PL of Diovan comp, referral procedure EMEA/H/A-30/1000. At the time when the content of the PL was approved by the commission the requirements for readability were already in force. The applicant therefore assumes that no user testing is needed with regard to the content of the PL. This is acceptable.

The applicant will use the company layout, as set up by the company style guidelines, to the given content of the PL. Several package leaflets in accordance with the company style guide has already been tested and approved via the decentralised procedure, e.g. Irbesartan – DE/H/1491/001-003/DC; Pramipexol – DE/H/1258/001-004/DC and Rivastigmin – DE/H/1585/001-004/DC. The applicant therefore refers to these procedures and claims that no user testing of the layout is needed in this procedure. This is acceptable.

The risk/benefit ratio is considered positive and Valsartan/Hydrochlorothiazide ratiopharm is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Valsartan/Hydrochlorothiazide ratiopharm was successfully finalised on 2010-12-21.

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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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