LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Valsartan ratiopharm
(valsartan)

SE/H/747/01-04/DC

This module reflects the scientific discussion for the approval of Valsartan 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 ratiopharm, film-coated tablets 40 mg, 80 mg, 120 mg and 160 mg claiming essential similarity to Diovan, film-coated tablet, 40 mg, 80 mg and 160 mg marketed in the EU by Novartis. The application for the 120 mg tablet is submitted in accordance with the "article 10(3) hybrid application" of the Directive 2001-83/EC. The product contains valsartan as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Tareg, film-coated tablet, 160 mg marketed by Novartis Pharma S.A.S. in France.

II. QUALITY ASPECTS

II.1 Introduction

Valsartan ratiopharm, film-coated tablets contains 40 mg, 80 mg, 120 mg or 160 of valsartan. The excipients are silicified microcrystalline cellulose (microcrystalline cellulose and colloidal anhydrous silica), Croscarmellose sodium and magnesium stearate in the tablet core. The 40 mg strength is a yellow tablet coated with Opadry II light yellow (partially hydrolyzed polyvinyl alcohol, titanium dioxide, macrogol, talc, iron oxide yellow and iron oxide red). The 80 mg strength is a pink tablet coated with Opadry II pink (partially hydrolyzed polyvinyl alcohol, titanium dioxide, macrogol, talc and iron oxide red). The 120 mg strength is a white tablet coated with Opadry II white (partially hydrolyzed polyvinyl alcohol, titanium dioxide, macrogol and talc). The 160 mg strength is a yellow tablet coated with Opadry II yellow (partially hydrolyzed 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

Valsartan has a monograph published in Ph Eur 6.6.

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 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

Valsartan ratiopharm, film-coated tablets 40 mg, 80 mg, 120 mg and 160 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 substance.

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

One bioequivalence study (including bioanalysis) with the tablet strength 160 mg was performed at Anapharm, Montreal, Canada between 14th and 29th of August 2006. The relative bioavailability of Valsartan 160 mg (ratiopharm inc.) and Tareg 160 mg (Novartis Pharma) was established by comparing the pharmacokinetics in a randomised, single-dose, open-label, two-way crossover bioequivalence study in healthy volunteers. Valsartan in plasma was determined with a validated LC-MS-MS method. Bioequivalence was demonstrated regarding C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for valsartan using the acceptance range 80-125%. The absence of a study with the 40, 80 and 120 mg strengths is considered acceptable from a pharmacokinetic point as the pharmacokinetics of valsartan 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 ratiopharm, film-coated tablets 40 mg, 80 mg, 120 mg and 160 mg are recommended for approval.

VI. APPROVAL

The Decentralised procedure for Valsartan ratiopharm, film-coated tablets 40 mg, 80 mg, 120 mg and 160 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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