LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Valsartan ratiopharm
(valsartan)

SE/H/944/01/DC

This module reflects the scientific discussion for the approval of Valsartan ratiopharm, 320 mg, film-coated tablet. The procedure was finalised at 2010-11-30. 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, 320 mg film-coated tablet claiming essential similarity to Diovan 320 mg filmdragerade tabletter marketed in Sweden by Novartis. 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 160 mg tablets marketed by Novartis Pharma S.A.S in France.

II. QUALITY ASPECTS

II.1 Introduction

Valsartan ratiopharm film-coated tablets contains 320 mg of valsartan as active substance. The excipients are croscarmaellose sodium, magnesium stearate, silicified microcrystalline cellulose (microcrystalline cellulose, colloidal silicon dioxide), polyvinyl alcohol, titanium dioxide, macrogol, talc and iron oxide yellow. The tablets appear to be beige in colour, capsule-shaped in form, and furnished with a score line. The tablets are packed in PVC/PE/PVDC/Al blister or in HDPE bottles.

II.2 Drug Substance

Valsartan has a monograph published in the 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 active substance specification is in line with the monograph in the Ph. Eur., and includes relevant and justified tests and limits for residual solvents impurities/degradation products. 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 320 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 (except titanium dioxide, talc and iron oxide which are mineral 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. The tablet in the blister packaging should be stored below 30 ^{o}C and kept in the original package to protect from moisture. However, tablet in the HDPE bottle does not require any special storage condition.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since these products have 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) with the tablet strength 160 mg were performed between 14th and 29th of August 2006 and between 10th and 25th of February 2008. Different reference products were used in the two studies; Tareg 160 mg capsules from the Italian market and Tareg 160 mg film-coated tablet from the French market. The bioequivalence studies were randomised, single-dose, open-label, two-way crossover bioequivalence studies 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%. From a pharmacokinetic point o f view, given that valsartan shows linear pharmacokinetics within the dose range 40-320 mg, the results from the study can be extrapolated to the tablet strength 320 mg. Bioequivalence has been sufficiently shown and approval is recommended from a pharmacokinetic point of view.

IV.2 Discussion on the clinical aspects

Since these products have 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
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report, making reference to Valsartan Teva film-

coated tablets, DK/H/1517/01-04/DC. The bridging report submitted by the applicant has been found 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, 320 mg, film-coated tablet is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Valsartan ratiopharm, 320 mg, film-coated tablet were successfully finalised on 2010-11-30.

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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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