IPAR

IRISH MEDICINES BOARD

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Valsartan Ranbaxy 40 mg, 80 mg & 160 mg film−coated tablets

VALSARTAN

PA 408/69/1-3

The Public Assessment Report reflects the scientific conclusion reached by the Irish Medicines Board (IMB) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the IMB for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the IMB leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

The Public Assessment Report reflects the scientific conclusion reached by the Irish Medicines Board (IMB) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the IMB for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the IMB leading to the approval of the medicinal product for marketing in Ireland.

Based on the review of the data on quality, safety and efficacy, the IMB has granted a marketing authorisations for Valsartan Ranbaxy 40 mg, 80 mg 160 mg film-coated tablets, from Ranbaxy Ireland Ltd on 21st October 2011 for local symptomatic relief of pain and inflammation in the trauma of the tendons, ligaments, muscles and joints and in localised forms of soft tissue rheumatism.

These applications for a marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a 'generic' application. Valsartan Ranbaxy has the same qualitative and quantitative composition in terms of the active substance and the same pharmaceutical form as Diovan film-coated tablets.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the IMB's website at www.imb.ie

Name of the product	Valsartan Ranbaxy 40 mg, 80 mg 160 mg film-coated tablets
Name of the active substance (INN)	Valsartan
Pharmacotherapeutic classification (ATC code)	C09CA03
Pharmaceutical form and strengths	40 mg, 80 mg 160 mg Tablets
Marketing Authorisation Numbers (PA)	408/69/1-3
Marketing Authorisation Holder	Ranbaxy Ireland Ltd
Date of last revision	

II QUALITY ASPECTS

2.1.1 Overview

This application is for Valsartan Ranbaxy 40 mg, 80 mg 160 mg film-coated tablets.

2.1.2 Drug substance

The active substance is valsartan, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

2.1.3 Medicinal product

P.1 Composition

The 40 mg tablets are yellow, film-coated, oval tablets debossed with 'V & 3' on either side of a breakline on one face, and with a breakline on the other face.

The 80 mg tablets are orange-coloured, film-coated, oval tablets debossed with 'V & 2' on either side of a breakline on one face, and with a breakline on the other face.

The 160 mg tablets are pink, film-coated, oval tablets debossed with 'V &1' on either side of a breakline on one face, and with a breakline on the other face.

The tablets contain 40 mg, 80 mg or 160 mg of valsartan.

The other ingredients in the tablet cores are: microcrystalline cellulose, crospovidone (type A), colloidal anhydrous silica, magnesium stearate, pregelatinised starch, and talc.

The film coatings contain hypromellose, titanium dioxide (E171), macrogol 400, talc, and macrogol 4000; the 40 mg strength contains yellow iron oxide (E172), the 80 mg strength contains yellow and red iron oxides (E172), and the 160 mg strength contains red and black iron oxides (E172) as colorants.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances)*

All ingredients comply with Ph. Eur. where such exist, or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for coated tablets; the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production sites have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is packaged in oriented polyamide/aluminium/PVC blisters within an outer carton. The 40 mg tablets are supplied in packs of 14 or 28 tablets; the 80 mg and 160 mg tablets are supplied in packs of 28, 56 or 98 tablets.

Evidence has been provided that the blisters comply with EU legislation for packaging materials that come in contact with foodstuffs.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 2 years; no special storage conditions are required.

2.1.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Valsartan Ranbaxy 40 mg, 80 mg 160 mg film-coated tablets.

III NON-CLINICAL ASPECTS

3.2.1 Overview

This active substance has been available on the European/Irish market for more than 10 years. No new preclinical data have been submitted as preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

IV CLINICAL ASPECTS

3.3.1 Overview

Valsartan is a well known active substance with established efficacy and tolerability.

The content of the SPCs approved during the national procedure are in accordance with that accepted for the reference product Diovan marketed by Novartis Ireland Limited.

For these generic applications, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Valsartan 160 mg tablets is compared with the pharmacokinetic profile of the reference product Tareg 160 mg tablets of Novartis Pharma.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Valsartan 160 mg tablets Ranbaxy Laboratories Limited, was compared to the reference product Tareg 160 mg tablets of Novartis Pharma. Based on the pharmacokinetic parameters of active substance the reference tablet Tareg 160 mg tablets marketed by Novartis Pharma and test tablet Valsartan 160 mg tablets are bioequivalent with regard to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The Valsartan Ranbaxy 40 mg, 80 mg coated tablets are dose proportional with the Valsartan Ranbaxy 160 mg film-coated tablets. The pharmacokinetics of the active substance are linear over the therapeutic range. The results of the bioequivalence study performed with the Valsartan 160 mg tablets therefore apply to the other strengths.

The IMB has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

3.3.2 Pharmacokinetics

Absorption:
Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (Cmax) by about 50%, although from about 8 h post-dosing plasma valsartan concentrations are similar for the fed and fasted groups.

This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution:
The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

Biotransformation:
Valsartan is not biotransformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Excretion:
Valsartan shows multiexponential decay kinetics (t½_ <1 h and t½ß about 9 h). Valsartan is primarily eliminated by biliary excretion in faeces (about 83% of dose) and renally in urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

In heart failure patients:
The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to that observed in healthy volunteers. AUC and Cmax values of valsartan are almost proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day). The average accumulation factor is about 1.7.

The apparent clearance of valsartan following oral administration is approximately 4.5 l/h. Age does not affect the apparent clearance in heart failure patients.

Special populations

Elderly
A somewhat higher systemic exposure to valsartan was observed in some elderly subjects than in young subjects; however, this has not been shown to have any clinical significance.

Impaired renal function
As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan. Dose adjustment is therefore not required in patients with renal impairment (creatinine clearance >10 ml/min). There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients.

Valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis.

Hepatic impairment
Approximately 70% of the dose absorbed is eliminated in the bile, essentially in the unchanged form.
Valsartan does not undergo any noteworthy biotransformation. A doubling of exposure (AUC) was observed in patients with mild to moderate hepatic impairment compared to healthy subjects. However, no correlation was observed between plasma valsartan concentration versus degree of hepatic dysfunction. Valsartan has not been studied in patients with severe hepatic dysfunction

Paediatric population
In a study of 26 paediatric hypertensive patients (aged 1 to 16 years) given a single dose of a suspension of valsartan (mean: 0.9 to 2 mg/kg, with a maximum dose of 80 mg), the clearance (litres/h/kg) of valsartan was comparable across the age range of 1 to 16 years and similar to that of adults receiving the same formulation.

Impaired renal function
Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium
should be closely monitored

3.3.3 Pharmacodynamics

Pharmacotherapeutic group: Angiotensin II Antagonists, plain, ATC code: C09CA03
Valsartan is an orally active, potent, and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT1 receptor blockade with valsartan may stimulate the unblocked AT2 receptor, which appears to counterbalance the effect of the AT1 receptor. Valsartan does not exhibit any partial agonist activity at the AT1 receptor and has much (about 20,000 fold) greater affinity for the AT1 receptor than for the AT2 receptor. Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Valsartan does not inhibit ACE (also known as kininase II) which converts Ang I to Ang II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing. In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of dry cough was significantly ($p<0.05$) less in patients treated with
valsartan than in those treated with an ACE inhibitor (2.6% versus 7.9% respectively).

In a clinical trial of patients with a history of dry cough during ACE inhibitor therapy, 19.5% of trial subjects receiving valsartan and 19.0% of those receiving a thiazide diuretic experienced cough compared to 68.5% of those treated with an ACE inhibitor ($p<0.05$).

3.3.4 Clinical Efficacy

The clinical efficacy of valsartan is well established.

3.3.5 Clinical Safety

The clinical safety of valsartan is well established. A Risk Management Plan is not required in line with the known safety profile.

The schedule for Periodic Safety Update Reports (PSUR) submission should be addressed

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

V OVERALL CONCLUSIONS

BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Valsartan 160 mg tablets Ranbaxy Laboratories Limited is a generic form of Diovan 160mg film -coated tabletsis a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The IMB, on the basis of the data submitted considered that Valsartan 160 mg tablets Ranbaxy Laboratories Limited demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI REVISION DATE

October 2011