LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Everolimus Teva
(everolimus)

SE/H/1608/01-04/DC

This module reflects the scientific discussion for the approval of Everolimus Teva. The procedure was finalised on 2017-05-03. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

The application for Everolimus Teva, 2.5 mg, 5 mg, 10 mg, tablets, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The application for Everolimus Teva 7.5 mg, tablets is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The applicant, Teva Sweden AB applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LV, NL, NO, PL, PT, SI, SK, UK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Certican, 0,25 mg, tablets, authorised in SE since 2003, with Novartis Sverige AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Afinitor, 10 mg, tablets, from NL with Novartis Europharm Limited as marketing authorisation holder.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

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 have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

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

Bioequivalence was evaluated in two pivotal single dose bioequivalence studies with the 10 mg strength, one in the fasted (study 2015-3909) and one in the fed state (study 2015-3910). Everolimus Teva is a product with specific formulation characteristics. Everolimus is converted into a solid dispersion with a hydrophilic polymer (HPMC) to increase its solubility and bioavailability. For products with specific formulation characteristics (e.g. microemulsions, solid dispersions), bioequivalence studies performed under both fasted and fed conditions are required unless the product must be taken only in the fasted state or only in the fed state. According to the SmPC of the reference product, Afinitor should be administered orally once daily at the same time every day, consistently either with or without food. Therefore, both fasting and fed studies are appropriate.

Study 2015-3909

Bioequivalence was evaluated in one single-dose, three-way crossover study conducted in 48 healthy volunteers, comparing Everolimus Teva, 10 mg, tablet with Afinitor, 10 mg, tablet from the NL market and Afinitor, 10 mg, tablet from the Canadian market under fasting conditions. The study was conducted at Pharma Medica Research Inc., Canada between 14th November and 24th December 2015. Blood samples were collected pre-dose and up to 72 hours post-dose. The study design is considered acceptable. Blood concentrations of everolimus were determined with an adequately validated LC-MS/MS method. For AUC_{0-72h} and C_{max} the 90% confidence interval for the ratio of the test product and reference product from the EU market fell within the conventional acceptance range of 80.00-125.00%.

Study 2015-3910

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 80 healthy volunteers, comparing Everolimus Teva, 10 mg, tablet with Afinitor, 10 mg, tablet from the NL market under fed conditions (high-fat, high-calorie breakfast). The study was conducted at Pharma Medica Research Inc., Canada between 23rd January and 9th February 2016. Blood samples were collected pre-dose and up to 72 hours post-dose. The study design is considered acceptable. Blood concentrations of everolimus were determined with an adequately validated LC-MS/MS method. For AUC_{0-72h} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

From a pharmacokinetic point of view, absence of studies with the additional strengths (2.5, 5 and 7.5 mg) is acceptable, as the pharmacokinetics of everolimus is linear between 2.5 mg and 10 mg.
Based on the submitted bioequivalence studies, Everolimus Teva is considered bioequivalent with Afinitor.

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.

IV.3 Risk Management Plan

The MAH has submitted an updated Risk management plan (version 1.1, dated 31 October 2016). The data lockpoint for this RMP is 29 February 2016.

Safety specification
The summary of safety concerns has been updated to be in line with the ´safety concerns of the reference product Afinitor.

Summary of safety concerns	
Important identified risks	• Non-infectious pneumonitis • Severe infections • Hypersensitivity (anaphylactic reactions) • Stomatitis • Wound healing complications • Increased creatinine / proteinuria / renal failure • Hyperglycaemia/new onset diabetes mellitus • Dyslipidaemia • Hypophosphatemia • Cardiac failure • Cytopenia • Haemorrhages • Thrombotic and embolic events • Female fertility (including secondary amenorrhea) • Pre-existing infection (reactivation, aggravation, or exacerbation) • Safety in patients with hepatic impairment • Interaction with strong and moderate CYP3A4 inhibitors and PgP inhibitors • Interaction with strong CYP3A4 inducers and PgP inducers • Interaction with CYP3A4 substrates and PgP substrates • Increased risk for angioedema when combining mTOR inhibitors and ACE inhibitors
Important potential risks	• Postnatal developmental toxicity • Pregnant or breast-feeding women • Intestinal obstruction / ileus • Male infertility • Pancreatitis • Cholelithiasis • Muscle-wasting / muscle-loss • Everolimus with concomitant exemestane use

Summary of safety concerns	
Missing information	• Off-label use in paediatric and adolescent patients • Patients with renal impairment • Patients with CNS metastases • Patients with uncontrolled cardiac disease • Patients with impairment of GI function • Long-term safety • Onset of benign or malignant tumours • Comparative safety of everolimus and exemestane therapy vs. everolimus monotherapy • Safety in breast cancer patients pre-treated with cytotoxic therapies

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The summary of the RMP has been updated according to request. There are no outstanding issues concerning the RMP.

The RMP is approved

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Everolimus Teva, is found adequate. There are no objections to approval of Everolimus Teva from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.

The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Everolimus Teva, 2.5 mg, 5 mg, 7.5 mg and 10 mg, tablet was positively finalised on 2017-05-03.

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MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se