

Public Assessment Report Scientific discussion

Everolimus Ethypharm (everolimus)

SE/H/1707/01-03/DC

This module reflects the scientific discussion for the approval of Everolimus Ethypharm. The procedure was finalised on 2018-06-08. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

The application for Everolimus Ethypharm, 2.5 mg, 5 mg and 10 mg tablet is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Ethypharm applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and the following concerned member states (CMS): DE, ES, IT, UK.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Certican, 1 mg, tablet authorised in Sweden since 2003, with Novartis Sverige AB as marketing authorisation holder.

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

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

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

To support the application, the applicant has submitted two pivotal single dose bioequivalence studies with the 10 mg strength, one in the fasted (study EHR-P0-345) and one in the fed state (study EHR-P4-332). In addition, two pilot comparative bioavailability studies with the 5 mg strength (one in the fasted and one in the fed state) were submitted. Everolimus Ethypharm is a product with specific formulation characteristics. Everolimus is converted into a solid dispersion 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 tablets 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 EHR-P0-345

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 60 healthy volunteers, comparing Everolimus Ethypharm, 10 mg, tablet with Afinitor, 10 mg, tablet from the FR market under fasting conditions. The study was conducted between 1st and 21st 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%.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, t_{max} median, range) for everolimus in fasted pivotal study EHR-P0-345, n=55.

Treatment	AUC _{0-72h} ng*h/ml	C _{max} ng/ml	t _{max} h
Test	476 $\pm$ 128	67.0 $\pm$ 19.3	1.00 (0.50-3.00)
Reference	492 $\pm$ 181	73.8 $\pm$ 21.4	0.75 (0.25-4.00)
*Ratio (90% CI)	99.08** (94.50-103.87)	90.50 (85.13-96.22)	-
AUC _{0-t} area under the plasma concentration-time curve from time zero to t hours C _{max} maximum plasma concentration t _{max} time for maximum plasma concentration			

*calculated based on ln-transformed data

**n=54

Study EHR-P4-332

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 44 healthy volunteers, comparing Everolimus Ethypharm, 10 mg, tablet with Afinitor, 10 mg, tablet from the FR market under fed conditions (high-fat, high-calorie breakfast). The study was conducted between 2nd and 22nd 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 and reference products fell within the conventional acceptance range of 80.00-125.00%.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, t_{max} median, range) for everolimus in fed pivotal study EHR-P4-332, n=42.

Treatment	AUC _{0-72h} ng*h/ml	C _{max} ng/ml	t _{max} h
Test	378 $\pm$ 90	36.9 $\pm$ 10.0	1.50 (0.50-4.00)
Reference	387 $\pm$ 108	38.3 $\pm$ 12.5	2.13 (0.50-6.00)
*Ratio (90% CI)	98.65 (95.32-102.10)	97.66 (89.27-106.83)	-
AUC _{0-t} area under the plasma concentration-time curve from time zero to t hours C _{max} maximum plasma concentration t _{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

Absence of studies with the additional strengths of 2 and 5 mg is acceptable, as all conditions for biowaiver for additional strengths, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of everolimus is linear between 2.5 mg and 10 mg.

Based on the submitted bioequivalence studies, Everolimus Ethypharm is considered bioequivalent with Afinitor tablets.

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 10 November 2017), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Everolimus Ethypharm.

Safety specification

Summary table of safety concerns as proposed in RMP

Summary of safety concerns	
Important identified risks	Non-infectious pneumonitis Severe infections Hypersensitivity (anaphylactic reactions) Stomatitis Wound healing complications Increased creatinine / proteinuria / renal failure Hyperglycemia/ new onset diabetes mellitus Dyslipidemia 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 Drug-drug interactions: Strong CYP3A4 inhibitors and PgP inhibitors Moderate CYP3A4 inhibitors and PgP inhibitor Strong CYP3A4 inducers and PgP inducers 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 Male infertility Muscle-wasting / muscle-loss Drug-drug interactions: Everolimus with concomitant exemestane use

Missing information	Off-label use in pediatric and adolescent patients Patients with uncontrolled cardiac disease Long-term safety Onset of benign or malignant tumors Comparative safety of everolimus and exemestane therapy vs. everolimus monotherapy Safety in breast cancer patients pre-treated with cytotoxic therapies
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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.

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 Ethypharm, is found adequate. There are no objections to approval of Everolimus Ethypharm, 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/EC 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 Ethypharm, 2.5 mg, 5 mg and 10 mg tablet was positively finalised on 2018-06-08.

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)