COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Everolimus Sandoz 2.5 mg, 5 mg and 10 mg, tablets

(everolimus)

NL/H/4282/001-003/DC

Date: 7 November 2019

This module reflects the scientific discussion for the approval of Everolimus Sandoz tablets. The procedure was finalised at 7 January 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Everolimus Sandoz 2.5 mg, 5 mg and 10 mg, tablets from Sandoz BV.

Hormone receptor-positive advanced breast cancer
Everolimus Sandoz is indicated for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor.

Neuroendocrine tumours of pancreatic origin
Everolimus Sandoz is indicated for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease.

Neuroendocrine tumours of gastrointestinal or lung origin
Everolimus Sandoz is indicated for the treatment of unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) non-functional neuroendocrine tumours of gastrointestinal or lung origin in adults with progressive disease (see sections 4.4 and 5.1).

Renal cell carcinoma
Everolimus Sandoz is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Afinitor 2.5 mg, 5 mg and 10 mg, tablets which has been registered in the EEA by Novartis Europharm Limited since 18 December 2012 via a centralised procedure (EMEA/H/C/001068).

The concerned member states (CMS) involved in this procedure were Germany and Italy.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

Orphan similarity

The MAH has provided a similarity assessment. The MAH indicates that currently one product is licensed as orphan drug for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease, namely Lutathera (lutetium (177Lu) oxodotreotide)

The MAH concludes that the mechanism of action of Everolimus is distinct from that described for Lutathera (lutetium (177Lu) oxodotreotide). The MAH indicates that everolimus does not share the same principal molecular structure with the product mentioned above and the differences in molecular structure are not only minor.

The member states agree with the MAH that the mechanism of action of Lutathera is different from everolimus, since Lutathera's MoA is based on radioactivity, whereas everolimus is receptor mediated. There are currently no other products with an orphan designation for the same indication as everolimus, and which are currently marketed.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Lutathera in the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease does not prevent the granting of the proposed indication of Everolimus Sandoz.

II. QUALITY ASPECTS

II.1 Introduction

Everolimus Sandoz is a white to slightly yellow, elongated tablet with a bevelled edge.

- 2.5 mg: engraved with "LCL" on one side and "NVR" on the other
- 5 mg: engraved with "5" on one side and "NVR" on the other
- 10 mg: engraved with "UHE" on one side and "NVR" on the other

And contains as active substance 2.5 mg, 5 mg or 10 mg of everolimus.

The tablets are packed in polyamide/aluminium/PVC-Aluminium blisters.

The excipients are butylhydroxytoluene (E321), magnesium stearate (E470B), lactose, hypromellose type 2910 and crospovidone type A.

The 2.5 mg, 5 mg and 10 mg tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is everolimus, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a white to faintly yellow powder. The stabilised drug substance is amorphous. It is practically insoluble in water. The configuration is sufficiently guaranteed.

Manufacturing process
Adequate information is provided on the manufacturing process of the drug substance. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches of each manufacturing site.

Stability of drug substance
Stability studies are carried out under ICH conditions. A sufficient number of batches of each manufacturing site have been included. On the basis of the provided stability data, the claimed re-test period of 60 months when stored in a very tight packaging (water permeation <0.5 mg/day/litre) under protective gas, at 2-8 °C, protected from light is justified.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. Sufficient information has been provided on formulation and manufacturing process development. The product development has taken into consideration the physico-chemical characteristics of the active substance such as poor aqueous solubility and stability.

No clinical studies have been carried out with the product at issue as it is identical to the authorised product Afinitor.

Manufacturing process
The manufacturing process consists of preparation of the solid depression, preparation of the compression blend and followed by compression. The manufacturing process has been sufficiently described. Process validation data on the product have been presented for sufficient full scale batches in accordance with the relevant European guidelines.

Control of excipients
All excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, particle size, water content, residual solvents, degradation products, microbiological quality and assay. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have

been provided. Batch analytical data from ten batches of the sold dispersion from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided for three batches of the 2.5 mg and 10 mg strength stored at 25°C/60% RH (up to 48 months), 30°C/75% RH (up to 48 months), 50°C/75% RH (3 months), 5°C (6 months) and -20°C (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Some batches were also exposed to light under ICH Q1B conditions. The batches were stored in the proposed packaging.
Based on the provided stability data, a shelf life is granted of 36 months. The storage conditions are: "Do not store above 30°C . Store in the original package to protect from moisture and light."

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Everolimus Sandoz has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Everolimus Sandoz is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Afinitor which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is

no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Everolimus is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver

The MAH of the reference product has submitted an identity statement that the products under review here, Everolimus Sandoz tablets, and the reference (innovator) product Afinitor are identical. Hence, Everolimus Sandoz is produced with the same qualitative and quantitative composition, at the same manufacturing site, using the same manufacturing procedure and the same source of active substance as their currently manufactured reference product.

As the member states have been ensured that Everolimus Sandoz tablets are identical to the reference product Afinitor, a biowaiver has been granted.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, 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 Sandoz.

Table 1. Summary table of safety concerns as approved in RMP

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 - Strong CYP3A4 inhibitors and PgP inhibitors - Moderate CYP3A4 inhibitors and PgP inhibitors - 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 - Everolimus with concomitant exemestane use
Missing information	- Off-label use in paediatric and adolescent patients - Long-term safety - Onset of benign or malignant tumours - Patients with uncontrolled cardiac disease - Comparative safety of everolimus and exemestane therapy vs. everolimus monotherapy - Safety in breast cancer patients pre-treated with cytotoxic therapies

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Afinitor. No new clinical studies were conducted. The MAH of the reference product demonstrated through an identity statement that the Everolimus Sandoz is identical to the reference product. Therefore bioequivalence testing is not required. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The MAH did not perform a user consultation for Everolimus Sandoz tablets as the package insert belongs to the same medicinal class, and the key messages on it, are identical to

reference product Afinitor. In addition, the Sandoz layout and design was successfully tested previously. The member states agree that additional user testing is not required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Everolimus Sandoz 2.5 mg, 5 mg and 10 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form of Afinitor 2.5 mg, 5 mg and 10 mg, tablets. Afinitor is a well-known medicinal product with an established favourable efficacy and safety profile.

The MAH did not submit a bioequivalence study, but provided sufficient information to demonstrate that the product has the same quantitative and qualitative composition as Afinitor and is produced in the same manufacturing site.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Everolimus Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 7 January 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/4282/001/P/001	To align PL section 6 with SmPC section 4.8 - eyelid oedema	Yes	10-07-2019	Approved	-