COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

(everolimus)

NL/H/3977/001-003/DC

Date: 23 November 2018

This module reflects the scientific discussion for the approval of Everolimus Synthon 2.5 mg, 5 mg and 10 mg, tablets. The procedure was finalised on 30 May 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
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 Synthon 2.5 mg, 5 mg and 10 mg, tablets, from Synthon B.V.

The product is indicated for:
Hormone receptor-positive advanced breast cancer
This product 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
This product 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
This product 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.

Renal cell carcinoma
This product 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 have been registered in the EEA by Novartis Europharm Limited since 18 December 2012 through a centralised procedure (EU/1/09/538).

The active substance everolimus was first registered in the EU as Certican (0.10, 0.25, 0.50, 0.75 and 1.0 mg tablets) for the treatment of kidney transplant rejection. Certican was first registered in Sweden on 16 July 2003 via a national procedure. It was subsequently approved in other EU member states via a mutual recognition procedure which was positively concluded on 2 December 2003. Subsequently, Afinitor was registered in the EU on 3 August 2009 via a Centralised Procedure, for oncology indications. Both the Certican and Afinitor marketing authorisations are granted to Novartis.
Because both Certican and Afinitor contain the same active substance, they belong to the same Global Marketing Authorisation (GMA). The differences between Afinitor and Certican are only the strengths and the indications and based on Article 6(1) second subparagraph of Directive 2001/83/EC, Afinitor and Certican can be considered to belong to the same GMA.

Since both Certican and Afinitor belong to the same GMA, the start date for data exclusivity is the date of the first approval within the GMA, i.e. 16 July 2003. This implies that the 10 year protection period is applicable until July 2013.

The concerned member state (CMS) involved in this procedure was Luxembourg.

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

The MAH has submitted similarity assessment, since Torisel and Lutathera has ongoing orphan market exclusivity for treatment of renal cell carcinoma and treatment of gastroenteropancreatic neuroendocrine tumours at the time of submission for this application. During the procedure, the orphan market exclusivity for Torisel expired (21/11/2017), and the similarity assessment has therefore been removed from the Final AR.

Lutathera contains lutetium (177Lu) oxodotreotide. This product was designated an orphan medicine on 31 January 2008. As the active substance lutetium (177Lu) oxodotreotide does not contain the same principal molecular structural features as everolimus active substance and differ in the mechanism of action, everolimus is not similar to Lutathera (lutetium (177Lu) oxodotreotide) within the meaning of Article 3 of Commission Regulation EC No. 847/2000, with reference to Article 8 of Regulation EC No 141/2000.
As such, Everolimus 2.5, 5 and 10 mg tablets cannot be considered a similar medicinal product to Lutathera, for the purpose of Regulations (EC) No 141/2000 and 847/2000.

II. QUALITY ASPECTS

II.1 Introduction

Everolimus Synthon is a white to off white, oval, biconvex tablet. The 2.5 mg strength is debossed with “E9VS” on one side and “2.5” on the other side. The 5 mg and 10 mg strength are debossed with “E9VS 5” and “E9VS 10” on one side respectively. The tablets contain 2.5, 5 mg or 10 mg everolimus.

The tablets are packed in oPA/Al/PVC/Al blisters.

The excipients are: butylhydroxytoluene (E321), hypromellose (E464), lactose, lactose monohydrate, crospovidone (E1202) and magnesium stearate (E470b).

II.2 Drug Substance

The active substance is everolimus, an established active substance, not described in any pharmacopoeia. A draft monograph has been published in Pharmeuropa 29.3. The active substance is a white to pale brown/yellow amorphous powder. It is soluble in alcohol,

dichloromethane, acetone, acetonitrile, toluene, and ethyl acetate. It is insoluble in water and heptanes. It is hygroscopic and exhibits polymorphism (amorphous form).

The Active Substance Master File (ASMF) procedure is used for both manufacturers of the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the MAH or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The active substance has been adequately described and is synthesised in two synthetic steps. The specifications for the starting materials and the key intermediate are acceptable. No class-1 solvents or metal catalyst have been used in the synthesis.

Quality control of drug substance

The active substance specification is established in-house by the MAH and is based on the specifications of the ASMF-holders. The specification includes tests for appearance, identity, water content, sulphated ash, residual solvents, impurities, stabiliser content, assay and microbiological contamination (non-routine) and is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for seven full scaled batches.

Stability of drug substance

Manufacturer one - Stability data on the active substance(s) have been provided for three full scaled batches 20°C (24 months), 5°C (24 months), 25°C/60% RH (24 months), 30°/65% RH (12 months) and 40°C/75% RH (6 months), as well as three full scaled batches stored at 20°C (18 months), 5°C (18 months) and 25°C/60% RH (6 months). No clear up- or downward trends are observed for any of the parameters, up to 24 months at all storage temperatures up to 25°C. However, at higher temperatures (30°C and 40°C) increases in water content (out-of-specification results) and unknown impurities are observed. Therefore the proposed retest period of 18 months, with the storage condition: "Store under Nitrogen in an air tight container protected from light below 25°C"
is accepted. All (future) stability studies will be performed with the long term condition 25°C/60% RH and up to the accepted shelf-life, under these conditions.

Manufacturer two - Stability data on the active substance(s) have been provided for full scaled batches stored at 5°C (3 batches 48 months; 3 batches 12 months) and 25°C/60% RH (4 batches, 6 months). No clear up- or downward trends are observed for any of the parameters tested under long term conditions (5 °C), whereas, under accelerated conditions (25°C/60% RH) an out-of-specification for impurity was observed, after 3 months, for two batches. Based on the provided data the proposed shelf-life of 48 months, with the storage condition "Store in the original packaging at 2-8°C under an inert atmosphere" is accepted.

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 are explained. The objective of the pharmaceutical development phase was to obtain everolimus tablets with similar composition and essentially similar dissolution behaviour as the originator tablets. The excipients used were based on the originator formulation to avoid stability and compatibility risks, as everolimus is known to be extremely sensitive to oxidation an antioxidant was added and its level has been justified.

Two bioequivalence studies have been performed with the 10 mg strength. Dissolution studies were performed in support of the bioequivalence studies in QC medium and in three different pH media (pH 1.2, 4.5, 6.8) and the dissolution profiles of everolimus 10 mg tablets and the reference product were shown to be comparable. For the 2.5 and 5 mg strength tablets a biowaiver was claimed based on dissolution studies in QC medium and in three different pH media (pH 1.2, 4.5, 6.8 without surfactant). In the QC medium and in dissolution media pH 4.5 and 6.8, more than 85% of the drug is dissolved within 15 minutes; therefore the dissolution profiles can be regarded as similar. In the dissolution medium pH 1.2, sink conditions cannot be achieved for the 10 mg strength, and therefore, similarity of the dissolution profiles was demonstrated by the use of equal amounts of drug substance (i.e. 2 x 5 mg or 4 x 2.5 mg versus 10 mg). As *in vitro* dissolution similarity was demonstrated under all conditions and also the other requirements for a biowaiver of additional strengths were fulfilled, the requested biowaiver is acceptable. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consists of preparation of a solid dispersion, preparation of pre-lubricated blend, preparation of final blend and compression into tablets. This non-standard process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scaled batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. requirements. 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, residual solvents, dissolution, identification, assay, uniformity of dosage units and impurities. 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 three full scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three full scaled batches per strength stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The batches were stored in the proposed packaging and in accordance with ICH stability guidelines. Photostability studies were performed and showed that the product is stable to light when packed in blisters. Some changes were seen, however remained within specification. Based on the results, the claimed shelf-life of 2 years with storage condition 'Store in the original package in order to protect from light' and 'This medicinal product does not require any special temperature storage conditions' is justified.

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

Lactose and lactose monohydrate are of bovine origin. A statement that the BSE-risk in the pharmaceutical grade lactose is negligible has been provided by the supplier of lactose and lactose monohydrate. In addition, a statement that the active substance and the other excipients are not of animal origin has been provided by the manufacturer of the drug product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Everolimus Synthon 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 Synthon 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.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Everolimus Synthon 10 mg, tablets (Synthon B.V., NL) is compared with the pharmacokinetic profile of the reference product Afinitor 10 mg tablets (Novartis Europharm Limited, Ireland) under fasting and fed conditions.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
In accordance with the general biowaiver criteria, as described in the "Guideline on the Investigation of Bioequivalence":

- the pharmaceutical products are manufactured by the same manufacturing process
- the qualitative composition of the different strengths is the same
- the composition of the strengths are quantitatively proportional
- dissolution has been investigated at different pH values (pH 1.2, 4.5 and 6.8), as well as in the QC medium, and the similarity of in vitro dissolution was demonstrated at all conditions for all strengths
- at pH values where sink conditions were not achievable for all strengths, it was shown that this was drug substance rather than formulation related by showing similar profiles at the same dose (2*5 mg vs. 10 mg and 4*2.5 mg vs. 10 mg).

The biowaiver for the additional 2.5 and 5 mg strengths is acceptable.

Bioequivalence studies
Design
The design of both studies is acceptable. According to European Medicines Agency product specific bioequivalence guidance for everolimus, in case of oncologic indication only, 2 single dose studies, i.e. 10 mg intact tablet fasted and fed, should be carried out to support such an application. In case the 10 mg tablet may be suspended, a study with the suspended tablet under fasting conditions should also be carried out.
The reference product (tablets – either intact or as a suspension) should be consistently taken with or without food according to the SmPC. Since the specific formulation (e.g.

particle size and excipients) is known to be critical to the performance of the formulation in fed conditions, it cannot be assumed that the impact of food will be the same regardless of formulation. According to the SmPC, Afinitor tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed. As the tablets may not be suspended, the 2 studies submitted, i.e. a fast and fed study, are considered sufficient.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence study I – fasting conditions
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy (24 male/12 female) subjects, aged 23-52 years. Each subject received a single dose (10 mg) of one of the 2 everolimus formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.50, 0.75, 1.00, 1.33, 1.67, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0, 48.0 and 72.0 after administration of the products.

Results
All subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of everolimus under fasted conditions.

Treatment N=36	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	367 ± 100	434 ± 113	62 ± 14	0.75 (0.50 – 1.67)	29 ± 5
Reference	405 ± 114	473 ± 136	61 ± 15	0.75 (0.50 – 3.0)	28 ± 5
***Ratio (90% CI)**	0.91 (0.86 – 0.97)	--	1.02 (0.94 – 1.10)	--	--
CV (%)	15.2	--	19.1	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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 concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Bioequivalence study II – fed conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 36 healthy (22 male/14 female) subjects, aged 20-54 years. Each subject received a single dose (10 mg) of one of the 2 everolimus formulations. The tablet was orally administered with 240 ml water after intake of a high fat, high caloric breakfast (consisting of a hard-boiled egg, strawberry jam, butter, a roll, salami, sugar and a fruit tea). There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1.00, 1.33, 1.67, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 24.0, 48.0 and 72.0 after administration of the products.

Results

Two subjects dropped-out after administration in the washout period, one due to an adverse event (extraction of wisdom tooth) and a serious adverse event (gastritis with the necessity of hospitalisation in a local hospital). 34 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of everolimus under fed conditions

Treatment N=34	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	363 ± 112	428 ± 129	44 ± 11	1.33 (0.67 – 3.50)	28 ± 6
Reference	371 ± 119	438 ± 136	46 ± 11	1.0 (0.67 – 3.0)	27 ± 6
***Ratio (90% CI)**	0.98 (0.94 – 1.02)	--	0.96 (0.89 – 1.04)	--	--
CV (%)	10.5	--	18.7	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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 concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

<u>Conclusion on bioequivalence studies</u>

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Everolimus Synthon is considered bioequivalent with Afinitor under fasted and fed conditions.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 Synthon.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Cardiac failure - Cytopenia - Drug interaction with ACE inhibitors and increased risk of angioedema - Drug interaction with CYP3A4 substrates and PgP substrates - Drug interaction with moderate CYP3A4 inhibitors and PgP inhibitor - Drug interaction with strong CYP3A4 inducers or PgP inducers - Drug interaction with strong CYP3A4 inhibitors and PgP inhibitors - Dyslipidaemia - Female fertility (including secondary amenorrhea) - Haemorrhages - Hyperglycaemia/new onset diabetes mellitus - Hypersensitivity (anaphylactic reactions) - Hypophosphataemia - Increased creatinine / proteinuria / renal failure - Non-infectious pneumonitis - Pre-existing infection (reactivation, aggravation, or exacerbation) - Safety in patients with hepatic impairment - Severe infections - Stomatitis - Thrombotic and embolic events - Wound healing complications
Important potential risks	- Drug interaction with exemestane - Male infertility - Muscle-wasting / muscle-loss

	- Postnatal developmental toxicity - Pregnant or breast-feeding women
Missing information	- Comparative safety of everolimus and exemestane therapy versus everolimus monotherapy - Long-term safety - Off-label use in paediatric and adolescent patients

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 demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Afinitor 2.5 mg, 5 mg and 10 mg tablets (which is considered user tested). The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Everolimus Synthon 2.5 mg, 5 mg and 10 mg, tablets have proven chemical-pharmaceutical quality and are generic forms 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.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 Synthon with the

reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 30 May 2018.

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/3977/1-3/IB/002	Changes in the manufacturing process of the active substance; minor change to the restricted part of an Active Substance Master File	No	05-10-2018	Approved	-