COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

(everolimus)

NL/H/3914/001-003/DC

Date: 27 November 2018

This module reflects the scientific discussion for the approval of Everolimus CF 2.5 mg, 5 mg and 10 mg, tablets. The procedure was finalised on 22 March 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 CF 2.5 mg, 5 mg and 10 mg, tablets, from Centrafarm B.V.

The product is indicated for:
Hormone receptor-positive advanced breast cancer
The 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
The 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
The 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
The 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 states (CMS) involved in this procedure were Austria, Belgium, Czech Republic, Germany, Denmark, Spain, Finland, France, Croatia, Italy, Luxembourg, Poland, Sweden and Slovak Republic.

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 CF is a white to off white coloured, oval, flat shaped tablet debossed with ‘EVR’ on one side. On the other side the strengths 2.5 mg, 5 mg and 10 mg are respectively debossed with ‘2.5’, ‘5’ and ‘NAT’ and they contain 2.5 mg, 5.0 mg or 10 mg everolimus.

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

The excipients are: butylhydroxytoluene (E321), hypromellose Type 2910 (E464), lactose, crospovidone Type A (E1202) and magnesium stearate.

II.2 Drug Substance

The active substance is everolimus, an established active substance. Everolimus is not subject of a monograph described in the European Pharmacopoeia (Ph.Eur.), although a

draft monograph has been published in Pharmeuropa. Everolimus is a white to light yellow coloured powder, soluble in methanol, acetonitrile and ethanol and insoluble in water. The drug substance contains 15 asymmetric carbon atoms and four substituted double bonds. Everolimus is known to exist in both crystalline and amorphous forms. For the manufacturing process of this drug product, the amorphous form of the drug substance is employed. As the drug substance is dissolved in acetone during the manufacturing process, the polymorphic form of the active substance is not considered as critical for the drug product. There are two different active substance manufacturers used for this product.

The Active Substance Master File (ASMF) procedure is used for 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

Both drug substance manufacturers do not use class 1 organic solvents or heavy metal catalysts. Critical process parameters have been identified and respective process ranges and/or set points have been satisfactorily established. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. All in-house methods for drug substance control by both manufacturers are adequately described and validated in the dossier. A set of forced degradation studies demonstrate that the methods for control of related substances and assay are stability indicating. All manufactured batches comply with the proposed specification. Batch analytical data demonstrating compliance with this specification have been provided for three batches of each strength.

Stability of drug substance

Drug substance from both manufacturers is generally very stable in the protective packaging at the proposed respective accelerated and long-term conditions and no specific degradational trends are being observed. The proposed re-test periods from the two manufacturers are 24 and 36 months when stored under the proposed conditions.

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 drug product Everolimus tablets was developed as a generic equivalent to Afinitor by Novartis from the European market. The product is intended as an immediate release product. In-line with the reference

product, Everolimus tablets are manufactured with the addition of an antioxidant, this approach has been sufficiently justified.
The dissolution characteristics of the 10 mg test product were compared to the innovator Afinitor from the European market. The same batches were employed in the bioequivalence study. The difference in assay between the two products is less than 5% and CoA's for both products are provided.
The MAH is seeking for a biowaiver for the lower 2.5 mg and 5 mg strengths on the basis of the successful "fasting" bioequivalence study conducted on the 10 mg strength, the common blend manufacturing strategy and the comparable in vitro dissolution of both test product strengths in three different release media. No release is observed in 0.1N HCl for all product strengths. Only partial dissolution is observed in buffers of pH 4.5 and 6.8 for all strengths; however, the same dissolution behaviour is observed for all 10 mg doses and similarity factors f2 above 50 are obtained in all cases. All product strengths are sufficiently soluble in the proposed QC medium and fast release of the active (greater 85% after 15 min) is observed in all cases. The conditions for granting a biowaiver are therefore considered fulfilled.

Manufacturing process

The manufacturing process consists of wet granulation followed by compression. The in-process controls are sufficient for an immediate release product. Since the formula of all strengths is proportional, a common blend approach is used. The common blend can be split into sub-batches of different strengths. The process was validated on 6 production scale batches of the common blend, compressed into three batches of the 2.5 mg, 5 mg and 10 mg tablets, respectively. The batch used in the bioequivalence study is part of the performed process validation. A summary of the in-process information during manufacture is provided to confirm that the proposed Everolimus 2.5 mg, 5 mg and 10 mg tablets can be manufactured according to the proposals in the dossier. All parameters and attributes were found to be within acceptable ranges and according to acceptance criteria.

Control of excipients

All excipients are commonly used in medicinal products and comply with their respective monographs in the Ph. Eur., this is 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, average weight, uniformity of dosage units, water content, assay, dissolution, related substances, residual acetone and microbiological quality. 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 for 3 batches of each tablet strength 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 nine batches (three batches of each strength) stored at 25°C/60 %RH (24 months) and 40°C/75 %RH (6 months). All results

remained well within the specified limits. A photostability study has been performed on the three batches of the 10 mg strength. The conditions of the study were selected according to the ICH guideline. The drug product did only show slight signs of degradation after exposure to light without the protection of the primary packaging material. As these results are well within the specification limits, the drug product is not considered to be photosensitive.
The proposed shelf-life of 24 months with storage condition 'This medicinal product does not require any special temperature storage conditions; Store in the original package to protect from light' for the finished product in Al/Al blisters is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose is of bovine origin and BSE statements from the suppliers are provided. No other excipients of human or animal origin are used in the manufacturing. The supplier of lactose certified that the milk is sourced from healthy animals in the same conditions as milk collected for human consumption and that the lactose is prepared without the use of other ruminant materials.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Everolimus CF 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 CF 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 CF (Centrafarm B.V., NL) is compared with the pharmacokinetic profile of the reference product Afinitor 10 mg, tablets (Novartis Pharma B.V., NL) under fasted and fed conditions.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing. Since the product must be taken consistently either with or without food, two bioequivalence studies under fasting and fed conditions are necessary.

Biowaiver
For the 2.5 mg and 5 mg strengths a biowaiver was requested. All conditions for granting biowaiver are met, i.e. the same manufacturer, same qualitative composition, same ratio between active substance and excipients, comparable in vitro dissolution profile. Everolimus is a drug with very low solubility of 0.0 at pH 1.2 and 0.003 mg/ml at pH 4.5 and 6.8. For this reason, no sink conditions are achieved in different media and thus there are differences in the dissolution between different strengths. It is therefore appropriate to demonstrate similarity in the dissolution between different strengths at the same 10 mg dose. The MAH used 500 ml of the dissolution media while the Guideline on Investigation of Bioequivalence recommends the use of 900 ml. It is however expected that the use of 900 ml of dissolution media would generate similar dissolution profiles. A biowaiver for the 2.5 and 5 mg tablet is acceptable.

Bioequivalence studies
Bioequivalence study I – 10 mg tablets, fasted conditions
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male and female subjects, aged 32-78 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 a fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is considered appropriate. Considering a long terminal elimination half-life of around 30 hours, a sampling schedule up to 72 hrs is appropriate as the absorption phase for immediate release products is expected to be completed within 72 hours post-dose. The wash out period is long enough to assure no carry over effect. There were also no pre-dose concentrations in any subject in the second period.

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.

Results
All 36 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_{0-72}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	518 ± 136	81 ± 18	0.75 (0.50-2.00)
Reference	531 ± 142	84 ± 24	1.00 (0.50-3.00)
***Ratio (90% CI)**	0.98 (0.93-1.02)	0.98 (0.92-1.05)	--

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

Bioequivalence study II – 10 mg tablets, fed conditions
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 200 healthy male subjects, aged 19-44 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 30 minutes after the start of the high-fat, high-calorie breakfast (consisting of bread, milk, walnuts, cutlet, green chutney and tomato chutney). There were 2 dosing periods, separated by a washout period of at least 16 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1.00, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.33, 3.67, 4.0, 4.5, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours after administration of the products.

The design of the study is considered appropriate. Considering a long terminal elimination half-life of around 30 hours, a sampling schedule up to 72 hrs is appropriate as the absorption phase for immediate release products is expected to be completed within 72 hours post-dose. The wash out period is long enough to assure no carry over effect. There were also no pre-dose concentrations in any subject in the second period.

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.

Results
A total of 16 subjects were wiredrawn from the study; 12 subjects did not report to the facility before the second period, 3 subjects were withdrawn due to adverse events (vomiting, axillary swelling and accidental injury) and 1 subject did not complete the breakfast. Therefore, 184 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=184	**AUC_{0-72}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	711 ± 213	61 ± 19	2.33 (1.00-8.00)
Reference	762 ± 248	64 ± 20	2.34 (0.67-16.00)
***Ratio (90% CI)**	0.93 (0.91-0.96)	0.95 (0.92-0.99)	--

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

Conclusion on bioequivalence studies
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 CF is considered bioequivalent with Afinitor.

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).

The results of the studies with 10 mg formulation can be extrapolated to other strengths 2.5 mg and 5 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 CF.

- 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 - 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
Important potential risks	- Postnatal developmental toxicity - Pregnant or breast-feeding women - Intestinal obstruction/ileus - Male infertility - Pancreatitis - Cholilithiasis - Muscle-wasting/muscle-loss
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

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

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 test consisted of: a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. 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

Everolimus CF 2.5 mg, 5 mg and 10 mg, tablets have a 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 CF with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 March 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/3914/1-3/IB/001	Change in the (invented) name of the medicinal product; for nationally authorised products	-	05-08-2018	Approved	-