COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Everolimus Biocon 2.5 mg/5 mg and 10 mg tablets
(everolimus 0.2% BHT)

NL/H/5047/001-003/DC

Date: 17 January 2022

This module reflects the scientific discussion for the approval of Everolimus Biocon. The procedure was finalised at 26 October 2021. 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 Biocon 2.5 mg/5 mg and 10 mg tablets, from Biocon Pharma Malta I Limited.

The product is can be used for the following therapeutic indications:

Hormone receptor-positive advanced breast cancer
Everolimus Biocon 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 Biocon 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 Biocon 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 of the SmPC).

Renal cell carcinoma
Everolimus Biocon 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/10 mg tablets which has been authorised in the EU via the centralised procedure (EU/1/09/538) by Novartis Europharm Limited since 2009 (original product).

Scientific Advice
The MAH has received scientific advice from EMA (EMEA/H/SA/2873/1/2014/II; dated 25 September 2014) and MHRA/UK (917/Everolimus; dated 1 May 2015). These scientific advices have been included in the dossier.

Information relating to Orphan Market Exclusivity of Lutathera
The MAH has provided the comparison below of their product and Lutathera 370 MBq/mL solution for infusion and concludes that Lutetium (177Lu) oxodotreotide is different from proposed API molecule i.e. Everolimus in terms of molecular structure, molecular formula,

molecular mass and having different mechanism of action. As such, Everolimus 2.5 mg, 5 mg 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.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Everolimus Biocon 2.5 mg tablets
White to off-white, capsule shaped, flat faced bevelled edge tablet of approximately 10.00 mm in length and 4.50 mm in width debossed, with B 2.5 on one side and plain on other side.

Everolimus Biocon 5 mg tablets
White to off-white, capsule shaped, flat faced bevelled edge tablet of approximately 12.00 mm in length and 5.00 mm in width, debossed with B 5 on one side and plain on other side.

Everolimus Biocon 10 mg tablets
White to off-white, capsule shaped, flat faced bevelled edge tablet of approximately 16.50 mm in length and 6.75 mm in width, debossed with B 10 on one side and plain on other side.

The 2.5 mg, 5 mg and 10 mg tablets contain as active substance 2.5 mg, 5 mg or 10 mg of everolimus, respectively.

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

The excipients are butylated hydroxytoluene (E321), hypromellose 2910 (E464), lactose anhydrous, lactose monohydrate, crospovidone (E1202) and magnesium stearate (E470b).

The three tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is everolimus, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is amorphous powder, practically insoluble in water and heptane, but very soluble in anhydrous ethanol, light sensitive, hydroscopic and optically active. Everolimus exhibits polymorphism and is consistently produced in its amorphous form.

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 applicant 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 manufacturing process of everolimus consists of the following steps: synthesis of the chemical precursor, two chemical steps, purification, concentration, crystallisation and lyophilisation. Everolimus (0.2% BHT) has been adequately characterised and acceptable specifications for the starting material and other solvents and reagents used in the manufacturing process have been adopted. The use of BHT as well as its quantity (0.2%) have been justified.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., with additional requirements for identity; impurities A and B; colour of solution; butylated hydroxytoluene content; residual solvents, alcohol content and microbiological quality. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three full scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for six production scaled batches stored at 2-8°C (12 months) and 25°C/60% RH (6 months). The batches were stored in LDPE bags and finally enclosed in an aluminium container. No out of specifications, clear up- or downward trends are observed for any of the parameters, at real time (i.e. 2-8°C) and accelerated (i.e. 25°C/60% RH) conditions. The proposed retest period of 18 months by the drug substance supplier, with storage condition 'Store under nitrogen in an air tight container protected from light below at 2-8°C for the drug substance is justified. The finished product manufacturer applies a retest period of 12 months.

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 development of the product has been described, the choice of excipients is justified and their functions explained. Sufficient information is provided on relevant properties of the active substance and on the choice of excipients. The drug substance is dissolved with the butylated hydroxytoluene solution for granulation, therefore drug substance particle size is not considered critical for

the drug product. An excipient compatibility study has been performed with satisfactory results.

A Quality by Design (QbD) approach is used to develop Everolimus tablets 2.5 mg, 5 mg and 10 mg, with Afinitor 2.5 mg, 5 mg and 10 mg tablets as reference product. The need for an antioxidant, butylated hydroxytoluene, in the formulation and its level have been justified. The same antioxidant is present in the reference product.

The proposed dissolution method is acceptable. A bioequivalence (BE) study has been performed with the 10 mg product versus the 10 mg strength of the reference product. The 10 mg test batch used in the BE study is a representative batch. For the additional strengths a biowaiver is claimed. The pharmaceutical development of the product has been adequately performed. Comparative in vitro dissolution tests complementary to the bioequivalence studies have been adequately performed.

Manufacturing process

The manufacturing process consists of sifting, granulation, drying, milling, sifting of extra granular and lubricated materials, mixing, pre-lubrication, lubrication, blend division, compression and packing. In view of the low drug content, the manufacturing process is considered non-standard. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three production scaled batches per strength in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. requirements. The functionality-related characteristics have been adequately discussed. 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, appearance of the desiccant tablets, identification, water content, dissolution, related substances, assay, BHT content, uniformity of dosage units, residual solvents, elemental impurities and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life limits are identical except for assay, related substances and BHT content. The specification is acceptable.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three full scaled batches per strength from the proposed production site has been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three production scaled batches per strength stored at 25°C/60% RH (24 months), 30°/65% RH (12 months) and 40°C/75% RH (six

months) in accordance with applicable European guidelines demonstrating the stability of the product for 24 months. The batches were stored in Al-Al blister with desiccant tablets. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light. No significant change and/or no clear trends is seen for appearance, water content, dissolution, and microbial examination of the finished product. On basis of the data submitted, a shelf life was granted of 24 months with storage condition "Do not store above 25°C. Store in the original package in order to protect from light and moisture".

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 for lactose anhydrous and lactose monohydrate 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 Biocon 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 Biocon 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 with the 10 mg tablet under fasting and fed conditions.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Everolimus 10 mg tablets (Biocon Pharma Limited, India) is compared with the pharmacokinetic profile of the reference product Afinitor 10 mg tablets (Novartis Europharm Limited, UK) under fasting and fed conditions.

According to CHMP's product specific bioequivalence guidance for everolimus, in case of oncologic indication only, two 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. As the tablets may not be suspended, the two studies submitted, i.e. a fast and fed study, are considered sufficient.

Biowaiver

A biowaiver of strengths was requested by the MAH for the 2.5 mg and the 5 mg strengths. The following criteria have been fulfilled to support a biowaiver for additional strengths:
- 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.

Furthermore, the MAH provided an adequate bootstrapping analysis using correct calculations for the confidence intervals. This was confirmed by the provided raw data output. The calculations are acceptable and similarity of dissolution profiles can be claimed. The biowaiver for the additional 2.5 mg and 5 mg strengths is acceptable from a chemical point of view.

The design of the study is acceptable.

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 studies

Study 1: single dose, 10 mg tablet under fasting conditions
Design
A randomized, balanced, open label, two treatment, two period, two sequence, single dose, crossover, pivotal bioequivalence study was carried out under fasted conditions in 70 healthy male subjects, aged 18-44 years. Each subject received a single dose (10 mg) of one of either the test or reference everolimus formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected at 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 hours after administration of the products.

Results
Out of a total of 70, 66 subjects were eligible for pharmacokinetic analysis. Four subjects did not report to the facility in period two.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of everolimus (10 mg) under fasted conditions.

Treatment N=66	**AUC_{0-72h}** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	910 ± 304	103 ± 31	1.0 (0.50 – 4.0)
Reference	972 ± 298	114 ± 28	1.0 (0.50 – 3.0)
***Ratio (90% CI)**	0.93 (0.89 – 0.98)	0.89 (0.84 – 0.94)	--
CV (%)	17.9	19.2	--

AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
CV	coefficient of variation
CI	confidence interval

**ln-transformed values*

Study 2: single dose, 10 mg tablet under fed conditions

Design

A randomized, balanced, open label, two treatment, two period, two sequence, single dose, crossover, pivotal bioequivalence study was carried out under fed conditions in 48 healthy male subjects, aged 21-43 years. Each subject received a single dose (10 mg) of one of either the test or reference everolimus formulations 30 min after start of intake of a high caloric high fat meal (bread, omelette, chicken tikka, hash brown potatoes and milk) . The tablet was orally administered with 240 ml water. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected at pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.0, 48.0 and 72.0 hours after administration of the products.

Results

Out of a total of 48, 47 subjects were eligible for pharmacokinetic analysis. One subjects did not report to the facility in period two.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of everolimus (10 mg) under fed conditions.

Treatment N=47	AUC_{0-72h} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	754 ± 169	64 ± 18	2.67 (1.25 – 8.0)
Reference	804 ± 207	69 ± 21	2.67 (0.50 – 6.0)
***Ratio (90% CI)**	0.94 (0.91 – 0.98)	0.93 (0.86 – 1.00)	--
CV (%)	11.3	22.5	--

AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
CV	coefficient of variation
CI	confidence interval

**ln-transformed values*

Conclusion on bioequivalence studies:

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Everolimus Biocon 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).

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 Biocon.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	- None
Important potential risks	- None
Missing information	- None

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 two bioequivalence studies 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 (PL) 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 PL was English. The test consisted of: a pilot test with four participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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 Biocon 2.5 mg/5 mg and 10 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Afinitor. 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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Everolimus Biocon with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 October 2021.

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