COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Syrleno 2.5 mg, 5 mg and 10 mg tablets (everolimus)

NL/H/5526/001-003/MR

Date: 17 February 2026

This module reflects the scientific discussion for the approval of Syrleno 2.5 mg, 5 mg and 10 mg tablets. The procedure was finalised on 23 May 2024. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 Syrleno 2.5 mg, 5 mg and 10 mg tablets, from Alkaloid - INT d.o.o.

The product is indicated for:
Hormone receptor-positive advanced breast cancer
Syrleno 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
Syrleno 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
Syrleno 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
Syrleno 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 up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this mutual recognition procedure, essential similarity is proven between the new product and the innovator product Afinitor 2.5 mg, 5 mg and 10 mg tablets, which has been registered in the EU via a centralised procedure (EU/1/09/538) since 18 December 2012 by Novartis Pharma B.V.

The concerned member states (CMS) involved in this procedure were Bulgaria, Croatia, Romania and Slovenia.

Scientific advice was given by Germany, the Netherlands and Spain.

Similarity assessment
According to Article 8(1) of Regulation (EC) No 141/2000, no marketing authorisation can be granted for a product similar to an orphan medicinal product for a period of ten years, when this concerns a similar medicinal product with the same therapeutic indication. A similarity assessment has been performed between Syrleno and Lutathera, which obtained orphan market exclusivity on 31 January 2008, based on designation EU/3/07/523. The similarity

assessment report was completed in January 2024, concluding the two products were not similar based on mechanism of action and principal molecular structure. 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.

II. QUALITY ASPECTS

II.1 Introduction

Syrleno is a white to off white oval biconvex tablet. The three different tablet strengths can be distinguished by their appearance, based on size and debossing, as follows:

- 2.5 mg tablet: approximately 10 x 5 mm, debossed with E9VS on one side and 2.5 on the other side.
- 5 mg tablet: approximately 13 x 6 mm, debossed with E9VS 5 on one side.
- 10 mg tablet: approximately 16 x 8 mm, debossed with E9VS 10 on one side.

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

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

The three different tablet strengths are fully dose proportional.

The tablets are packed in Aluminium blisters or Aluminium perforated unit-dose blisters (oriented polyamide/aluminium/ polyvinyl chloride/aluminium; oPA/Al/PVC/Al).

II.2 Drug Substance

The active substance is everolimus, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to pale brown/yellow amorphous powder and is almost insoluble in water.

Three CEP procedures are used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
Three CEPs have been submitted; therefore no details on the manufacturing process have been included.

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 of the CEPs for butylhydroxytoluene (BHT), impurities, and residual solvents as well as a test for microbiological contamination. Batch analytical data demonstrating compliance with this specification have been provided for three batches per active substance manufacturer.

Stability of drug substance
The active substance is stable for 24-48 months (depending on active substance manufacturer) when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

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. 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 the antioxidant BHT was added and its level has been justified.

Manufacturing process
The tablets are manufactured by the following steps: preparation of a solid dispersion, preparation of the pre-lubricated blend, preparation of the final blend, and compression into tablets. The non-standard manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scale 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 of everolimus, assay of everolimus, identification of BHT, assay of BHT, uniformity of dosage units and impurities. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate

nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data three full scaled batches of each 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 three full scale batches per strength stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable to light, when packed in blisters. On basis of the data submitted, a shelf life was granted of three years. The labelled storage conditions are "Store in the original package in order to protect from light. This medicinal product does not require any special temperature storage conditions."

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

Scientific data and/or certificates of suitability issued by the EDQM for excipients lactose and lactose monohydrate 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 Syrleno 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 Syrleno is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was 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 was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided,

which was 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 member states agreed that no further clinical studies are required, besides the 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 Syrleno 2.5 mg, 5 mg and 10 mg tablets (Alkaloid - INT d.o.o., Slovenia) was compared with the pharmacokinetic profile of the reference product Afinitor 2.5 mg, 5 mg and 10 mg tablets (Novartis Europharm Limited, Ireland).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

In accordance with the general biowaiver criteria for a waiver for additional strength, as described in the "Guideline on the Investigation of Bioequivalence", the following general requirements are met:

a. the pharmaceutical products are manufactured by the same manufacturing process
b. the qualitative composition of the different strengths is the same
c. the composition of the strengths are quantitatively proportional
d. 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
e. 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 x 5 mg vs. 10 mg and 4 x 2.5 mg vs. 10 mg).

The dissolution was investigated according to the EMA Bioequivalence guideline. The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and

100% suggests that the two dissolution profiles are similar. The biowaiver for the additional 2.5 mg and 5 mg strengths is acceptable.

Bioequivalence studies

Study 493/14 (single dose 10 mg fasting conditions)

Design

A single-dose, randomised, open-label, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male and female subjects, aged 23-52 years. Each subject received a single dose (10 mg) of one of the two everolimus formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of fourteen days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 12, 24, 48 and 72 hours after administration of the products.

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.

Results

No subjects were withdrawn from the study. All 36 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of everolimus, 10 mg 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)**
Test	367 ± 100	434 ± 113	62 ± 14	0.75 (0.50-1.67)
Reference	405 ± 114	473 ± 136	61 ± 15	0.75 (0.50-3.00)
***Ratio (90% CI)**	0.91 (0.86-0.97)	-	1.02 (0.94-1.10)	-

$AUC_{0-\infty}$	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 = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 499/14 (single dose 10 mg fed conditions)

Design

A single-dose, randomised, open-label, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 36 healthy male and female subjects, aged 20-54 years. Each subject received a single dose (10 mg) of one of the two everolimus formulations. The tablet was orally administered with 240 ml water after an high-fat and high-calorie breakfast (966 kcal). There were two dosing periods, separated by a washout period of fourteen days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Food effect

In healthy subjects, high fat meals reduced systemic exposure to everolimus 10 mg (as measured by AUC) by 22% and the peak plasma concentration Cmax by 54%. Light fat meals reduced AUC by 32% and Cmax by 42%. Food, however, had no apparent effect on the post absorption phase concentration-time profile.

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

During the study there were two drop-outs. One subject dropped-out in the washout period because of an extraction of wisdom tooth and the other subject dropped-out because of gastritis with the necessity of hospitalisation in a local hospital. Of the 36 subjects enrolled in the study, 34 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of everolimus, 10 mg 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)
Test	363 ± 112	428 ± 129	44 ± 11	1.33 (0.67-3.50)
Reference	371 ± 119	438 ± 136	46 ± 11	1.00 (0.67-3.00)
***Ratio (90% CI)**	0.98 (0.94-1.02)	-	0.96 (0.89-1.04)	-

$AUC_{0-\infty}$	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 = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**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 Syrleno 10 mg is considered bioequivalent with Afinitor 10 mg.

The results of the bioequivalence studies with the 10 mg formulation can be extrapolated to the other strengths of 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.

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 Syrleno. At the time of approval, the most recent version of the RMP was version 1.0 dated 16 December 2021.

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. 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

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, EU/1/09/538. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Syrleno 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 Syrleno with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 23 May 2024.

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/5526/001-003/R/001	Renewal	No	26-11-2025	Approved	N.A.