COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sunitinib Koanaa 12.5 mg, 25 mg, 37.5 mg and 50 mg hard capsules (sunitinib malate)

NL/H/5339/001-004/DC

Date: 5 April 2022

This module reflects the scientific discussion for the approval of Sunitinib Koanaa 12.5 mg, 25 mg, 37.5 mg and 50 mg hard capsules. The procedure was finalised at -0043 February 2022. 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
GIST	Gastrointestinal stromal tumour
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MRCC	Metastatic renal cell carcinoma
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
pNET	Pancreatic neuroendocrine tumours
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 Sunitinib Koanaa 12.5 mg, 25 mg, 37.5 mg and 50 mg hard capsules, from Koanaa Healthcare GmbH.

The products are indicated for:

- Gastrointestinal stromal tumour (GIST)
  Sunitinib is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) in adults after failure of imatinib treatment due to resistance or intolerance.

- Metastatic renal cell carcinoma (MRCC)
  Sunitinib is indicated for the treatment of advanced/metastatic renal cell carcinoma (MRCC) in adults.

- Pancreatic neuroendocrine tumours (pNET)
  Sunitinib is indicated for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression in adults.

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 products Sutent, 12.5 mg, 25 mg, 37.5 mg and 50 mg hard capsules which have been registered in the EEA by Pfizer Europe MA EEIG since 19 July 2006 through a centralised procedure (EU/1/06/347/001-008).

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

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

Similarity assessment in view of the orphan drug legislation

The MAH provided a similarity assessment between generic Sunitinib Koanaa and Lutathera (Lutetium (^{177}Lu) oxodotreotide, EU/1/17/1226) for the treatment of gastro-entero-pancreatic neuroendocrine tumours, and Ayvakyt (avapritinib, EU/1/20/1473) and Qinlock (ripretinib, EMEA/H/C/005614) for the treatment of GIST. The MAH addressed the three criteria that have been defined by the Regulation on Orphan medicinal products: therapeutic indication, mechanism of action and principal molecular structural features. Having considered the arguments presented by the MAH, and with reference to Article 8 of Regulation (EC) No. 141/2000, generic Sunitinib Koanaa is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Lutathera or Ayvakyt or Qinlock.

II. QUALITY ASPECTS

II.1 Introduction

Sunitinib Koanaa are hard, gelatine capsules.

- Sunitinib Koanaa 12.5 mg is a capsules with orange opaque cap and orange opaque body. The capsule is imprinted with white ink “SML” on the cap and “20” on the body. It contains orange granular powder. Each capsule contains sunitinib malate equivalent to 12.5 mg of sunitinib.
- Sunitinib Koanaa 25 mg is a capsule with caramel opaque cap and orange opaque body. The capsule is imprinted with white ink “SML” on the cap and “21” on the body. It contains orange granular powder. Each capsule contains sunitinib malate equivalent to 25 mg of sunitinib.
- Sunitinib Koanaa 37.5 mg is a capsule with yellow opaque cap and yellow opaque body. The capsule is imprinted with black ink “SML” on the cap and “22” on the body. It contains orange granular powder. Each capsule contains sunitinib malate equivalent to 37.5 mg of sunitinib.
- Sunitinib Koanaa 50 mg is a capsules with caramel opaque cap and caramel opaque body. The capsule is imprinted with white ink “SML” on the cap and “23” on the body. It contains orange granular powder. Each capsule contains sunitinib malate equivalent to 50 mg of sunitinib.

The capsules are packed in PVC/Aclar/Aluminium blister pack or high-density polyethylene (HDPE) bottle with a polypropylene child resistant closure.

The excipients are:
Capsule content

- *all strengths* - mannitol (E421), croscarmellose sodium (E468), povidone (K-25) and magnesium stearate (E470b)

Capsule shell

- 12.5 mg capsule - gelatine (E441), titanium dioxide (E171) and iron oxide Red (E172)
- 25 mg capsule - gelatine (E441), titanium dioxide (E171), iron oxide Red (E172), iron oxide yellow (E172) and iron oxide Black (E172)
- 37.5 mg capsule - gelatine (E441), titanium dioxide (E171) and iron oxide yellow (E172)
- 50 mg capsule - gelatine (E441), titanium dioxide (E171), iron oxide Red (E172), iron oxide yellow (E172) and iron oxide Black (E172)

Printing ink

- *12.5 mg capsule* - shellac (E904), propylene glycol (E1520), sodium hydroxide (E524), povidone (E1201) and titanium dioxide (E171)
- *25 mg capsule* - shellac (E904), propylene glycol (E1520), sodium hydroxide (E524), povidone (E1201) and titanium dioxide (E171)

- *37.5 mg capsule* - shellac (E904), propylene glycol (E1520), potassium hydroxide (E525), iron oxide black (E172) and ammonia solution concentrated (E527)
- *50 mg capsule* - shellac (E904), propylene glycol (E1520), sodium hydroxide (E524), povidone (E1201) and titanium dioxide (E171)

The four capsule strengths are dose proportional.

II.2 Drug Substance

The active substance is sunitinib malate, an established active substance not described in the European, British or American Pharmacopoeia (Ph.Eur., BP or USP, respectively). Sunitinib malate is a pale yellow to yellow crystalline powder. The substance is slightly soluble in water. Sunitinib shows polymorphism but only crystalline form 1 is manufactured and considered stable.

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 consists of three steps. The first step is the isolation of an intermediate, afterwards several additional steps are taken to obtain the malate salt of sunitinib hydrochloride. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification has been established in-house and is mostly in line with the specification of the active substance supplier. 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 three production scale batches in accordance with applicable European guidelines, demonstrating the stability of the active substance at 25°C/60% RH (36 months) and 40°C/75% RH (six months). Only for loss on drying a slight increase is seen at both storage conditions. Based on the data submitted, a retest period could be granted of 36 months when stored in a well closed container at controlled room temperature (20-25°C).

II.3 Medicinal Products

Pharmaceutical development

The products are an established pharmaceutical form and their development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. Compatibility of the excipients with the drug substance was demonstrated. The pharmaceutical development is based on similarity with the reference product Sutent. The quality control dissolution method has been adequately established. A bioequivalence (BE) study was performed with the 50 mg test product versus the 50 mg reference product. The 50 mg test batch used in the bioequivalence study was manufactured according to the finalised composition and manufacturing process at a representative scale. Comparative dissolution testing at 3 pH's has been successfully studied in support of the bioequivalence study and biowaiver for the additional lower strengths. Pharmaceutical development of the product has been adequately performed. Further, photostability studies on the different strengths were performed.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The product is manufactured using conventional manufacturing techniques, consisting of the following steps: sifting, dry mixing, granulation, drying, milling of dried granules, blending, lubrication, capsule filling and packing. Process validation data on the product have been presented for three pilot scale blend batches of each strength. Process validation for full scaled batches will be performed post authorisation.

Control of excipients

The excipients comply with the Ph.Eur. requirements, except for the hard gelatine capsules and imprinting ink for which an in-house specification is provided. These specifications are acceptable.

Quality control of drug products

The finished product specifications are adequate to control the relevant parameters for the dosage forms. The specification includes tests for description, identification of Sunitinib, water content, uniformity of dosage units, dissolution, assay, related substances and water activity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the products. The release and shelf life acceptance criteria are mostly the same, except for water content and assay of sunitinib. The specification is acceptable.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided for three pilot scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for three production scale batches of the lowest (12.5 mg) and highest strengths (50 mg). For the other strengths (25 mg and 37.5 mg) a bracketing approach is followed in accordance with ICH Q1D. The batches are stored at

25°C/60% RH (18 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in both the PVC/Aclar-Aluminium blister and HDPE bottles with cap. Photostability studies were performed in accordance with ICH recommendations on the 12.5 mg, 37.5 mg and 50 mg strengths, demonstrating that the product is stable when exposed to light. Further, an in-use study has been performed on the 50 mg strength for the HDPE bottles for a period of 28 days at 25°C/60% RH.
On basis of the data submitted, a shelf life was granted of 18 months. No specific storage conditions need to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Certificates of suitability issued by the EDQM have been provided for gelatine 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 Sunitinib Koanaa 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 Sunitinib Koanaa 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 Sutent 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

Sunitinib malate 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 one bioequivalence study, which is discussed below. A biowaiver is applied for the lower strengths of 12.5 mg, 25 mg and 37.5 mg.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Sunitinib Malate Capsules, 50 mg (Shilpa Medicare Limited, India) is compared with the pharmacokinetic profile of the reference product Sutent 50 mg, hard capsules (Pfizer Europe MA EEIG, Belgium).
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the EU reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
The MAH applied for a biowaiver for the lower strengths of 12.5 mg, 25 mg and 37.5 mg capsules. All strengths are manufactured by the same process and the composition of the different strengths is qualitatively the same. The composition of the different strengths is dose proportional. Based on the dissolution data, complete dissolution within 15 minutes was observed at the lowest pH. Dissolution media of the two higher pH levels was slower, however, similarity between the biobatch and all other strengths could be concluded. In conclusion, the biowaiver for the additional lower strengths could be granted.

Bioequivalence study
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, two-way crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 19-43 years. Each subject received a single dose (50 mg) of one of the two sunitinib 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 21 days.
Blood samples were collected within 1 hour prior to drug administration and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 18, 24, 36, 48, 60 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
All 24 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=24	AUC_{0-t} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	1461.885 (±253.9198)	37.261 (±6.2191)	7.00 (5.00-13.00)	41.427 (9.8512)
Reference	1428.303 (±249.3123)	36.940 (±5.2432)	7.00 (5.00 – 12.00)	42.802 (11.4168)
***Ratio (90% CI)**	1.02 (0.99-1.06)	1.00 (0.97-1.04)	-	-
CV (%)	6.65	6.97	-	-

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*

Conclusion on bioequivalence study
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 study, Sunitinib Koanaa is considered bioequivalent with Sutent.

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 bioequivalence study can be extrapolated to the lower strengths of 12.5 mg, 25 mg and 37.5 mg according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6. The dissolution requirements in the bioequivalence study guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, 2010) for granting a biowaiver are fulfilled as well.

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 Sunitinib Koanaa.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Cardiotoxicity (Torsade de pointes, left ventricular dysfunction/heart failure, pericardial events, cardiac ischaemic events) • Reversible posterior leukoencephalopathy syndrome • Hepatic failure • Osteonecrosis of the jaw • Severe cutaneous adverse reactions • Renal failure
Important potential risks	• Carcinogenicity
Missing information	• Severe hepatic impairment

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 Sutent. 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 Capecitabine Koanaa 150 mg & 500 mg film-coated tablets for design and layout (DE/H/5462/001-002/DC) and Sutent 12.5 mg, 25 mg, 37.5 mg and 50 mg hard capsules for scientific content and key information (EMEA/H/C/000687). 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

Sunitinib Koanaa 12.5 mg, 25 mg, 37.5 mg and 50 mg hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Sutent, 12.5 mg, 25 mg, 37.5 mg and 50 mg hard capsules. Sutent 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 Sunitinib Koanaa with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 February 2022.

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