COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

NL/H/5132/001-004/DC

Date: 22 November 2021

This module reflects the scientific discussion for the approval of Sunitinib Sun 12.5 mg, 25 mg, 37.5 mg and 50 mg, hard capsules. The procedure was finalised at 11 June 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
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 Sun 12.5 mg, 25 mg, 37.5 mg and 50 mg, hard capsules, from Sun Pharmaceutical Industries Europe B.V.

The product is indicated for:

- Gastrointestinal stromal tumour (GIST)
  Sunitinib Sun 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 Sun is indicated for the treatment of advanced/metastatic renal cell carcinoma (MRCC) in adults.

- Pancreatic neuroendocrine tumours (pNET)
  Sunitinib Sun 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 2006 through a centralised procedure (EU/1/06/347/001-008).

The concerned member states (CMS) involved in this procedure were Poland and Romania.

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 reference product Sutent was originally designated an orphan medicine for the orphan indications renal cell carcinoma and malignant gastrointestinal stromal tumours. Sutent was withdrawn from the Community register of orphan medicinal products in July 2008 upon request of the MAH.

The MAH provided a similarity assessment between generic sunitinib and Lutathera (lutetium (^{177}Lu) oxodotreotide, EU1/17/1226) and Ayvakyt (avapritinib, EU/1/20/1473). 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, generic Sunitinib Sun is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Lutathera and Ayvakyt.

II. QUALITY ASPECTS

II.1 Introduction

Sunitinib Sun are hard, self-locking, gelatine capsules.

- Sunitinib Sun 12.5 mg is a capsule with opaque reddish brown cap and opaque reddish brown body. The capsule is imprinted with 'RM53' on the cap and 'RM53' on the body in white ink. It contains yellow to orange coloured powder. Each capsule contains sunitinib malate, equivalent to 12.5 mg of sunitinib.
- Sunitinib Sun 25 mg is a capsule with opaque caramel cap and opaque reddish brown body. The capsule is imprinted with 'RM54' on cap and 'RM54' on body in white ink. It contains yellow to orange coloured powder. Each capsule contains sunitinib malate, equivalent to 25 mg of sunitinib.
- Sunitinib Sun 37.5 mg is a capsule with opaque yellow cap and opaque yellow body. The capsule is imprinted with 'RM55' on cap and 'RM55' on body in black ink. It contains yellow to orange coloured powder. Each capsule contains sunitinib malate, equivalent to 37.5 mg of sunitinib.
- Sunitinib Sun 50 mg is a capsule with opaque caramel cap and opaque caramel body. The capsule is imprinted with 'RM56' on cap and 'RM56' on body in white ink. It contains yellow to orange coloured powder. Each capsule contains sunitinib malate, equivalent to 50 mg of sunitinib.

The capsules are packed in PVC/PCTFE/Al blisters or in HDPE bottles with polypropylene screw cap and induction seal liner.

The excipients are:
Capsule content

- *all strengths* - mannitol (E421), croscarmellose sodium (E468), povidone (K-30) (E1201) and magnesium stearate (E470b)

Capsule shell

- *12.5 mg capsule*- gelatine, red iron oxide (E172) and titanium dioxide (E171)
- *25 mg capsule* - gelatine, red iron oxide (E172), titanium dioxide (E171), yellow iron oxide (E172) and black iron oxide (E172)
- *37.5 mg capsule* - gelatine. titanium dioxide (E171) and yellow iron oxide (E172)
- *50 mg capsule* - gelatine, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172) and black iron oxide (E172)

Printing ink

- *all strengths* - shellac (E904), propylene glycol (E 1520), titanium dioxide (E171), potassium hydroxide (E525) and (only for the 37.5 mg strength) black iron oxide (E172)

The four strengths are dose proportional.

II.2 Drug Substance

The active substance is sunitinib malate, an established active substance. It is not described in the European Pharmacopoeia (Ph.Eur.), British Pharmacopoeia or United States of America Pharmacopoeia. Sunitinib malate is a light yellow to brownish orange powder. The substance is soluble in dimethylsulfoxide, slightly soluble in water and practically insoluble in n-heptane. Sunitinib malate is manufactured as polymorphic form I. Batch data have sufficiently demonstrated that the manufacturing process consistently produces form I.

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 two synthetic 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 of the drug product manufacturer is in line with that of the ASMF-holder. The particle size distribution is tested for information while the acceptance criteria have been defined based on the drug substance batch used to manufacture the biobatch of the test product. The active substance specification is considered adequate to control the quality. The drug product manufacturer uses the same analytical methods as the ASMF-holder. The methods were adequately validated by the ASMF-holder. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scale batches, analysed by the ASMF-holder and the drug product manufacturer. The controls on critical steps, in-process controls and controls on intermediates are considered adequate.

Stability of drug substance

Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines, demonstrating the stability of the active substance at 25°C/60% RH (18 months) and at 40°C/75% RH (six months). All available long-term and accelerated results are meeting the set requirements. Based on the data submitted, a retest period could be granted of 24 months without special storage 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 choice of excipients is justified and their functions explained. The routine dissolution testing method is acceptable. The acceptance criterion reflects the dissolution profile of the biobatch of the test product sufficiently. The discriminatory nature of the method has been sufficiently shown. The comparative dissolution studies complementary to the bioequivalence study showed comparable dissolution profiles. Also the dissolution studies supported the biowaiver of strength for the 12.5, 25 and 37.5 mg capsules from a chemical-pharmaceutical point of view (see also IV.2 of this PAR). No formal photostability results have been provided. However, photostability of the drug substance was sufficiently demonstrated by the results of the forced degradation studies.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The straightforward manufacturing process mainly consists of wet granulation, mixing and encapsulation. The manufacturing process is considered standard and has been sufficiently described. The holding times for intermediate products are adequately investigated. In-process controls conducted on the blend and during filling are adequately described. Process validation data on the product have been presented for three production scaled batches per strength in accordance with the relevant European guidelines. These data indicate that the process consistently and reproducibly yields the product that meets predetermined attributes for the product.

Control of excipients

All excipients of the capsule filling and of the printing ink as well as the colourants are of pharmacopoeial grade and/or in accordance with Commission Regulation 231/2012. The specifications are acceptable. Magnesium stearate is of vegetable origin.

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 of active substance and colorants, average fill weight, uniformity of dosage units, water content, dissolution, assay, related substances and microbial enumeration test. The proposed release and shelf life specifications differ regarding the acceptance criteria for water content. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The drug product specification is acceptable.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data of three production scale batches per strength from the proposed production site have been provided, demonstrating compliance with the release specification. A risk evaluation on the presence of nitrosamine impurities has been provided and concluded that there is no risk of presence of nitrosamines.

Stability of drug product

Stability data on the product have been provided for three production scale batches each per strength package and per packaging, stored at 25°C/60% RH (six months) and 40°C/75% RH (six months). The studies have been conducted in accordance with applicable European guidelines. At both accelerated and long term conditions an slight increase in any unknown and total impurities was observed. However, the results remained well within the specification limits. No other trends are observed and no differences between tablets packed in the blister pack or HDPE container were observed. A photostability study was performed in line with ICH Q1B. No changes or trends were observed. Hence the drug product is considered as photostable. An in-use study has been performed wherein the drug product was tested at day 0 and day 28 at beginning of shelf life and after 5 months of shelf life.
On basis of the data submitted, a shelf life was granted of 2 years. 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

Scientific data and/or certificates of suitability (gelatine) issued by the EDQM 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 Sunitinib Sun 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 Sun 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

A bioequivalence study was carried out comparing the generic product Sunitinib 50 mg hard capsules to the reference Sutent 50 mg, hard capsules taken from the Dutch market.

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Sunitinib Sun 50 mg, hard capsules (Sun Pharmaceutical Industries Europe B.V., the Netherlands) 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.

<u>Biowaiver</u>
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, the comparative dissolution studies complementary to the bioequivalence study were comparable. The biowaiver for the additional lower strengths could be granted.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 30 healthy Asian male subjects, aged 19-44 years. Each subject received a single dose (50 mg) of one of the two sunitinib malate formulations. The tablet was orally administered with 240 ml of drinking water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of 31 days. The fasting state was continued until four hours post-dose.

Blood samples were collected at pre-dose (duplicate) and at 1, 2, 3, 4, 4.5, 5, 5.5, 6., 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 12, 14, 16, 20, 24, 48 and 72 hours after administration of the products.

The design of the study is acceptable. Sunitinib malate may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of sunitinib malate. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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

One subject dropped out from the study. The other 29 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=29	**AUC_{0-72} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	1201.6787 (±247.42474)	38.3122 (±7.75856)	6.000 (4.500 – 8.000)
Reference	1215.6738 (±275.32560)	37.7769 (±8.95721)	6.500 (4.500 – 8.000)
***Ratio (90% CI)**	0.99 (0.97 – 1.01)	1.02 (0.99-1.05)	-
CV (%)	4.93	6.34	-

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

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-72h}, and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Sunitinib Sun 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 Sun.

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

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 two 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 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

Sunitinib Sun 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 Sun capsules with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 June 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