COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sunitinib Synthon 12.5 mg and 50 mg, hard capsules
(sunitinib malate)

NL/H/5062/001, 004/DC

Date: 8 November 2021

This module reflects the scientific discussion for the approval of Sunitinib Synthon 12.5 mg and 50 mg, hard capsules. The procedure was finalised at 23 April 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 Sunitinib Synthon 12.5 mg and 50 mg, hard capsules, from Synthon B.V.

The product is indicated for:

- Unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) in adults after failure of imatinib treatment due to resistance or intolerance;
- Advanced/metastatic renal cell carcinoma (MRCC) in adults;
- 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 product Sutent 12.5 and 50 mg hard capsules by Pfizer Europe. Sutent has been centrally authorized in the European community since 19/07/2006 (EU/1/06/347).

The concerned member states (CMS) involved in this procedure were Estonia, Spain, Finland Croatia, Hungary, Lithuania, Latvia, Poland and Sweden.

Scientific advice
The scientific advice concerned the required conditions in a bioequivalence study and was followed by the MAH.

Similarity
At day 0 a similarity discussion has been provided with regard to Lutathera (EU1/17/1226). At day 70 is was concluded that lutetium (177Lu) oxodotreotide was considered not to be similar based on therapeutic indication, mechanism of action and principal molecular structure. However, in the meanwhile AYVAKYT (avapritinib), Blueprint Medicines (Netherlands) B.V. has been granted an MA which required an updated similarity discussion which was has been provided by the MAH with their day 160 responses. It is concluded that also avapritinib is considered not to be similar based on therapeutic indication, mechanism of action and principal molecular structure.

Orphan medicinal product
According to the application form and a check of the Community Register of orphan medicinal products, medicinal product(s) have been designated as orphan medicinal products, but not yet been granted a marketing authorisation in the EU. The MAH should monitor these products during the entire procedure up till granting National MA to check if a marketing authorisation has been granted. In case a marketing authorisation is granted, the MAH should update the report on similarity (Module 1.7.1) and, if applicable, submit the data to support derogation from orphan market exclusivity (Module 1.7.2).

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

II. QUALITY ASPECTS

II.1 Introduction

Sunitinib Synthon are hard capsules, specific appearance information can be found below:

Sunitinib Synthon 12.5 mg capsule
Hard gelatin capsule with orange cap and orange body, printed with white imprint "SNB" and "12.5" on the body. The capsule is filled with orange powder.

Sunitinib Synthon 50 mg capsule
Hard gelatin capsule with caramel cap and caramel (light brown) body, printed with black imprint "SNB" and "50" on the body. The capsule is filled with orange powder.

And contains as active substance 16.71 mg or 66.83 mg of sunitinib malate respectively, equivalent to 12.5 mg or 50 mg of sunitinib.

The hard capsules are packaged in one of three packaging materials:

- High density polyethylene (HDPE) containers with a child resistant polypropylene (PP) closure with desiccant;
- oPA/Al/PE/Al peel off blisters with desiccant;
- oPA/Al/PE/Al unit dose peel off blisters with desiccant.

The excipients are:

Sunitinib Synthon 12.5 mg capsule
Capsule content - povidone K30 LP, cellulose - microcrystalline (grade 102), croscarmellose sodium and magnesium stearate.

Capsule shell – gelatin, titanium dioxide (E171), red iron oxide (E172) and yellow iron oxide (E172).

Printing ink – shellac, titanium dioxide (E171) and propylene glycol.

Sunitinib Synthon 50 mg capsule
Capsule content - povidone K30 LP, cellulose - microcrystalline (grade 102), croscarmellose sodium and magnesium stearate.

Capsule shell - gelatin, titanium dioxide (E171), red iron oxide (E172), yellow iron oxide (E172) and black iron oxide (E172).

Printing ink - shellac, black iron dioxide (E172) and propylene glycol.

The two capsule strengths are dose proportional.

II.2 Drug Substance

The active substance is sunitinib malate, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). Two different crystalline forms I and II of the same supplier are used presented in separate ASMFs. Both forms are very poorly soluble in water but solubility in aqueous media was shown and dependent of pH and crystalline form. As the drug substance is fully dissolved, the polymorphic form of sunitinib malate is not relevant for the quality of the 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

Sunitinib malate is manufactured by condensation of the starting material after which the intermediate products are treated with several solvents. 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 is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three production scale batches. The stability indicating nature of the methods for assay and related substances was demonstrated by means of forced degradation studies. Descriptions of the analytical procedures have been provided. Where applicable, reference is made to the Ph.Eur. Validation reports for the in-house methods have been provided, this is considered to be adequate.

Stability of drug substance

Stability data on the active substance have been provided for three batches of polymorphic form I (storage conditions: 25°C/60% RH (up to 24 months) and 40°C/75% RH (six months)) and three batches of polymorphic form II (storage conditions: 5°C (up to 24 months) and 25°C/60% RH (six months)) in accordance with applicable European guidelines demonstrating

the stability of the active substances polymorphic form I and polymorphic form II for 24 months. No formal photostability results have been provided. However, photostability of the drug substance was sufficiently demonstrated by the results of the forced degradation studies. Based on the data submitted, for polymorphic form I a retest period could be granted of 36 months without specific storage requirements. For polymorphic form II a retest period could be granted of 24 months with the following storage conditions: 'Store in between 2-8°C in original packing and protect from light.

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.

With respect to the drug substance, the final product contains an amorphous form which is obtained by dissolution of the (manufactured) crystalline forms I and II in an appropriate solvent as part of the manufacturing process. The proposed routine dissolution testing method is acceptable. In line with the *Reflection paper on the dissolution specification for generic oral immediate release products*, the updated dissolution limit is acceptable. The discriminatory nature of the method has been sufficiently shown. In view of the three submitted and accepted pharmacokinetic studies, with the highest and lowest strengths, and where these strengths covers the extreme of the two dose-proportional strengths.

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. A common blend is used for all strengths. Process validation data on the product have been presented for six batches in accordance with the relevant European guidelines and the *Guideline on process validation for finished products*.

Control of excipients

All excipients are of pharmacopeial grade and/or in accordance with Commission Regulation 231/2012. It has been confirmed that magnesium stearate is of vegetable origin. 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, water content, dissolution, uniformity of dosage units, identification, assay, impurities and microbiological purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Analytical methods were adequately described and validated. Based on a forced degradation study the methods are shown to be stability indicating. The provided results of batch analysis demonstrate compliance with the specification limits. A suitable risk evaluation on the presence of nitrosamine impurities has been provided. Batch analytical data

from nine batches (12.5 mg capsules) and six batches (50 mg capsules) from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for nine production scale batches of the 12.5 mg strength and six batches of the 50 mg strength. Stability data has been provided at 25°C/60% RH and 40°C/75% RH, and the drug product was shown to be photostable under ICH Q1B conditions. This is in accordance with applicable European guidelines and in line with the *Guideline Bracketing and matrixing* (ICH Q1). Since for both types of packaging six months of accelerated stability testing are provided, the available 12 to 18 months of real-time stability data may be extrapolated in line with the *Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products*. As a result, the proposed shelf life of 24 months for Sunitinib capsules packed in both blisters and HDPE containers has been justified. It has been substantiated that in-use shelf-life studies do not need to be undertaken.

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 gelatin and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated. The vegetable origin of magnesium stearate has been confirmed.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Sunitinib Synthon 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 Synthon 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 three bioequivalence studies, which are discussed in the next section.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies (pharmacokinetic study 1 and 2) in which the pharmacokinetic profile of the test product Sunitinib Synthon 50 mg hard capsules (Synthon B.V.) is compared with the pharmacokinetic profile of the reference product Sutent 50 mg hard capsules (Pfizer Ltd.) under fasting and fed conditions.

One additional bioequivalence study (pharmacokinetic study 3) in which the pharmacokinetic profile of the test product Sunitinib Synthon 12.5 mg hard capsules (Synthon B.V.) is compared with the pharmacokinetic profile of the reference product Sutent 12.5 mg hard capsules (Pfizer Ltd.) under fasting conditions was conducted as well.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The design of the studies is acceptable.

Analytical/statistical methods
The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in these studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence studies

Pharmacokinetic study 1

Design

A single-dose, randomized, open label, laboratory blinded, two treatment, two period, two sequence, cross-over bioequivalence study was carried out under fasted conditions in 24 healthy adults subjects, aged 32-39 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 water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of 13 days.

Blood samples were collected pre-dose and at 1.0, 2.0, 4.0, 5.0, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 11.0, 12.0, 14.0, 16.0, 24.0, 48.0 and 72.0 hours after administration of the products.

Results

Out of a total of 24 subjects, 22 subjects were eligible for pharmacokinetic analysis. Two subjects were withdrawn due to adverse events (vomiting, itching).

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sunitinib malate (50 mg) under fasted conditions.

Treatment N=22	**AUC_{0-72} (ng.h/ml)**	**t_{max} (h)**	**C_{max} (ng/ml)**
Test	1196.498 ± 228.1134	9 (5 – 12)	32.138 ± 5.9945
Reference	1165.379 ± 240.7487	9 (5 – 11)	31.893 ± 6.3184
Geometric mean Ratio (90% CI)	103.3 (99.38 – 107.34)	--	100.9 (97.65 – 104.34)
CV (%)	7.4	--	6.4

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
CI confidence interval
CV coefficient of variation

**ln-transformed values*

Pharmacokinetic study 2

Design

A single-dose, randomized, open label, laboratory blinded, two treatment, two period, two sequence, cross-over bioequivalence study was carried out under fed conditions in 24 healthy adults subjects, aged 29-34 years. Each subject received a single dose (50 mg) of one of the two sunitinib malate formulations. After an overnight fast of at least ten hours the subjects were served a high-fat, high-calorie breakfast (chicken, milk, potatoes, eggs, bread and ghee)

which they consumed completely within 30 minutes. The drug administration took place 30 minutes after serving the breakfast with 240 mL of water. There were two dosing periods, separated by a washout period of 13 days.

Blood samples were collected pre-dose and at 1.0, 2.0, 4.0, 5.0, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 11.0, 12.0, 14.0, 16.0, 24.0, 48.0 and 72.0 hours after administration of the products.

Results
All 24 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sunitinib malate (50 mg) under fed conditions.

Treatment N=24	**AUC_{0-72} (ng.h/ml)**	**t_{max} (h)**	**C_{max} (ng/ml)**
Test	1459.060 ± 285.5741	11.5 (6.5 – 24)	33.058 ± 7.0828
Reference	1447.844 ± 342.3717	11 (6 – 24)	33.346 ± 6.9099
Geometric mean Ratio (90% CI)	101 (95.73 – 106.55)	--	98.8 (93.92 – 104)
CV (%)	10.3	--	10.3

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
CI confidence interval
CV coefficient of variation

Pharmacokinetic study 3
Design
A single-dose, randomized, open label, laboratory blinded, two treatment, two period, two sequence, cross-over bioequivalence study was carried out under fasted conditions in 24 healthy adults subjects, aged 32-39 years. Each subject received a single dose (12.5 mg) of one of the two sunitinib malate formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 1.0, 2.0, 4.0, 5.0, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 11.0, 12.0, 14.0, 16.0, 24.0, 48.0 and 72.0 hours after administration of the products.

Results
Out of a total of 24 subjects, 23 subjects were eligible for pharmacokinetic analysis. One subject withdrew on his/her own accord.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sunitinib malate (12.5 mg) under fasted conditions.

Treatment N=23	AUC_{0-72} (ng.h/ml)	t_{max} (h)	C_{max} (ng/ml)
Test	271.515 ± 53.8401	8.5 (6 – 11)	7.163 ± 1.3795
Reference	275.707 ± 57.7131	7.5 (4 – 10)	7.217 ± 1.5480
Geometric mean Ratio (90% CI)	99.3 (95.41 – 103.40)	--	98.5 (95.15 – 101.96)
CV (%)	6.8	--	7.9

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
CI confidence interval
CV coefficient of variation

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, t_{max} and C_{max} are within the bioequivalence acceptance range of 80 – 125. Based on the submitted bioequivalence studies Sunitinib Synthon is considered bioequivalent with Sutent.

The MEB has been assured that the bioequivalence studies have 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 Sunitinib Synthon.

Table 4. 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 three 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 Sutent 12.5 mg and 50 mg hard capsules (EMEA/H/C/000687) for content and key safety messages and Clozapine (NL/H/4201/001) 12.5 mg orodispersable tablets for design and layout. 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 Synthon 12.5 mg and 50 mg, hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Sutent 12.5 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.

A board meeting was held where an issue regarding the starting material was raised. The MAH submitted additional data, which was considered to be adequate. No further issues remain.

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 Synthon with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 April 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