COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sunitinib Stada 12.5 mg, 25 mg, 37.5 mg and 50 mg, hard capsules

(sunitinib base)

NL/H/4255/001-004/DC

Date: 20 June 2019

This module reflects the scientific discussion for the approval of Sunitinib Stada. The procedure was finalised at 27 February 2019. 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
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 Stada 12.5 mg, 25 mg, 37.5 mg and 50 mg, hard capsules from Stada Arzneimittel AG.

The product is indicated for:

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

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

Pancreatic neuroendocrine tumours (pNET)
Sunitinib Stada is indicated for the treatment of unresectable or metastatic, well-differentiated 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 mg, 25 mg, 37.5 mg and 50 mg hard capsules which has been centrally registered (EU/1/06/347/001-008) in the EEA by Pfizer Europe MA EEIG since 19 July 2006.

The concerned member states (CMS) involved in this procedure were Hungary (except 37.5 mg strength) and Poland.

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

Orphan similarity
Where a designated orphan medicinal product has been authorised for the condition which covers the proposed therapeutic indication applied for, and a period of market exclusivity is in force, possible similarity should be discussed with the authorised orphan medicinal products.

Market exclusivity currently applies for the orphan indication “treatment of gastro-entero-pNET” for the orphan medicinal product Lutathera. Following similarity assessment, Sunitinib Stada and the orphan medicinal product Lutathera are considered non-similar medicinal products.

II. QUALITY ASPECTS

II.1 Introduction

Sunitinib Stada is a hard capsule available in four strengths:

- *12.5 mg hard capsules* - orange cap and orange body, printed with white ink "12.5 mg" on the body and containing yellow to orange granules
- *25 mg hard capsules* – caramel cap and orange body, printed with white ink "25 mg" on the body and containing yellow to orange granules
- *37.5 mg hard capsules* – yellow cap and yellow body, printed with black ink "37.5 mg" on the body and containing yellow to orange granules
- *50 mg hard capsules* – caramel cap and caramel body, printed with white ink "50 mg" on the body and containing yellow to orange granules

The hard capsules are packed in Aluminium-OPA/Alu/PVC blisters and High Density Polyethylene (HDPE) bottles with a polypropylene (PP) child resistant closure (screw cap).

The excipients are:

- *Capsule content* – microcrystalline cellulose (E460), mannitol (E421), croscarmellose sodium, povidone (E1201), magnesium stearate (E470b)
- *Capsule shell* - red iron oxide (E172) (12.5 mg, 25 mg, 50 mg strength), black iron oxide (E172) (25 mg, 50 mg strength), yellow iron oxide (E172) (25 mg, 37.5 mg, 50 mg strength), titanium dioxide (E171) (12.5 mg, 25 mg, 37.5 mg, 50 mg strength), gelatin (12.5 mg, 25 mg, 37.5 mg strength, 50 mg strength)
- *Printing ink, white (12.5 mg, 25 mg, 50 mg strength)* –shellac, titanium dioxide (E171), propylene glycol (E1520)
- *Printing ink, black (37.5 mg strength)* – shellac, black iron oxide (E172), propylene glycol (E1520), ammonium hydroxide (E527)

The four tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is sunitinib base, an established active substance not described in any Pharmacopoeia. The active substance is a yellow to orange crystalline powder which is not hygroscopic. The solubility in aqueous solution is pH dependent; below a pH of 6 sunitinib base is soluble in aqueous solution whereas above pH 7 it is only sparingly soluble in water. Several forms (>30) of sunitinib base are known in the literature. The process followed by the MAH consistently produces sunitinib base of form III, which form is stable when exposed to extreme humidity, temperature and mechanical conditions.

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 synthesis of sunitinib consists of three synthetic steps and a final purification step, performed in ethanol. Three starting materials have been defined. These starting materials are acceptable. No class 1 organic solvents have been used. The specifications for starting materials and intermediates are appropriate. The active substance has been adequately characterized and acceptable specifications have been adopted for the used solvents and reagents.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three production scale batches.

Stability of drug substance

Stability data on the active substance have been provided for three full scale batches stored at 25°C/60% RH (up to nine months) and 40°C/75% RH (up to six months). No clear up- or downward trends are observed, under accelerated or long term conditions, therefore a retest period of 12 months, with the storage condition “Store protected from light. Store at temperature between 2 and 8°C” is granted.

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 aim of the formulation development was to obtain a robust, stable, immediate release formulation containing quantitatively the same active substance as the reference product. Different manufacturing processes were considered in early development, and on the basis of these studies, wet granulation was selected for final production. Furthermore, the quantity of binder was investigated, and the optimum amount was selected. The pharmaceutical development of the product has been adequately performed, and the choices of the packaging and manufacturing process have been justified.

The batch used in the bioequivalence studies has the same quantitative composition and was manufactured according to the proposed manufacturing process. The batch size of the biobatch is acceptable given the proposed batch size of the commercial batches. Comparative dissolution studies with the biobatch of the test product versus the biobatch of the reference product were performed at three pH levels (0.1N HCl (pH ~1.2), pH 4.5 acetate buffer, and pH 6.8 phosphate buffer). Only in 0.1N HCl and pH 4.5 comparable dissolution

was demonstrated. In pH 6.8, the dissolution profiles were not comparable, however, as bioequivalence has been shown *in vivo*, and the differences have been justified by the difference in solubility between sunitinib base (test product) and sunitinib maleate (reference product), this can be accepted.

Similarity between the dissolution profiles of the 50 mg biobatch and the other strengths has been shown at three pH levels (0.1N HCl (pH ~1.2), pH 4.5 acetate buffer, and pH 6.8 phosphate buffer). A biowaiver for the 12.5 mg, 25 mg and 37.5 mg strength is acceptable from a chemical pharmaceutical point of view.

Manufacturing process

The manufacturing process consists of a granulation phase, milling of the granules and mixing with external phase, encapsulation of the final blend into the hard capsules, and packaging of the capsules. The product is manufactured using conventional manufacturing techniques. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for sufficient full scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the 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 description of capsule and capsule content, identification, identification of titanium dioxide and iron oxide, assay, related substances, dissolution, uniformity of dosage units, water content, uniformity of mass and microbiological examination. The release and shelf-life requirements/limits are identical, except for related substances. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

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

Stability of drug product

Stability data on the product has been provided for at least three production scale batches per strength stored at 25°C/60% RH (maximum 12 months) and 40°C/75% RH (6 months). The batches were stored in the intended packaging. Under both storage conditions, the batches remained well within specification; no trends are observed. The claimed shelf-life of 24 months is acceptable. No specific storage conditions are needed.

Photostability studies were performed showed that the product is stable when exposed to light.

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.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Sunitinib Stada 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 Stada 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 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 below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence study in which the pharmacokinetic profile of the test product Sunitinib Stada 50 mg hard capsules (Stada Arzneimittel AG., Germany) is compared with the pharmacokinetic profile of the reference product Sutent 50 mg hard capsules (Pfizer Ltd, United Kingdom).

The choice of the reference product in the bioequivalence studies is accepted as Sutent is registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

In general, for an immediate release formulation of a substance indicated to be taken with or without food intake, a single dose study under fasting conditions using the highest strength is considered appropriate. Such a study design is also in line with the Sunitinib Product specific Bioequivalence Guidance (EMA/CHMP/315233/2014). However, the guidance is referring to sunitinib maleate as active pharmaceutical ingredient in Sutent while Sunitinib Stada capsules contain sunitinib base. Sunitinib base is less soluble than sunitinib maleate at pH 6.8, thus although the comparative bioavailability study was conducted under fasting condition, in addition the effect of food on drug absorption was studied with the 50 mg capsules.

An additional pooled analysis is conducted for the two studies under fed conditions, because one study failed to demonstrate bioequivalence. Biowaiver for lower strengths (i.e. 12.5, 25 and 37.5 mg) is requested based on proportional of composition with the highest strength (50 mg).

Biowaiver

A biowaiver for a bioequivalence study for the additional lower strengths (12.5 mg, 25 mg and 37.5 mg) of sunitinib is applied for by the MAH. All the proposed products were 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. According to sunitinib product-specific guidance (EMA/CHMP/315233/2014), the pharmacokinetics for sunitinib is linear, thus, in principle, the biowaiver request for the additional lower strengths applicable.

Both test and reference product contain mannitol in all strengths. There is overall a small quantitative difference in mannitol between the strengths of test and reference product. As comparative bioavailability studies have been performed for the highest strength (50 mg), in the light of conclusion of bioequivalence, the difference in mannitol between test and reference product with the 50 mg strength is considered to not affect the absorption of sunitinib. The difference in the lower strengths is also not considered to have clinical impact because considering the therapeutic dose the total mannitol given every occasion with

Sunitinib Stada will be lower than it with Sutent. Thus criteria for requesting the biowaiver for additional strengths are met.

The details and complete dissolution data of Sunitinib Stada 12.5 mg, 25 mg, 37.5 mg and 50 mg capsules are adequately presented. At pH 1.2, all four strengths dissolved more than 85% within 15 minutes. For pH 4.5 and 6.8, f2 values for all three lower strengths are greater than 50 compared with the 50 mg capsules. Overall, similarity in dissolution has been demonstrated at the three requested pH levels between all the additional lower strengths and the 50 mg strength of Sunitinib Stada.

Therefore, the conclusion of the bioequivalence studies with sunitinib 50 mg strength can be extrapolated to the lower strengths of 12.5 mg, 25 mg and 37.5 mg capsules.

Bioequivalence studies

Single dose bioequivalence study under fasting conditions (2134)

Design

A single-dose, randomised, open-label, two-period, two-treatment, two-sequence, two-way crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 43 ±13 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 ten hours. There were two dosing periods, separated by a washout period of 21 days.

Blood samples were collected at 1, 3, 4, 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 13, 14, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. Taking into account the expected elimination half-life of sunitinib in plasma the wash-out period of 21 days is considered to be adequate to avoid any carry-over effects. Pre-dose level was observed in one subject in Period II but the concentration was lower than 5% of C_{max}, so no action is needed. The sample collection period of 72 hours sufficiently covers the absorption phase of sunitinib, and is acceptable according to the guideline for bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) and also the sunitinib product-specific guidance (EMA/CHMP/315233/2014).
The sampling scheme is considered appropriate, as the sampling is frequent around the expected t_{max}.

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 voluntarily withdrew prior to period 2 dosing. Therefore 23 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=23	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	1126 ± 286	1522 ± 426	31.9 ± 7.8	6.0 (5.0 - 12.0)
Reference	1144 ± 303	1568 ± 450	32.2 ± 8	6.7 (6.0 - 10.0)
***Ratio (90% CI)**	1.01 (0.97 - 1.05)	0.97 (0.90 - 1.05)	0.98 (0.89 - 1.08)	--
CV (%)	6.5	13.4	18	--

$AUC_{0-\infty}$ 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 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Single dose bioequivalence study under fed conditions (2135)

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, two-way crossover bioequivalence study was carried out under fed conditions in 24 healthy male subjects, aged 42 ± 12 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 ten hours and consuming a high fat (60% of the total calorie) high calorie (total calorie = 965 kcal) breakfast. There were two dosing periods, separated by a washout period of 21 days.

Blood samples were collected at 1, 3, 4, 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 13, 14, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. Taking into account the expected elimination half-life of sunitinib in plasma the wash-out period of 21 days is considered to be adequate to avoid any carry-over effects. Pre-dose level was observed in one subject in Period II but the concentration was lower than 5% of C_{max}, so no action is needed. The sample collection period of 72 hours sufficiently covers the absorption phase of sunitinib, and is acceptable according to the guideline for bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) and also the sunitinib product-specific guidance (EMA/CHMP/315233/2014).
The sampling scheme is considered appropriate, as the sampling is frequent around the expected t_{max}.

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
Five subjects did not complete the study entirely. Reasons for withdrawal are acceptable. Therefore, 19 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=19	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	1260 ± 320	1743 ± 461	33.0 ± 9.3	10.5 (6.0 - 16.0)
Reference	1252 ± 197	1754 ± 299	33.5 ± 7.3	10 (6.0 - 16.0)
***Ratio (90% CI)**	0.94 (0.80 - 1.12)	0.93 (0.79 - 1.11)	0.92 (0.77 - 1.11)	--
CV (%)	29	30	32	--

$AUC_{0-\infty}$ 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 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

One subject had demonstrated very low concentration values on the test product during period 1. An in-house outlier test was also conducted, and the subject was identified as a statistical outlier using a cut-off value of |2|. Additional pharmacokinetic statistical analysis was conducted upon the exclusion of data obtained from this subject. The results of the ratios and 90% CIs for AUC and C_{max} are shown in the table below (Table 3).

Table 3. The ratios and 90% CIs of pharmacokinetic parameters for sunitinib N=18 subjects (excluded the outlier)

Pharmacokinetic Parameter	Test/Reference Ratio of Geometric Means (90% Confidence Interval) (%)	Intra-Subject CV (%)
AUC_{72}	104.59 (101.38 - 107.90)	5.33
C_{max}	102.54 (96.24 - 109.24)	10.85

Bioequivalence with respect to the rate and extent of absorption of sunitinib has not been shown for the 50 mg strength between test and reference product under fed conditions.

For the comparison of the test and reference product under fed conditions, the calculated 90% CI for AUC_{0-72} for sunitinib were within the 0.80-1.25 acceptance range, but not for Cmax. The failure to demonstrate bioequivalence was due to an outlier i.e. Subject no. 10 who has very low exposure of Test product. When excluding this subject, the study could demonstrate bioequivalence between the test and the reference product. The CV% of both C_{max} and AUC_{0-72} was also reduced to <20% (used in the power calculation). Based on these, the MAH repeated the fed study in a large group of subjects (study 17-VIN-0703). This is acceptable.

Single dose bioequivalence study under fed conditions (17-VIN-0703)

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 50 healthy male subjects, aged 42 ± 12 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 ten hours and consuming a high fat (60% of the total calorie) high calorie (total calorie = 965 kcal) breakfast. There were two dosing periods, separated by a washout period of 21 days.

Blood samples were collected at 1, 3, 4, 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 14, 16, 20, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. Taking into account the expected elimination half-life of sunitinib in plasma the wash-out period of 21 days is considered to be adequate to avoid any carry-over effects. Pre-dose level was observed in one subject in Period II but the concentration was lower than 5% of C_{max}, so no action is needed. The sample collection period of 72 hours sufficiently covers the absorption phase of sunitinib, and is acceptable according to the guideline for bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) and also the sunitinib product-specific guidance (EMA/CHMP/315233/2014).
The sampling scheme is considered appropriate, as the sampling is frequent around the expected t_{max}.

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
In total, seven subjects were withdrawn due to vomiting during the breakfast or "incomplete breakfast", and seven extra subjects were recruited. The replacement is considered acceptable because the withdrawn subjects were not dosed, and the replacement occurred before the complete of both treatments.

Four subjects were withdrawn during the study:
- One subject was withdrawn due to vomiting after dosing of period 1
- One subject did not report to facility during admission of period 2
- One subject withdrew consent in period 2
- One subject did not complete high fat, high calorie breakfast in period 1

Therefore, 46 subjects were eligible for pharmacokinetic analysis.

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of sunitinib under fed conditions.

Treatment N=46	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	950.6 ± 179	1270 ± 283	24.0 ± 5.1	10.5 (3.0 - 24.0)
Reference	950.6 ± 220	1294 ± 348	24.1 ± 5.7	9.75 (5.0 -24.0)
***Ratio (90% CI)**	1.01 (0.97 - 1.05)	--	1.0 (0.96 - 1.04)	--
CV (%)	10	--	11	--

$AUC_{0-\infty}$ 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 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Pooled analysis for fed studies (17-VIN-0889)
The MAH conducted a pooled analysis (n=65) for the two bioequivalence studies under fed conditions, which is in line with the bioequivalence guideline.

Results
The statistical results for primary pharmacokinetic parameters of Sunitinib are summarized below:

Table 5. Pharmacokinetic parameters of sunitinib under fed conditions (pooled analysis).

Parameters (Units)	Arithmetic Mean ± SD (%CV) (N = 65)	
	Reference Product (R)	Test Product (T)
C_{max} (ng/mL)	26.870 ± 7.4962 (27.90%)	26.649 ± 7.7255 (28.99%)
#T_{max} (hr)	10.000 (5.00 - 24.00)	10.500 (3.00 - 24.00)
AUC_{0-72}(hr*ng/mL)	1040.080 ± 253.4297 (24.37%)	1041.920 ± 267.6496 (25.69%)

For T_{max} median (min – max)

Pharmacokinetic Parameter	Test/Reference Ratio of Geometric Means (90% Confidence Interval) (%)	Intra-Subject CV (%)
AUC_{72} (ng.h/mL)	99.31 (94.37-104.51)	17.55
Cmax (ng/mL)	97.90 (92.48-103.64)	19.65

Considering the CV% for AUC and C_{max} (around 30%) were high (higher than the estimation used for the CV=20% in Determination of Sample Size), the study with 24 subjects may not be powered, therefore it is acceptable to conduct another study with larger population.

In the results, the calculated 90% CI for AUC_{0-72} and C_{max} for sunitinib were within the 0.80-1.25 acceptance range. Both the larger study (n=46 subjects) and the pooled analysis demonstrate bioequivalence between the test and the reference product under fed conditions.

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 Sunitinib Stada 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 Stada.

Table 6. Summary table of safety concerns as approved in RMP

Important identified risks	• Hypertension
	• Haemorrhagic events
	• Cytopenic events
	• Cardiotoxicity
	  • Torsade de pointes
	  • Left ventricular dysfunction/Heart failure
	  • Pericardial events
	  • Cardiac ischemic events
	• Fatigue and asthenia
	• Thyroid dysfunction
	• Serious infection
	  • Necrotizing fasciitis
	• Thrombotic microangiopathy
	• Proteinuria/nephrotic syndrome
	• Reversible Posterior Leukoencephalopathy Syndrome
	• Fistula formation
	• Hepatic failure
	• Embolic and thrombotic/embolism and thrombosis
	• Gastrointestinal perforation
	• Pancreatitis
	• Myopathy/rhabdomyolysis
	• Osteonecrosis of the jaw
	• Esophagitis
	• Toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme
	• Renal failure
	• Adrenal gland dysfunction
	• Cholecystitis
	• Tumour lysis syndrome
	• Angioedema
	• Hypoglycaemia

Important potential risks	• Carcinogenicity
	• Other potential cardiac effects
	  • Conduction defect events
	  • Tachycardia events
	• Retinal detachment
	• Reproductive and developmental toxicity

Identified and potential interactions	• Drug interaction with CYP3A4 inhibitor or inducer
Missing information	• Paediatric patients • Severe hepatic impairment • Cardiac 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 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 (content) and Darunavir 400 mg and 800 mg (NL/H/3609/001-006/DC) (lay-out). 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 Stada 12.5 mg, 25 mg, 37.5 mg and 50 mg, hard capsules has a proven chemical-pharmaceutical quality and is a generic form 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 Stada with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 February 2019.

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