COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

NL/H/5100/001-004/DC

Date: 17 January 2022

This module reflects the scientific discussion for the approval of Sunitinib Glenmark 12.5 mg, 25 mg, 37.5 mg and 50 mg, hard capsules. The procedure was finalised at 19 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
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

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Sunitinib Glenmark 12.5 mg, 25 mg, 37.5 mg and 50 mg, hard capsules, from Glenmark Arzneimittel GmbH.

The product 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.
- the treatment of advanced/metastatic renal cell carcinoma (MRCC) in adults.
- 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 by the centralised procedure (EU/1/06/347).

The concerned member states (CMS) involved in this procedure were:
For the 12.5 mg, 25 mg and 50 mg strength: Czech Republic, Germany, Poland, Spain, Slovakia and Sweden.
For the 37.5 mg strength: Slovakia

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

Similarity assessment

The reference product 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 marketing authorisation holder. A similarity discussion has been provided in module 1.7 with regard to Lutathera (EU1/17/1226), SomaKit TOC (EU/1/16/1141) and AYVAKYT (EU/1/20/1473). Having considered the arguments presented by the MAH and with reference to Article 8 of Regulation (EC) No 141/2000, Sunitinib Glenmark is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Lutathera and SomaKit TOC.

II. QUALITY ASPECTS

II.1 Introduction

- Sunitinib Glenmark 12.5 is a hard capsule with a orange cap and orange body, printed with white ink "12.5 mg" on the body and containing yellow to orange granules. Each hard capsule contains 12.5 mg sunitinib.
- Sunitinib Glenmark 25 mg is a hard capsule with a caramel cap and orange body, printed with white ink "25 mg" on the body and containing yellow to orange granules. Each hard capsule contains 25 mg sunitinib.
- Sunitinib Glenmark 37.5 mg is a hard capsule with a yellow cap and yellow body, printed with black ink "37.5 mg" on the body and containing yellow to orange granules. Each hard capsule contains 37.5 mg sunitinib.
- Sunitinib Glenmark 50 mg is a hard capsule with a caramel cap and caramel body, printed with white ink "50 mg" on the body and containing yellow to orange granules. Each hard capsule contains 50 mg sunitinib.

The hard capsules are packed in Aluminium-OPA/Alu/PVC perforated unit-dose blisters or 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 content of the four capsule strengths are dose proportional.

II.2 Drug Substance

The active substance is sunitinib, 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 is soluble in aqueous solution whereas above pH 7 it is only sparingly soluble in water. Several polymorphic forms (>30) of sunitinib base are known in the literature. The process followed by the manufacturer consistently produces sunitinib of form III, which 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 manufacturing process consists of three synthetic steps and a final purification step, performed in ethanol. In the proposed synthesis no class I organic solvents have been used. The specifications for starting materials and intermediates are appropriate. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification has been established in-house by the MAH and is considered adequate to control the quality. 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 production scale batches.

Stability of drug substance

Stability data on the active substance have been provided for four production scaled batches stored at 2-8°C (up to 36 months) and six production scaled batches stored at 25°C/60% RH (6 months) in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 42 months when stored in a closed container protected from light and stored at a temperature between 2 and 8°C.

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 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 (0.1 N HCl (pH ~1.2), pH 4.5 acetate buffer, and pH 6.8 phosphate buffer). Only in 0.1 N 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 malate (reference product), this can be accepted. Similarity between the dissolution profiles of the 50 mg biobatch and the other strengths has been shown at 3 pH's (0.1 N HCl (pH ~1.2), pH 4.5 acetate buffer, and pH 6.8 phosphate buffer).

Manufacturing process

The manufacturing process consists of the following phases: 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 guidelines. Process validation data on the product have been presented for three full scaled batches per strength in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the Ph.Eur. requirements. The hard gelatin capsules are controlled according to in-house specifications. 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, identity, assay, related substances, dissolution, uniformity of dosage units (by content uniformity), water content, uniformity of mass and microbiological examination. 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 sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for at least three production scaled batches per strength from each manufacturing site stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Except for a slight increase in impurities, no clear trends or changes were seen at both storage conditions. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 36 months. No specific storage conditions are required.

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 the used 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 Glenmark 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 Glenmark 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 studies in which the pharmacokinetic profile of the test product Sunitinib Glenmark 50 mg, hard capsules (Glenmark Arzneimittel GmbH, Germany) 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.

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 Glenmark 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 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 Glenmark 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 Glenmark 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 Glenmark.

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

Bioequivalence study I: single dose under fasting conditions

Design
A monocentric, open label, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 23-62 years. Each subject received a single dose (50 mg) of one of the two sunitinib formulations. The capsules were orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and 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. 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_{0-72h} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	1126 ± 286	32 ± 7.8	6.0 (5.0 – 12.0)
Reference	1145 ± 303	32 ± 8.0	6.73 (5.0 – 10.0)
***Ratio (90% CI)**	1.01 (0.97 – 1.04)	0.98 (0.90 – 1.08)	-
CV (%)	6.5	17.9	-

AUC_{0-72h} area under the plasma concentration-time 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*

Bioequivalence study II: single dose under fed conditions

Design
A monocentric, open label, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study was carried out under fed conditions in 24 healthy male subjects, aged 23-62 years. Each subject received a single dose (50 mg) of one of the two sunitinib formulations. The capsules were administered with 240 ml water 30 minutes after intake of a high fat, high caloric breakfast (60% of the total caloric content, total caloric content 965 kcal). There were two dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and 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 in its entirety. Two subjects withdrew due to personal reasons. One subject was dismissed due to a positive cotinine test. Another subject was dismissed due to a positive benzodiazepines test. The fifth subject was dismissed due to rash and pruritus. 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	**$AUC_{0\text{-}72h}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	1260 ± 320	33 ± 9.3	10.5 (6.0 – 16.0)
Reference	1253 ± 197	34 ± 7.3	10.0 (6.0 – 16.0)
***Ratio (90% CI)**	0.95 (0.81 - 1.12)	0.93 (0.77 - 1.11)	-
CV (%)	29	32	-

$AUC_{0\text{-}t72h}$ area under the plasma concentration-time 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*

One subject had demonstrated very low concentration values on the test product during period 1. 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	***Ratio (90% CI)**	**Intra-Subject CV(%)**
$AUC_{0\text{-}72h}$	1.04 (1.01 – 1.08)	5.33

C_{max}	1.03 (0.96 – 1.09)	10.85

**ln-transformed values*

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 C_{max}. The failure to demonstrate bioequivalence was due to an outlier who had 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. This is acceptable.

Bioequivalence study III: single dose under fed conditions

A monocentric, open label, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study was carried out under fed conditions in 50 (+7 standby) healthy male subjects, aged 22-42 years. Each subject received a single dose (50 mg) of one of the two sunitinib formulations. The capsules were administered with 240 ml water 30 minutes of a high fat, high caloric breakfast (57% of the total caloric content, total caloric content 987 kcal). There were two dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and 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.

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, eight subjects were withdrawn due to vomiting during the breakfast or “incomplete breakfast”, and seven extra subjects were recruited.

Four subjects were withdrawn from the study:
- One subject was withdrawn due 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
In total, 46 subjects were included in the pharmacokinetic and statistical analysis.

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

Treatment N=46	AUC_{0-72h} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	951 ± 180	24 ± 5.2	10.5 (3.0 – 24.0)
Reference	951 ± 220	24 ± 5.7	9.75 (5.0 – 24.0)
***Ratio (90% CI)**	1.01 (0.98 – 1.05)	1.00 (0.96 – 1.04)	-
CV (%)	10.0	11.2	-

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
CV coefficient of variation

**ln-transformed values*

Pooled analysis for fed studies

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 summarised below

Table 5. Summarised pooled pharmacokinetic data of studies II and III (fed conditions).

Treatment N=65	AUC_{0-72} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)	λ_z (1/hr)	AUC_t/AUC_{inf} (ng.h/ml)
Test	1041.920 ± 267.6496	1412.153 ± 410.1746	26.649 ± 7.7255	10.500 (3.00 – 24.00)	33.533 ± 7.2378	0.022 ± 0.0044	74.728 ± 6.8745
Reference	1040.080 ± 253.4297	1427.232 ± 391.9779	26.870 ± 7.4962	10.000 (5.0 0– 24.00)	34.508 ± 7.8965	0.021 ± 0.0046	73.930 ± 7.5478
***Ratio (90% CI)**	0.99 (0.94 – 1.05)	-	0.98 (0.92 – 1.04)	-	-	-	-
CV (%)	17.55	-	19.65	-	-	-	-

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-72}	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
Λz	Individual estimate of the terminal elimination rate constant

**In-transformed values*

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 Glenmark 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).

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 Glenmark.

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

Important identified risks	• Cardiotoxicity
	  ○ Torsade de pointes
	  ○ Left ventricular dysfunction/heart failure
	  ○ Pericardial events
	  Cardiac ischemic 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 (Key safety messages) and Darunavir (NL/H/3609; 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 Glenmark 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 Sutinib Glenmark with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 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
NL/H/5100/001-004/IB/001	Type A.2.b). Change in the (invented) name of the medicinal product: for Nationally Authorised Products	-	16 December 2021	Approved	
NL/H/5100/001-004/IB/002	Type B.II.e).5.a).2. Change in the number of units (e.g. tablets, ampoules, etc.) in a pack: change outside the range of the currently approved pack sizes	-	6 January 2022	Approved	