LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Sunitinib Eugia

(sunitinib malate)

SE/H/2197/01-04/DC

This module reflects the scientific discussion for the approval of Sunitinib Eugia. The procedure was finalised on 2024-12-11. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Sunitinib Eugia, 12,5 mg, 25 mg, 37,5 mg, 50 mg, Capsule, hard.

The active substance is sunitinib malate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Sunitinib Eugia, 12.5 mg, 25 mg, 37.5 mg and 50 mg, capsule, hard, is a generic application made according to Article 10(1) of Directive 2001/83/EC.

The applicant, Aurobindo Pharma (Malta) Limited, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and the following concerned member states (CMS):

SE/H/2197/01-02,04/DC: *12.5, 25 and 50 mg* – DE, ES, FR, NL, PL, PT.
(BE, CZ and RO were withdrawn during clockstop.)
SE/H/2197/03/DC: *37.5 mg* – DE and PT only

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Sutent, 12.5 mg, hard capsules authorised in the European Union since 2006, with Pfizer Europe MA EEIG as marketing authorisation holder.

The reference product used in the bioequivalence study is Sutent, 50 mg, hard capsules from Denmark with Pfizer Europe MA EEIG as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products the following medicinal product(s) has/have been designated as orphan medicinal products, but not yet been granted a marketing authorisation in the EU: EU/3/17/1889, EU/3/17/1936, EU/3/21/2418 , EU/3/04/251, EU/3/06/356, EU/3/02/116, EU/3/05/270, EU/3/06/405, EU/3/06/417, EU/3/07/480, EU/3/06/429, EU/3/07/448, EU/3/16/1754, EU/3/15/1588, EU/3/14/1269, EU/3/07/523.

The applicant should monitor these products during the entire procedure to check if a marketing authorisation has been granted. In case a marketing authorisation is granted, the applicant 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 applicant has provided a similarity report (Module 1.7.1) due to potential similarity with authorised orphan medicinal product(s) under market exclusivity. The detailed RMS assessment of similarity is presented in the attached RMS Similarity AR.

Conclusion
Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Sunitinib Eugia, is considered **not similar** (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to **Ayvakyt**.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Ayvakyt, in the treatment of GIST, does not prevent the granting of the marketing authorisation of Sunitinib Eugia. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Sunitinib Eugia, is considered **not similar** (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to **Lutathera**.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Lutathera, in the treatment of GEP-NET, does not prevent the granting of the marketing authorisation of Sunitinib Eugia. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Sunitinib Eugia is considered **not similar** (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to **Qinlock**.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Qinlock, in the treatment of GIST, does not prevent the granting of the marketing authorisation of Sunitinib Eugia. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of sunitinib are well known. As sunitinib is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Sunitinib Eugia is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Sunitinib with the reference product Sutent.

Pharmacokinetic properties of the active substance

Absorption: After oral administration of sunitinib, C_{max} are generally observed from 6 to 12 hours-time to maximum concentration (t_{max}) post administration. Food has no effect on the bioavailability of sunitinib.

Linearity: In the dosing ranges of 25 to 100 mg, the area under the plasma concentration-time curve (AUC) and Cmax of sunitinib increase proportionally with dose.

Elimination: Following oral administration in healthy volunteers, the elimination half-lives of sunitinib and its primary active desethyl metabolite are approximately 40-60 hours and 80-110 hours, respectively.

Study C20195
Methods
This was a single-dose, two-way crossover study conducted in 48 healthy volunteers (36 subjects completed both study periods and were included in the pharmacokinetic analysis), comparing Sunitinib, 50 mg, capsules with Sutent, 50 mg, capsules under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of sunitinib were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-72} and C_{max}. The study was conducted between 18 February 2021 and 14 March 2021.

Results
The results from the pharmacokinetic and statistical analysis are presented in table 1 and 2.

Table 1. Summary of Pharmacokinetic parameters

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Parameters (Units)	**Un-transformed Data (Mean ± SD)**	
	Test Product (T) N=44	**Reference Product (R) N=41**
*T_{max} (hr)	7.00(5.00-12.00)	7.50(1.00-36.00)
C_{max} (ng/mL)	30.683±6.0098	31.823±8.1930
AUC_{0-72} (hr. ng./mL)	1152.076±247.1758	$1214.569±256.0544

- ** Median, Minimum and Maximum values reported for $T_{max.}$*
- *$ N = 38 Since the subjects did not fit with linear regression in the terminal phase.*

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Table 2. Statistical analysis for Sunitnib

Parameters (Units)	Geometric Least Squares Means				90% ConfidenceLimits	(T/R) %	Intra Subject CV %	Power (%)
	Test product (T)	N	Reference product (R)	N	(T vs. R)			
C_{max} (ng/mL)	29.550	36	31.128	36	91.40-98.60	94.93	9.5	100.0
AUC_{0-72} (hr. ng./mL)	1118.429	36	1165.684	36	92.93-99.06	95.95	7.9	100.0

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strengths of 12.5 mg, 25 mg and 37.5 mg.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) and was also in line with the Sunitinib Product-specific Bioequivalence Guidance (EMA/CHMP/315233/2014). The bioanalytical methods were adequately validated.

Absence of studies with the additional strengths of 12.5 mg, 25 mg and 37.5 mg is acceptable, as all conditions for biowaiver for additional strengths, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of sunitinib is linear between 25 mg and 100 mg.

Based on the submitted bioequivalence study, Sunitinib Eugia is considered bioequivalent with Sutent.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Eugia.

Safety specification

The MAH has submitted the version 1.1 RMP dated 14 Oct 2024 and proposed the following summary safety concerns.

Summary of safety concerns	
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

Assessor's comments: The submitted RMP is in line with the most recent RMP of the originator (Sutent).

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.
Issue is resolved.

The submitted Risk Management Plan, version 1.1 signed 14 Oct 2024 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Metoprolol Aurobindo, SE/H/1201/001-002/DC.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Sunitinib Eugia, is found adequate. There are no objections to approval of Sunitinib Eugia, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.

The benefit/risk is considered positive, and the applications are therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Sunitinib Eugia, 12,5 mg, 25 mg, 37,5 mg, 50 mg, Capsule, hard was positively finalised on 2024-12-11.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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