COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Lusmose 12.5 mg, 25 mg and 50 mg hard capsules (sunitinib cyclamate)

NL/H/5077/001-003/DC

Date: 5 August 2021

This module reflects the scientific discussion for the approval of Lusmose 12.5 mg, 25 mg and 50 mg hard capsules. The procedure was finalised at 11 March 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 Lusmose 2.5 mg, 25 mg and 50 mg hard capsules, from Egis Pharmaceuticals Plc.

The product is indicated for:

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

- Metastatic renal cell carcinoma (MRCC)
  Lusmose is indicated for the treatment of advanced/metastatic renal cell carcinoma (MRCC) in adults.

- Pancreatic neuroendocrine tumours (pNET)
  Lusmose is indicated for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression in adults.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Sutent 12.5, 25 and 50 mg hard capsules which have been registered in the EEA by Pfizer Europe MA EEIG since 2006 through a centralised procedure (EU/1/06/347).

The concerned member states (CMS) involved in this procedure were Austria, Croatia, Greece, Portugal and Slovenia.

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

Similarity assessment in view of the orphan drug legislation

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 Sutent was withdrawn from the Community register of orphan medicinal products in July 2008 upon request of the MAH.

The MAH provided a similarity assessment between generic sunitinib and Lutathera (EU1/17/1226), Somakit TOC (EU/1/16/1141), Onivyde pegylated liposomal (EU/1/16/1130) and Ayvakyt (EU/1/20/1473). The MAH addressed the three criteria that have been defined by the Regulation on Orphan medicinal products: therapeutic indication, mechanism of action and principal molecular structural features. The MAH indicates that the therapeutic indication and the mechanism of action are similar. However, the RMS considers the principal molecular

structures of the active substances to be non-similar within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Luthera, Somakit, Onivyde pegylated liposomal and Ayvakyt in the treatment of renal cell carcinoma and malignant gastrointestinal stromal tumours, does not prevent the granting of the marketing authorisation of Lusmose.

II. QUALITY ASPECTS

II.1 Introduction

Lusmose 12.5 mg is an unmarked, self-closing Coni Snap type, hard gelatine capsule. The cap is opaque, medium orange coloured, the body is opaque, rich yellow coloured, and the capsule is filled with orange coloured granules. Each capsule contains sunitinib cyclamate, equivalent to 12.5 mg of sunitinib.
Lusmose 25 mg is an unmarked, self-closing Coni Snap type, hard gelatine capsule. The cap is opaque, medium orange-coloured, the body is green coloured, and the capsule is filled with orange granules. Each capsule contains sunitinib cyclamate, equivalent to 25 mg of sunitinib.
Lusmose 50 mg is an unmarked, self-closing Coni Snap type, hard gelatine capsule. The cap is opaque, medium orange coloured, the body is opaque, medium orange coloured, and the capsule is filled with orange coloured granules. Each capsule contains sunitinib cyclamate, equivalent to 50 mg of sunitinib.

The capsules are packed in PVC/Aclar//Al blister or in HDPE Bottle closed with white polypropylene (PP) child resistant cap.

The excipients of the Lusmose 12.5 mg, 25 mg and 50 mg capsule fill are mannitol (E421), croscarmellose sodium, povidone K-30 and magnesium stearate.
The excipients of the 12.5 and 50 mg capsule shell are titanium dioxide (E171), gelatin, yellow iron oxide (E172) and red iron oxide (E172).
The excipients of the 25 mg capsule shell are titanium dioxide (E171), gelatin, yellow iron oxide (E172), red iron oxide (E172) and black iron oxide (E172).

The three capsule strengths are dose proportional.

II.2 Drug Substance

The active substance is sunitinib cyclamate, an established active substance. It is not described in the European or any other Pharmacopoeia. Previous applications have used the sunitinib maleate form, or sunitinib base as an active substance for a medicinal product.
Sunitinib cyclamate is an orange crystalline powder. It is slightly soluble in water up to neutral pH, slightly insoluble at pH 8 and above.

Sunitinib cyclamate is manufactured as polymorphic form A. The reference product is sunitinib maleate and comparison of polymorphic forms is therefore not applicable. Both forms are considered as soluble with maleate salt showing higher solubility at pH 1.2-4.5. Cyclamic acid is known as artificial sweeter used in the food industry.

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 steps: two synthetic steps and a saltification. Suppliers and acceptable specifications have been laid down for each starting material. Adequate specifications have been adopted for solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification is controlled by in-house specification, and follows ICH Q3A with regards to specified and unspecified impurities. Additional controls of note, solvents are controlled in line with ICH Q3C. The polymorphic form is controlled as an identification test, and particle size is controlled by single tier acceptance criteria. 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 batches.

Stability of drug substance

Stability data on the active substance have been provided for six batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 30 months. Based on the data submitted, a retest period could be granted of 30 months without special storage conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The pharmaceutical development of the product has been adequately performed. The proposed products have a similar manufacturing process and the same excipients as the reference product (Sutent). The developed formulations differ from the formulations of sunitinib (Sutent) in relation to the salt form. While Sutent hard capsules contain sunitinib as maleate salt, this product contains sunitinib cyclamate salt. The current definition for generic medicinal products is found in Directive 2001/83/EC, Article 10(2)(b), which states that a generic medicinal product is a

product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. According to the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr * (London, 20 January 2010), the different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy.

The development focused on investigating the relationship of process parameters (crystal form, particle size, solubility and stability) of the drug substance to critical quality attributes of the product. In principle, low risk was assigned to all parameters to affect the critical quality attributes.
The products used in the bioequivalence study are acceptable. The composition of the biobatch used in the bioequivalence study is the same as intended for marketing. The biobatch is manufactured according to the proposed commercial batch size and process.
Comparative dissolution testing at three pHs has been studied in support of the biowaiver for the lower strength capsules. During the application procedure, additional data were provided at pH 6.8. The results justified the biowaiver of strengths.
The quality control (QC) dissolution release method is demonstrated to be discriminatory for variations in excipient quantities and process parameters.

Manufacturing process
The product is manufactured using conventional manufacturing techniques: a standard wet granulation, followed by encapsulation. Process validation for full-scale batches has been completed for all strengths at three batches respectively.

Control of excipients
The excipients comply with Ph.Eur requirements. Information on functionality related characteristics has been included. 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, identity, assay, degradation impurities, water content, dissolution, disintegration, average mass, uniformity of mass of the capsules filling, uniformity of dosage units by content uniformity and microbial purity as a skip test.
Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. No widening is proposed for any of the shelf-life acceptance criteria. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from three batches of all strengths at 25°C/60%RH and 40°C/75%RH up to 36 months and 6 months, respectively, packed in HDPE bottles and PVC/Aclar/Al blisters, in accordance with applicable European guidelines. On basis of the data submitted, a shelf life was granted of 30 months. Based on open dish studies it has been demonstrated that an in-use shelf life is not necessary. No specific storage conditions need to be included in the SmPC or on the label.

Photostability studies were performed with capsules of three different strengths outside the primary pack, in accordance with ICH recommendations. These showed that the product is stable when exposed directly to light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Lusmose 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 Lusmose 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 cyclamate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below. In addition, one pilot study between the test sunitinib formulation and Sutent after a single dosis of 50 mg capsule was conducted prior to the bioequivalence study. A biowaiver is applied for the lower strengths of 12.5 and 25 mg capsules.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Lusmose 50 mg hard capsules (Egis Pharmaceuticals Plc, Hungary) 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.

The active substance in Lusmose differs from the reference product in that it is a salt form sunitinib cyclamate. There is an established acceptable daily intake for cyclamate which is above the daily intake as a result of the current product. Therefore the presence of cyclamate is of no safety concern.

Biowaiver

The MAH applied for a biowaiver for the lower strengths of 12.5 and 25 mg capsules. 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. The biowaiver request for the additional lower strengths is acceptable.

Bioequivalence studies

Design

A monocentric, open label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in eighteen healthy male subjects, aged 38 - 58 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 at least ten hours of fasting. Subjects were instructed not to touch, chew, bite or break the study drug. There were two dosing periods, separated by a washout period of 21 days.

Blood samples were collected at pre-dose and at 1.5, 3, 4, 5, 6, 6.5, 7, 7.5, 8, 9, 10, 11, 12, 14, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. Sunitinib cyclamate may be taken without reference to food intake. Lusmose capsules contain sunitinib cyclamate, while in Sutent the active pharmaceutical ingredient is sunitinib maleate. Sunitinib cyclamate is less soluble than sunitinib maleate but still can be considered highly soluble. Therefore the drug absorption is not expected to be different between Lusmose and Sutent under fed conditions (i.e. change of pH in the stomach).

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
All eighteen subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=18	AUC_{0-72h} (ng/ml/h)	$AUC_{0-\infty}$ (ng/ml/h)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	923±242	1259±453	24.1±5.2	10.0 (7.0-14.0)	34.0
Reference	952±248	1318±472	25.6±6.2	9.0 (6.5-12.0)	35.1
***Ratio (90% CI)**	0.97 (0.94-1.00)	0.96 (0.92 – 1.00)	0.94 (0.89-0.99)	-	-
CV (%), intra-subject	6.0	6.7	9.3	-	-

$AUC_{0-\infty}$ 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*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-72h}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Lusmose is considered bioequivalent with Sutent.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

The results of the bioequivalence study are extrapolated to the lower strengths of 12.5 mg and 25 mg. The dissolution requirements in the bioequivalence study guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, 2010) for granting a biowaiver are fulfilled as well.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Lusmose.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Cardiotoxicity (Torsade de pointes, left ventricular dysfunction/heart failure, pericardial events, cardiac 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 a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was Hungarian.
The test consisted of: a pilot test with four participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: findability, understandability and usability.
The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lusmose 12.5 mg, 25 mg and 50 mg hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Sutent 12.5 mg, 25 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 Lusmose with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 March 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