COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Syltezib 4 mg and 10 mg, hard capsules (lenvatinib besilate)

NL/H/6138/001-002/DC

Date: 18 November 2025

This module reflects the scientific discussion for the approval of Syltezib 4 mg and 10 mg, hard capsules. The procedure was finalised on 16 July 2025. 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
CQA	Critical Quality Attribute
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
GMA	Global Marketing Authorisation
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RCC	Renal Cell Carcinoma
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
VEGF	Vascular Endothelial Growth Factor
QTPP	Quality Target Product Profile (QTPP)

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Syltezib 4 mg and 10 mg, hard capsules, from Accord Healthcare B.V.

The product is indicated for the treatment of adults with advanced renal cell carcinoma (RCC):

- in combination with pembrolizumab, as first-line treatment.
- in combination with everolimus, following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Lenvima 4 mg and 10 mg, hard capsules, which has been registered in the EEA via a centralised procedure (EU/1/15/1002) since 28 May 2015 by the MAH Eisai GmbH (Germany). The product has the same pharmaceutical form and same amount of the active substance as Lenvima.

Beside the reference product Lenvima, Eisai GmbH also holds a marketing authorisation in the EU for Kisplyx. Kisplyx 4 mg and 10 mg, hard capsules is registered in the EEA via a centralised procedure (EU/1/16/1128) since 21 July 2016. According to the EPAR, Kisplyx is identical (from a quality point of view) to Lenvima, but has a separate registration since Lenvima was designated an orphan medicinal product.
In this procedure, the indications comprise the indications of Kisplyx.
The reference product used in the bioequivalence study is Lenvima 10 mg, hard capsules by Eisai GmbH, Germany.

The concerned member states (CMS) involved in this procedure were Czechia and Germany.

II. QUALITY ASPECTS

II.1 Introduction

Syltezib is a hard capsule. Each capsule contains lenvatinib besilate equivalent to 4 mg or 10 mg lenvatinib as active substance, depending on the strength.

The capsules are presented in two strengths which can be distinguished by their colour and debossing:
The 4 mg capsule has a caramel opaque body and caramel opaque cap, printed with 'L7VB' over '4'.
The 10 mg capsule has a rich yellow opaque body and caramel opaque cap, printed with 'L7VB' over '10'.

The excipients are:
Capsule contents - sodium hydrogen carbonate, mannitol, microcrystalline cellulose, hydroxypropylcellulose, low-substituted hydroxypropylcellulose and talc
Capsule shell 4 mg – hypromellose, black iron oxide (E172), yellow iron oxide (E172), red iron oxide (E172) and titanium dioxide (E171)
Capsule shell 10 mg – hypromellose, yellow iron oxide (E172) and titanium dioxide (E171)
Capsule cap – hypromellose, iron oxide black (E172), iron oxide yellow (E172), iron oxide red (E172) and titanium dioxide
Printing ink – shellac, potassium hydroxide and black iron oxide (E172)

The capsule contents of the two strengths are dose proportional.

The hard capsules are packed in oriented polyamide/aluminium/polyvinyl chloride/aluminium (oPA/Al/PVC/Al) blisters or in oPA/Al/PVC/polyethylene (PE)/Al blisters with desiccant.

II.2 Drug Substance

The drug substance is lenvatinib besilate, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). The substance is a crystalline powder and is practically insoluble in water. The substance shows polymorphism. For this product, polymorphic form I is consistently produced. Lenvatinib is achiral.

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 comprises three chemical transformation steps followed by a salt formation step. The first two starting materials are introduced in the first step of the synthesis. A third starting material is introduced in the third chemical transformation step. Two intermediates are isolated in the process. The process includes several purification and washing steps. No class 1 solvents are used. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification is in line with the specification of the ASMF, with additional requirements for particle size distribution and polymorphic form. The specification is considered adequate to control the quality. 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 three production scaled batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 36 months when stored under the stated 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 choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are justified. The main development studies performed were the characterisation of the reference products, the establishment of a Quality Target Product Profile (QTPP) and the derivation of Critical Quality Attributes (CQAs) thereof, the performance of risk assessments for the formulation variables and manufacturing process parameters and the performance of formulation optimisation and manufacturing process development studies based on these risk assessments.

A bioequivalence (BE) study was performed with the 10 mg product versus the respective reference product strength. The 10 mg BE study test batch was manufactured according to the finalised composition and manufacturing process at a representative scale. Comparative dissolution testing at 3 pHs has been successfully studied in support of the BE study and biowaiver for the 4 mg product. Studies to support the claim in the SmPC on the administration of the product as a suspension in water, apple juice or milk and the administration of the products through a feeding tube have been adequately performed. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The main steps of the manufacturing process are the mixing of intragranular components, wet granulation, mixing with extragranular components and final blending, encapsulation and packaging.

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three pilot scaled batches per

strength in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients

The excipients of the capsule content comply with Ph.Eur. requirements with additional requirements for functionality-related characteristics where relevant, and the pre-printed capsules comply with in-house 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 appearance, dissolution, identification, assay, uniformity of dosage units, impurities, one specific genotoxic impurity and microbial contamination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production sites have been provided on three pilot scaled batches per strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided on three production scaled batches stored at 25°C/ 60% RH (6-12 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. An increase in one specific genotoxic impurity was observed at accelerated conditions (most pronounced in the oPA/Al/PVC-Al blisters). No clear trends or changes were observed in any of the other tested parameters at accelerated conditions and in any of the tested parameters at long-term conditions. All parameters remained within the specification limits. 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 two years. The labelled storage conditions are ‘Store in the original package in order to protect from moisture’.

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 Syltezib 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 Syltezib is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Lenvima which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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

Lenvatinib is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides one bioequivalence study, which is discussed below. Additionally, the MAH has requested for a biowaiver of strengths for the lower 4 mg strength.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Syltezib 10 mg, hard capsules (Accord Healthcare B.V., the Netherlands) was compared with the pharmacokinetic profile of the reference product Lenvima 10 mg, hard capsules, (Eisai GmbH, Germany).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The following general requirements were met for the waiver for additional strength, according to the EMA Bioequivalence guideline:

a. Both strengths are manufactured by the same process.
b. The qualitative composition of the two different strengths is the same.
c. The composition of the two strengths is quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths.
d. *in vitro* dissolution data complementary to the *in vivo* BE study show similar dissolution in 0.1N HCl (QC), pH 4.5 and pH 6.8 media using a suitable dissolution method.

The dissolution of the 4 mg strength of the product was investigated versus the 10 mg study test batch according to the EMA Bioequivalence guideline. The calculated f2 similarity factor values, at three pH values (pH 1.2, pH 4.5 and pH 6.8), were within criteria (>50%). An f2 value between 50 and 100% suggests that the dissolution profiles of the two compared dissolution profiles are similar.

Bioequivalence study

Design

A single-dose, open label, randomised, four-period, crossover full replicate bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 19-48 years. Each subject received a single dose (10 mg) of one of the two lenvatinib formulations in each period. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were four dosing periods, separated by a washout period of ten days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 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

40 Subjects were enrolled in the study. One subject withdrew from the study before period II due to personal reasons. One subject withdrew before period IV, due to personal reasons, but could be included in the list of completed subjects as the first three periods were completed. A total of 39 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of lenvatinib, 10 mg under fasted conditions.

Treatment N=39	**AUC_{0-72} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	1074.4 ± 397.50	1126.2 ± 415.55	118.82 ± 50.73	2.00 (1.00-5.00)
Reference	1069.8 ± 372.76	1127.9 ± 394.20	117.43 ± 46.22	2.50 (1.00-5.00)
***Ratio (90% CI)**	0.99 (0.95 – 1.04)	--	0.99 (0.92 – 1.07)	N.A.

$AUC_{0-\infty}$	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 = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

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

Based on the data on the pH-solubility profile of the active substance in the pH range 1.2 – 6.8, on the effect of proton pomp inhibitors (PPI) on the absorption of active substance from the reference product, the excipient composition and the manufacturing process and i*n vitro* dissolution profiles of the test and reference product, the difference in salt form is not expected to influence the outcome of BE in gastric pH altered situations. Based on the initially submitted BE study, bioequivalence can be concluded.

The results of study LENV-1122-127 with 10 mg formulation can be extrapolated to the 4 mg strength, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 Syltezib. At the time of approval, the most recent version of the RMP was version 2.0 dated 20 May 2025.

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

Important identified risks	• Arterial thromboembolic events • Cardiac failure • Gastrointestinal perforation and fistula formation • Haemorrhagic events • Hepatotoxicity • Hypothyroidism • Non-gastrointestinal fistula formation (any fistula which does not involve the stomach or intestine) and pneumothorax • Posterior reversible encephalopathy syndrome • Proteinuria and nephrotic syndrome • QTc prolongation • Renal failure or impairment
Important potential risks	• Abnormal pregnancy outcome, excretion of lenvatinib in breast milk • Bone and teeth abnormalities in the paediatric population • Impaired wound healing • Interstitial lung disease-like conditions • Male and female fertility • Overdose (concomitant everolimus) (renal cell carcinoma) • Venous thromboembolic events
Missing information	• None

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 Lenvima. 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

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 Kisplyx, EMEA/H/C/004224, for the content and to Clozapine 12.5 mg orodispersable tablets, NL/H/4200-4204/001-005/DC, for the 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

Syltezib 4 mg and 10 mg, hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Lenvima 4 mg and 10 mg, hard capsules. Lenvima 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 Syltezib with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 16 July 2025.

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
-	-	-	-	-	-