Summary of the Risk Management Plan (RMP)

Lenvima® / Kisplyx® (lenvatinib)

Active substance:	Lenvatinib
Product(s) concerned (brand name[s]):	Lenvima®, Kisplyx® capsules
MAH/Applicant name:	Eisai Pharma AG
Document date:	10 Oct 2024
Document version:	2.0
Based on European Union RMP version:	16.0

Eisai Pharma AG
Leutschenbachstrasse 95
CH-8050 Zürich

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Lenvima/Kisplyx is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the local product information ("Arzneimittelinformation / Information sur le medicament") approved and published in Switzerland, eg, by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Lenvima/Kisplyx in Switzerland is the local product information ("Arzneimittelinformation / Information sur le medicament") (see www.swissmedic.ch) approved and authorized by Swissmedic. Eisai Pharma AG (Eisai) is fully responsible for the accuracy and correctness of the content of the published summary RMP of Lenvima/Kisplyx.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Lenvima / Kisplyx (lenvatinib)

This is a summary of the risk management plan (RMP) for Lenvima/Kisplyx. The RMP details important risks of Lenvima/Kisplyx, how these risks can be minimised, and how more information will be obtained about the risks and uncertainties (missing information) associated with Lenvima/Kisplyx.

The summary of product characteristics (SmPC) for Lenvima/Kisplyx and its package leaflet (PL) give essential information to healthcare professionals and patients on how Lenvima/Kisplyx should be used.

This summary of the RMP for Lenvima/Kisplyx should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of the RMP for Lenvima/Kisplyx.

I. The medicine and what it is used for

Lenvima/Kisplyx is authorised as monotherapy for the treatment of adult patients with progressive, locally advanced DTC and for the treatment of adult patients with advanced or unresectable HCC who have received no prior systemic therapy. Kisplyx is indicated in combination with everolimus for the treatment of adult patients with advanced RCC. Kisplyx is indicated in combination with pembrolizumab for the first-line treatment of adult patients with advanced (non-resectable or metastatic) renal cell carcinoma with intermediate/unfavourable risk profile. Lenvima is indicated in combination with pembrolizumab for the treatment of adult patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or DNA mismatch repair deficient (dMMR) who have disease progression following prior systemic platinum-based therapy and who are not candidates for curative surgery or radiation. It contains lenvatinib mesilate as the active substance and it is given orally once daily.

Further information about the evaluation of the benefits of Lenvima/Kisplyx can be found in the EPAR, including a plain-language summary, available on the EMA website under the medicine's webpage (web link to be provided by EMA).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Lenvima/Kisplyx, together with measures to minimise such risks and the proposed studies for learning more about the risks of Lenvima/Kisplyx are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status – the way a medicine is supplied to the patient (eg, with or without prescription) can help minimise its risks.

Together, these measures constitute ***routine risk minimisation*** measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute ***routine pharmacovigilance activities***.

If important information that may affect the safe use of Lenvima/Kisplyx is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Lenvima/Kisplyx are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Lenvima/Kisplyx. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Proteinuria and nephrotic syndrome • Renal failure or impairment • Cardiac failure • Posterior reversible encephalopathy syndrome (PRES) • Hepatotoxicity • Haemorrhagic events • Arterial thromboembolic events (ATEs) • QTc prolongation • Hypothyroidism • Gastrointestinal perforation and fistula formation

List of important risks and missing information	
	• Non-gastrointestinal fistula formation (any fistula which does not involve the stomach or intestine) and pneumothorax
Important potential risks	• Venous thromboembolic events (VTEs) • Abnormal pregnancy outcome, excretion of lenvatinib in breast milk • Male and female fertility • Bone and teeth abnormalities in the paediatric population • Impaired wound healing • Interstitial lung disease (ILD)-like conditions • Overdose (concomitant everolimus) (RCC)
Missing information	• Long-term use

II.B Summary of important risks

Important Identified Risk: Proteinuria and Nephrotic Syndrome	
Evidence for linking the risk to the medicine	Evidence from randomised clinical studies. In randomised clinical trials proteinuria was reported in more patients treated with lenvatinib than placebo. Nephrotic syndrome was identified from post-marketing surveillance and the pathological mechanism is similar to that of proteinuria.
Risk factors and risk groups	DTC The presence of hypertension during lenvatinib treatment appeared to be correlated with the development of protein in the urine (proteinuria). In addition, proteinuria was more common in women, Asians, people aged 75 years or more, and people with diabetes and kidney problems. RCC Proteinuria was more common in men and in those people with hypertension.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice on monitoring urine protein and managing proteinuria and nephrotic syndrome is provided. • PL Section 4 No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 307. See section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk: Renal Failure or Impairment	
Evidence for linking the risk to the medicine	Evidence from randomised clinical studies. In randomised clinical trials renal failure and impairment was reported in more patients treated with lenvatinib than placebo.
Risk factors and risk groups	Risk factors associated with renal impairment or failure in patients receiving lenvatinib included underlying chronic renal impairment, adrenal mass, sepsis, and dehydration and/or hypovolemia. The main risk factor for kidney failure or injury is dehydration (excessive loss of body water) resulting from diarrhoea or vomiting.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice on managing risk factors and managing renal failure or impairment is provided • PL Section 4 No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 307. See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk: Cardiac failure	
Evidence for linking the risk to the medicine (not missing information)	In randomised clinical trials decreased ejection fraction/cardiac failure was reported in more patients treated with lenvatinib than placebo.
Risk factors and risk groups	Most of the patients affected with heart failure during treatment with lenvatinib had other risk factors such as pre-existing heart disease, breathing difficulties, obesity, trouble with blood sugar control (diabetes mellitus), high BP, and prior anthracycline use (a type of chemotherapy drug).
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice on monitoring patients and managing cardiac failure is provided • PL Section 4 No additional risk minimisation measure.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 307. See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk: Posterior Reversible Encephalopathy Syndrome (PRES)	
Evidence for linking the risk to the medicine	A small number of events of PRES were reported in patients treated with lenvatinib and PRES is a known effect associated with other antiangiogenic agents.
Risk factors and risk groups	Blood pressure is elevated from baseline in most patients and systemic hypertension is a major risk factor. There are multiple well-defined conditions that can cause PRES in cancer patients, including hypertension and renal dysfunction, as can immunosuppressants, chemotherapeutic drugs, bone marrow/stem cell transplants, corticosteroids, and growth factors.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • PL Section 4 No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 307. See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	In randomised clinical trials liver-related reactions were reported in more patients treated with lenvatinib than placebo.
Risk factors and risk groups	Multiple confounding factors were observed in subjects in the clinical trial program, such as the presence of liver metastases or progression of preexisting liver metastases, concurrent medications, and contributing comorbidities. However, there were a few cases without any confounding factors that occurred shortly after the start of treatment with lenvatinib and that resolved upon discontinuation of lenvatinib.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Sections 4.2 and 4.4 where advice on monitoring liver function and managing hepatotoxicity is provided. • PL Section 4 No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Studies 307, 508. See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk: Haemorrhage	
Evidence for linking the risk to the medicine	In randomised clinical trials haemorrhage was reported in more patients treated with lenvatinib than placebo.

Important Identified Risk: Haemorrhage	
Risk factors and risk groups	The majority of intracranial haemorrhagic events in the lenvatinib clinical database were associated with the presence of tumour in the area of the bleed. These events were also often associated with the confounding factor of hypertension.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • PL Section 4 No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 307. See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk: Arterial Thromboembolic Events	
Evidence for linking the risk to the medicine	In randomised clinical trials ATEs were reported in more patients treated with lenvatinib than placebo.
Risk factors and risk groups (not missing information)	Risk factors associated with thromboembolic events in addition to the underlying malignant disease include age ≥65 years, smoking, hypertension, diabetes mellitus, obesity, atrial fibrillation, hyperlipidaemia, and prior thromboembolic disease.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Section 4.4 where advice to discontinue in case of ATE is given • PL section 4 No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 307. See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk: QTc Prolongation	
Evidence for linking the risk to the medicine	In randomised clinical trials QT/QTc prolongation was reported in more patients treated with lenvatinib than placebo.
Risk factors and risk groups	Many of the patients who had QTc prolongation also had risk factors such as hypocalcaemia (low calcium), hypothyroidism (underactive thyroid), arterial hypertension, and obesity, and many patients had changes in their body salt balance at the time of the event.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8

Important Identified Risk: QTc Prolongation	
	• SmPC Sections 4.2 and 4.4 where advice on monitoring electrolytes and managing QT interval prolongation is provided • PL Section 4 No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 307. See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk: Hypothyroidism	
Evidence for linking the risk to the medicine	In randomised clinical trials events of blood thyroid stimulating hormone increased were reported in more patients treated with lenvatinib than placebo and there were reports of hypothyroidism in patients treated with lenvatinib.
Risk factors and risk groups	Subjects with DTC who have undergone thyroidectomy and are receiving thyroid replacement therapy could develop low TSH due to thyroxine substitution. It is possible that treatment with lenvatinib may exacerbate thyroid dysfunction due to a direct effect on TSH levels.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Section 4.4 where advice on monitoring thyroid function is given • PL Section 4 No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 307. See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk: Gastrointestinal (GI) Perforation and Fistula Formation	
Evidence for linking the risk to the medicine	In randomised clinical trials events of GI perforation or fistula were reported in more patients treated with lenvatinib than placebo.
Risk factors and risk groups	The majority of these events occurred in areas of local tumour involvement. Many of the subjects had a medical history of GI bleed, gallstones, rectal abscess, diverticulitis, vaginal mass, diverticulosis of the large intestine, and colon resection for colon cancer. Subjects with oesophageal or tracheal fistula had prior neck surgery such as thyroidectomy and neck lymph node dissection.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 and 4.8 • Sections 4.2 where recommendations for dose modifications/ withdrawal are provided • PL Section 4

Important Identified Risk: Gastrointestinal (GI) Perforation and Fistula Formation	
	No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 307. See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk: Non-Gastrointestinal (GI) Fistula Formation and Pneumothorax	
Evidence for linking the risk to the medicine	Post-marketing reports of non-gastrointestinal fistula formation and pneumothorax in association with lenvatinib have been received.
Risk factors and risk groups	Prior surgery or radiotherapy may be risk factors for the development of non-GI fistulae. Patients with pre-existing fistulae treated with lenvatinib are at increased risk of worsening. Data from ongoing studies in solid tumours indicates that the risk of pneumothorax may be higher in certain types of tumours such as soft tissue sarcoma. The presence of lung metastases and tumours with high therapeutic responses to lenvatinib may increase the risk of pneumothorax.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • SmPC Section 4.4 where advice that lenvatinib should not be started in patients with fistulae and when to permanently discontinue lenvatinib is given. • PL Section 4 No additional risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 307. See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Potential Risk: Venous Thromboembolic Events (VTEs)	
Evidence for linking the risk to the medicine	In randomised clinical trials events of pulmonary embolism were reported in more patients treated with lenvatinib than placebo and there is a recognised potential class effect
Risk factors and risk groups	Risk factors associated with VTEs include underlying malignant disease, age ≥65 years, and immobility.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.8 • PL Section 4 No additional risk minimisation measures

Important Potential Risk: Venous Thromboembolic Events (VTEs)	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 307. See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Potential Risk: Abnormal Pregnancy Outcome, Excretion of Lenvatinib in Breast Milk	
Evidence for linking the risk to the medicine	Nonclinical data. There are insufficient clinical data to exclude a risk.
Risk factors and risk groups (not missing information)	Women of childbearing potential and lactating females.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.6 • PL Section 2 No additional risk minimisation measures

Important Potential Risk: Effect on Male and Female Fertility	
Evidence for linking the risk to the medicine	Nonclinical data. There are insufficient clinical data to exclude a risk.
Risk factors and risk groups	Men and women of reproductive age
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 No additional risk minimisation measures

Important Potential Risk: Bone and Teeth Abnormalities in the Paediatric Population	
Evidence for linking the risk to the medicine	Nonclinical data. There are currently insufficient clinical data to exclude or confirm a risk.
Risk factors and risk groups (not missing information)	Paediatric patients with an active growth plate and young enough to not yet have developed their permanent teeth.
Risk minimisations measures	Routine risk minimisation measures: • SmPC Section 5.3 No additional risk minimisation measures

Important Potential Risk: Impaired Wound Healing	
Evidence for linking the risk to the medicine	Known effect of some other medicines in the class; insufficient clinical data to exclude a risk.
Risk factors and risk groups	Surgery or radiotherapy within 4 weeks of treatment with a VEGF/VEGFR targeted therapy are risk factors for impaired wound healing.
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 307. See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Potential Risk: Interstitial Lung Disease (ILD) like Conditions	
Evidence for linking the risk to the medicine	"Interstitial lung disease-like events" have been reported for several other medicinal products from the same pharmacological class.
Risk factors and risk groups	Patients with underlying respiratory disorders may be at higher risk of developing ILD-like events with lenvatinib treatment
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study 307. See Section II.C of this summary for an overview of the post-authorisation development plan.

Potential Risk: Overdose (concomitant everolimus) (RCC)	
Evidence for linking the risk to the medicine	There is a potential for dosing errors as the dose of everolimus when used concomitantly with lenvatinib is lower than when everolimus is used alone in monotherapy. In the RCC Lenvatinib + Everolimus Safety Set, everolimus overdose was recorded in 4 subjects (0.6%). Two subjects in Study 307 had a planned dose of 0 mg and took 5 mg for 1 day. At a planned dose of 5 mg, 1 subject in Study 205 took 10 mg for 1 day and 1 subject in Study 307 took 10 mg for 4 days.
Risk factors and risk groups	Molecularly targeted drugs given in combination are usually administered at a dosage lower than that of their individual monotherapies so physicians and pharmacists prescribing or dispensing such drugs should be alert to this risk.
Risk minimisations measures	Routine risk minimisation measures: • SmPC Section 4.2 • PL Section 2 No additional risk minimisation measures

Missing Information: Long-term use of Lenvatinib	
Risk minimisations measures	No risk minimisation measures

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Lenvima/Kisplyx.

II.C.2 Other studies in post-authorisation development plan

Study Short Name	**Purpose of the Study**
DTC	
None	
RCC	
E7080-G000-307 – Study to compare the efficacy and safety of lenvatinib in combination with everolimus or pembrolizumab versus sunitinib alone in 1L treatment of subjects with advanced unresectable renal cell carcinoma.	Safety concerns addressed: all important identified and potential risks, continue to characterise/ confirm current safety profile of lenvatinib in RCC. Primary Objective: To demonstrate that lenvatinib in combination with everolimus or pembrolizumab is superior compared to sunitinib alone in improving PFS as 1L treatment in subjects with advanced renal cell carcinoma (RCC).
HCC	
E7080-M000-508 – To characterise hepatic-related toxicity and overall safety profile (SAEs, Grade 3-5 AEs, dose modifications, and discontinuations due to AEs) in real-life conditions in the EU (Western population) in HCC patients, including patients with Child-Pugh B.	Safety concerns addressed: hepatotoxicity in HCC patients. Primary Objective: To characterise hepatic-related toxicity and overall safety profile in real-life conditions in the EU (Western population) in HCC patients, including patients with Child-Pugh B. Overall survival data and detailed baseline characteristics will also be collected.