ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Kisplyx 4 mg hard capsules
Kisplyx 10 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Kisplyx 4 mg hard capsules

Each hard capsule contains 4 mg of lenvatinib (as mesilate).

Kisplyx 10 mg hard capsules

Each hard capsule contains 10 mg of lenvatinib (as mesilate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Kisplyx 4 mg hard capsules

A yellowish-red body and yellowish-red cap, approximately 14.3 mm in length, marked in black ink with "Є" on the cap, and "LENV 4 mg" on the body.

Kisplyx 10 mg hard capsules

A yellow body and yellowish-red cap, approximately 14.3 mm in length, marked in black ink with "Є" on the cap, and "LENV 10 mg" on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kisplyx is indicated for the treatment of adults with advanced renal cell carcinoma (RCC):
- in combination with pembrolizumab, as first-line treatment (see section 5.1).
- in combination with everolimus, following one prior vascular endothelial growth factor (VEGF)-targeted therapy (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated and supervised by a healthcare professional experienced in the use of anticancer therapies.

Posology

Kisplyx in combination with pembrolizumab as first-line treatment

The recommended dose of lenvatinib is 20 mg (two 10-mg capsules) orally once daily in combination with pembrolizumab either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes. The daily dose of lenvatinib is to be modified as needed according to the dose/toxicity management plan. Lenvatinib treatment should continue until disease

progression or unacceptable toxicity. Pembrolizumab should be continued until disease progression, unacceptable toxicity or the maximum duration of therapy as specified for pembrolizumab.

See the Summary of Product Characteristics (SmPC) for pembrolizumab for full pembrolizumab dosing information.

Kisplyx in combination with everolimus as second-line treatment

The recommended daily dose of lenvatinib is 18 mg (one 10-mg capsule and two 4-mg capsules) orally once daily in combination with 5 mg of everolimus once daily. The daily dose of lenvatinib and, if necessary, everolimus is to be modified as needed according to the dose/toxicity management plan.

See the SmPC for everolimus for full everolimus dosing information.

If a patient misses a dose of lenvatinib, and it cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration.

Treatment should continue as long as there is clinical benefit or until unacceptable toxicity occurs.

Dose adjustment and discontinuation for lenvatinib

Management of adverse reactions may require dose interruption, adjustment, or discontinuation of lenvatinib therapy (see section 4.4). Mild to moderate adverse reactions (e.g., Grade 1 or 2) generally do not warrant interruption of lenvatinib unless intolerable to the patient despite optimal management. Severe (e.g., Grade 3) or intolerable adverse reactions require interruption of lenvatinib until improvement of the reaction to Grade 0 to 1 or baseline.

Optimal medical management (i.e., treatment or therapy) for nausea, vomiting, and diarrhoea should be initiated prior to any lenvatinib therapy interruption or dose reduction; gastrointestinal toxicity should be actively treated in order to reduce the risk of development of renal impairment or renal failure (see section 4.4).

For toxicities thought to be related to lenvatinib (see Table 2), upon resolution/improvement of an adverse reaction to Grade 0 to 1 or baseline, treatment should be resumed at a reduced dose of lenvatinib as suggested in Table 1.

Table 1 Dose modifications from recommended lenvatinib daily dose[a]

	Lenvatinib dose in combination with pembrolizumab	**Lenvatinib dose in combination with everolimus**
Recommended daily dose	20 mg orally once daily (two 10-mg capsules)	18 mg orally once daily (one 10-mg capsule + two 4-mg capsules)
First dose reduction	14 mg orally once daily (one 10-mg capsule + one 4-mg capsule)	14 mg orally once daily (one 10-mg capsule + one 4-mg capsule)
Second dose reduction	10 mg orally once daily (one 10-mg capsule)	10 mg orally once daily (one 10-mg capsule)
Third dose reduction	8 mg orally once daily (two 4-mg capsules)	8 mg orally once daily (two 4-mg capsules)
[a] Limited data are available for doses below 8 mg		

When used in combination with pembrolizumab, one or both medicines should be interrupted as appropriate. Lenvatinib should be withheld, dose reduced, or discontinued as appropriate. Withhold or discontinue pembrolizumab in accordance with the instructions in the SmPC for pembrolizumab. No dose reductions are recommended for pembrolizumab.

For toxicities thought to be related to everolimus, treatment should be interrupted, reduced to alternate day dosing, or discontinued (see the SmPC for everolimus for dose adjustment recommendations regarding specific adverse reactions).

For toxicities thought to be related to both lenvatinib and everolimus, lenvatinib should be reduced (see Table 1) prior to reducing everolimus.

All treatments should be discontinued in case of life-threatening reactions (e.g., Grade 4) with the exception of laboratory abnormalities judged to be non-life-threatening, in which case they should be managed as severe reactions (e.g., Grade 3).

Grades are based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).

Table 2 Adverse reactions requiring dose modification of lenvatinib

Adverse reaction	**Severity**	**Action**	**Dose reduce and resume lenvatinib**
Hypertension	Grade 3 (despite optimal antihypertensive therapy)	Interrupt	Resolves to Grade 0, 1 or 2. See detailed guidance in Table 3 in section 4.4.
	Grade 4	Discontinue	Do not resume
Proteinuria	≥ 2 gm / 24 hours	Interrupt	Resolves to less than 2 gm / 24 hours.
Nephrotic syndrome	-------	Discontinue	Do not resume
Renal impairment or failure	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4*	Discontinue	Do not resume
Cardiac dysfunction	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume
PRES/RPLS	Any grade	Interrupt	Consider resuming at reduced dose if resolves to Grade 0-1.
Hepatotoxicity	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4*	Discontinue	Do not resume
Arterial thromboembolisms	Any grade	Discontinue	Do not resume
Haemorrhage	Grade 3	Interrupt	Resolves to Grade 0-1.
	Grade 4	Discontinue	Do not resume
GI perforation or fistula	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4	Discontinue	Do not resume
Non-GI fistula	Grade 4	Discontinue	Do not resume
QT interval prolongation	>500 ms	Interrupt	Resolves to <480 ms or baseline
Diarrhoea	Grade 3	Interrupt	Resolves to Grade 0-1 or baseline.
	Grade 4 (despite medical management)	Discontinue	Do not resume

*Grade 4 laboratory abnormalities judged to be non-life-threatening, may be managed as severe reactions (e.g., Grade 3)

Special populations

For information about clinical experience with the combination treatment of lenvatinib and pembrolizumab, see section 4.8.

Patients of age ≥65 years, with baseline hypertension or those with renal impairment appear to have reduced tolerability to lenvatinib (see section 4.8).

No data for the combination of lenvatinib and everolimus are available for most of the special populations. The following information is derived from clinical experience of single agent lenvatinib in patients with differentiated thyroid cancer (DTC; see SmPC for Lenvima).

All patients other than those with severe hepatic or renal impairment (see below) should initiate treatment at the recommended dose of 20 mg of lenvatinib daily with pembrolizumab or 18 mg of lenvatinib with 5 mg of everolimus taken once daily as indicated, following which the dose should be further adjusted on the basis of individual tolerability.

Patients with hypertension

Blood pressure should be well controlled prior to treatment with lenvatinib, and should be regularly monitored during treatment (see sections 4.4 and 4.8).

Patients with hepatic impairment

Limited data are available for the combination of lenvatinib with pembrolizumab in patients with hepatic impairment. No adjustment of starting dose of the combination is required on the basis of hepatic function in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. In patients with severe (Child-Pugh C) hepatic impairment, the recommended starting dose of lenvatinib is 10 mg taken once daily. Please refer to the SmPC for pembrolizumab for dosing in patients with hepatic impairment. Further dose adjustments may be necessary on the basis of individual tolerability. The combination should be used in patients with severe hepatic impairment only if the anticipated benefit exceeds the risk (see section 4.8).

No data for the combination of lenvatinib with everolimus are available in patients with hepatic impairment. No adjustment of starting dose of the combination is required on the basis of hepatic function in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. In patients with severe (Child-Pugh C) hepatic impairment, the recommended starting dose of lenvatinib is 10 mg taken once daily in combination with the dose of everolimus recommended for patients with severe hepatic impairment in the SmPC for everolimus. Further dose adjustments may be necessary on the basis of individual tolerability. The combination should be used in patients with severe hepatic impairment only if the anticipated benefit exceeds the risk (see section 4.8).

Patients with renal impairment

No adjustment of starting dose is required on the basis of renal function in patients with mild or moderate renal impairment. In patients with severe renal impairment, the recommended starting dose is 10 mg of lenvatinib taken once daily. Please refer to the SmPC for pembrolizumab or everolimus for dosing in patients with renal impairment. Further dose adjustments may be necessary based on individual tolerability. Patients with end-stage renal disease have not been studied, therefore the use of lenvatinib in these patients is not recommended (see section 4.8).

Elderly population

No adjustment of starting dose is required on the basis of age. Limited data are available on use in patients aged ≥75 years (see section 4.8).

Paediatric population

The safety and efficacy of lenvatinib in children aged 2 to <18 years have not been established. Currently available data are described in sections 4.8, 5.1, and 5.2 but no recommendation on a posology can be made.
Lenvatinib should not be used in children younger than 2 years of age because of safety concerns identified in animal studies (see section 5.3).

Ethnic Origin

No adjustment of starting dose is required on the basis of race (see section 5.2). Currently available data are described in section 4.8.

Body weight below 60 kg

No adjustment of starting dose is required on the basis of body weight. Limited data are available on treatment with lenvatinib in combination with everolimus in patients with a body weight below 60 kg with RCC (see section 4.8).

Performance status

Patients with an ECOG (Eastern Cooperative Oncology Group) performance status of 2 or higher were excluded from RCC Study 205 (see section 5.1). Patients with a KPS (Karnofsky Performance Status) <70 were excluded from Study 307 (CLEAR). Benefit-risk in these patients has not been evaluated.

Method of administration

Lenvatinib is for oral use. The capsules should be taken at about the same time each day, with or without food (see section 5.2). Caregivers should not open the capsule, in order to avoid repeated exposure to the contents of the capsule.

Lenvatinib capsules can be swallowed whole with water or administered as a suspension prepared by dispersing the whole capsule(s) in water, apple juice, or milk. The suspension may be administered orally or via a feeding tube. If administered via a feeding tube, then the suspension should be prepared using water (see section 6.6 for preparation and administration of suspension).

If not used at the time of preparation, lenvatinib suspension may be stored in a covered container and must be refrigerated at 2ºC to 8ºC for a maximum of 24 hours. After removal from the refrigerator the suspension should be shaken for approximately 30 seconds before use. If not administered within 24 hours, the suspension should be discarded.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Hypertension

Hypertension has been reported in patients treated with lenvatinib, usually occurring early in the course of treatment (see section 4.8). Blood pressure (BP) should be well controlled prior to treatment with lenvatinib and, if patients are known to be hypertensive, they should be on a stable dose of antihypertensive therapy for at least 1 week prior to treatment with lenvatinib. Serious complications of poorly controlled hypertension, including aortic dissection, have been reported. The early detection and effective management of hypertension are important to minimise the need for lenvatinib dose interruptions and reductions. Antihypertensive agents should be started as soon as elevated BP is confirmed. BP should be monitored after 1 week of treatment with lenvatinib, then every 2 weeks for the first 2 months, and monthly thereafter. The choice of antihypertensive treatment should be individualised to the patient's clinical circumstances and follow standard medical practice. For previously normotensive patients, monotherapy with one of the classes of antihypertensive should be started when elevated BP is observed. For those patients already on an antihypertensive medicinal product, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be added. When necessary, manage hypertension as recommended in Table 3.

Table 3 Recommended management of hypertension

Blood pressure (BP) level	Recommended action
Systolic BP ≥140 mmHg up to <160 mmHg or diastolic BP ≥90 mmHg up to <100 mmHg	Continue lenvatinib and initiate antihypertensive therapy, if not already receiving OR Continue lenvatinib and increase the dose of the current antihypertensive therapy or initiate additional antihypertensive therapy
Systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg despite optimal antihypertensive therapy	1. Withhold lenvatinib 2. When systolic BP ≤150 mmHg, diastolic BP ≤95 mmHg, and patient has been on a stable dose of antihypertensive therapy for at least 48 hours, resume lenvatinib at a reduced dose (see section 4.2)
Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Urgent intervention is indicated. Discontinue lenvatinib and institute appropriate medical management.

Aneurysms and artery dissections

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating lenvatinib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Women of childbearing potential

Women of childbearing potential must use highly effective contraception while taking lenvatinib and for one month after stopping treatment (see section 4.6). It is currently unknown if lenvatinib increases the risk of thromboembolic events when combined with oral contraceptives.

Proteinuria

Proteinuria has been reported in patients treated with lenvatinib, usually occurring early in the course of treatment (see section 4.8). Urine protein should be monitored regularly. If urine dipstick proteinuria ≥2+ is detected, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2). Cases of nephrotic syndrome have been reported in patients using lenvatinib. Lenvatinib should be discontinued in the event of nephrotic syndrome.

Renal failure and impairment

Renal impairment and renal failure have been reported in patients treated with lenvatinib (see section 4.8). The primary risk factor identified was dehydration and/or hypovolemia due to gastrointestinal toxicity. Gastrointestinal toxicity should be actively managed in order to reduce the risk of development of renal impairment or renal failure. Caution should be taken in patients receiving agents acting on the renin-angiotensin aldosterone system given a potentially higher risk for acute renal failure with the combination treatment. Dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

If patients have severe renal impairment, the initial dose of lenvatinib should be adjusted (see sections 4.2 and 5.2).

Cardiac dysfunction

Cardiac failure (<1%) and decreased left ventricular ejection fraction have been reported in patients treated with lenvatinib (see section 4.8). Patients should be monitored for clinical symptoms or signs of cardiac decompensation, as dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

Posterior reversible encephalopathy syndrome (PRES) / Reversible posterior leucoencephalopathy syndrome (RPLS)

PRES, also known as RPLS, has been reported in patients treated with lenvatinib (<1%; see section 4.8). PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. Appropriate measures should be taken to control blood pressure (see section 4.4, Hypertension). In patients with signs or symptoms of PRES, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

Hepatotoxicity

Liver-related adverse reactions most commonly reported in patients treated with lenvatinib included increases in alanine aminotransferase, increases in aspartate aminotransferase, and increases in blood bilirubin. Hepatic failure and acute hepatitis (<1%; see section 4.8) have been reported in patients treated with lenvatinib. The hepatic failure cases were generally reported in patients with progressive liver metastases. Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

If patients have severe hepatic impairment, the initial dose of lenvatinib should be adjusted (see sections 4.2 and 5.2).

Arterial thromboembolisms

Arterial thromboembolisms (cerebrovascular accident, transient ischaemic attack, and myocardial infarction) have been reported in patients treated with lenvatinib (see section 4.8). Lenvatinib has not been studied in patients who have had an arterial thromboembolism within the previous 6 months, and therefore should be used with caution in such patients. A treatment decision should be made based upon an assessment of the individual patient's benefit/risk. Lenvatinib should be discontinued following an arterial thrombotic event.

Haemorrhage

Serious tumour related bleeds, including fatal haemorrhagic events have occurred in clinical trials and have been reported in post-marketing experience (see section 4.8). In post-marketing surveillance, serious and fatal carotid artery haemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than in DTC or other tumour types. The degree of tumour invasion/infiltration of major blood vessels (e.g. carotid artery) should be considered because of the potential risk of severe haemorrhage associated with tumour shrinkage/necrosis following lenvatinib therapy. Some cases of bleeding have occurred secondarily to tumour shrinkage and fistula formation, e.g. tracheo-oesophageal fistulae. Cases of fatal intracranial haemorrhage have been reported in some patients with or without brain metastases. Bleeding in sites other than the brain (e.g. trachea, intra-abdominal, lung) has also been reported.

In the case of bleeding, dose interruptions, adjustments, or discontinuation may be required (see section 4.2, Table 2).

Gastrointestinal perforation and fistula formation

Gastrointestinal perforation or fistulae have been reported in patients treated with lenvatinib (see section 4.8). In most cases, gastrointestinal perforation and fistulae occurred in patients with risk factors such as prior surgery or radiotherapy. In the case of a gastrointestinal perforation or fistula, dose interruptions, adjustments, or discontinuation may be necessary (see section 4.2).

Non-gastrointestinal fistula

Patients may be at increased risk for the development of fistulae when treated with lenvatinib. Cases of fistula formation or enlargement that involve other areas of the body than stomach or intestines were observed in clinical trials and in post-marketing experience (e.g. tracheal, tracheo-oesophageal, oesophageal, cutaneous, female genital tract fistulae). In addition, pneumothorax has been reported with and without clear evidence of a bronchopleural fistula. Some reports of fistula and pneumothorax occurred in association with tumour regression or necrosis. Prior surgery and radiotherapy may be contributing risk factors. Lung metastases may also increase the risk of pneumothorax. Lenvatinib should not be started in patients with fistulae to avoid worsening and lenvatinib should be permanently discontinued in patients with oesophageal or tracheobronchial tract involvement and any Grade 4 fistula (see section 4.2); limited information is available on the use of dose interruption or reduction in management of other events, but worsening was observed in some cases and caution should be taken. Lenvatinib may adversely affect the wound healing process as do other agents of the same class.

QT interval prolongation

QT/QTc interval prolongation has been reported at a higher incidence in patients treated with lenvatinib than in patients treated with placebo (see section 4.8). Electrocardiograms should be monitored in all patients with a special attention for those with congenital long QT syndrome, congestive heart failure, bradyarrhythmics, and those taking medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics. Lenvatinib should be withheld in the event of development of QT interval prolongation greater than 500 ms. Lenvatinib should be resumed at a reduced dose when QTc prolongation is resolved to < 480 ms or baseline.

Electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia increase the risk of QT prolongation; therefore electrolyte abnormalities should be monitored and corrected in all patients before starting treatment. Periodic monitoring of ECG and electrolytes (magnesium, potassium and calcium) should be considered during treatment. Blood calcium levels should be monitored at least monthly and calcium should be replaced as necessary during lenvatinib treatment. Lenvatinib dose should be interrupted or dose adjusted as necessary depending on severity, presence of ECG changes, and persistence of hypocalcaemia.

Impairment of thyroid stimulating hormone suppression / Thyroid dysfunction

Hypothyroidism has been reported in patients treated with lenvatinib (see section 4.8). Thyroid function should be monitored before initiation of, and periodically throughout, treatment with lenvatinib. Hypothyroidism should be treated according to standard medical practice to maintain euthyroid state.

Lenvatinib impairs exogenous thyroid suppression (see section 4.8). Thyroid stimulating hormone (TSH) levels should be monitored on a regular basis and thyroid hormone administration should be adjusted to reach appropriate TSH levels, according to the patient's therapeutic target.

Diarrhoea

Diarrhoea has been reported frequently in patients treated with lenvatinib, usually occurring early in the course of treatment (see section 4.8). Prompt medical management of diarrhoea should be instituted in order to prevent dehydration. Lenvatinib should be discontinued in the event of persistence of Grade 4 diarrhoea despite medical management.

Wound healing complications

No formal studies of the effect of lenvatinib on wound healing have been conducted. Impaired wound healing has been reported in patients receiving lenvatinib. Temporary interruption of lenvatinib should be considered in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of lenvatinib following a major surgical procedure. Therefore, the

decision to resume lenvatinib following a major surgical procedure should be based on clinical judgment of adequate wound healing.

Osteonecrosis of the jaw (ONJ)

Cases of ONJ have been reported in patients treated with lenvatinib. Some cases were reported in patients who had received prior or concomitant treatment with antiresorptive bone therapy, and/or other angiogenesis inhibitors, e.g. bevacizumab, TKI, mTOR inhibitors. Caution should therefore be exercised when lenvatinib is used either simultaneously or sequentially with antiresorptive therapy and/or other angiogenesis inhibitors.

Invasive dental procedures are an identified risk factor. Prior to treatment with lenvatinib, a dental examination and appropriate preventive dentistry should be considered. In patients who have previously received or are receiving intravenous bisphosphonates, invasive dental procedures should be avoided if possible (see section 4.8).

Tumour lysis syndrome (TLS)

Lenvatinib can cause TLS which can be fatal. Risk factors for TLS include but are not limited to high tumour burden, pre-existing renal impairment and dehydration. These patients should be monitored closely and treated as clinically indicated, and prophylactic hydration should be considered.

Special populations

Limited data are available for patients of ethnic origin other than Caucasian or Asian, and in patients aged ≥75 years. Lenvatinib should be used with caution in such patients, given the reduced tolerability of lenvatinib in Asian and elderly patients (see section 4.8).

There are no data on the use of lenvatinib immediately following sorafenib or other anticancer treatments and there may be a potential risk for additive toxicities unless there is an adequate washout period between treatments. The minimal washout period in clinical trials was of 4 weeks.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on lenvatinib

Chemotherapeutic agents

Concomitant administration of lenvatinib, carboplatin, and paclitaxel has no significant impact on the pharmacokinetics of any of these 3 substances. Additionally, in patients with RCC the pharmacokinetics of lenvatinib was not significantly affected by concomitant everolimus.

Effect of lenvatinib on other medicinal products

CYP3A4 substrates

A clinical drug-drug interaction (DDI) study in cancer patients showed that plasma concentrations of midazolam (a sensitive CYP3A and Pgp substrate) were not altered in the presence of lenvatinib. Additionally, in patients with RCC the pharmacokinetics of everolimus was not significantly affected by concomitant lenvatinib. No significant drug-drug interaction is therefore expected between lenvatinib and other CYP3A4/Pgp substrates.

Oral contraceptives

It is currently unknown whether lenvatinib may reduce the effectiveness of hormonal contraceptives, and therefore women using oral hormonal contraceptives should add a barrier method (see section 4.6).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in females

Women of childbearing potential should avoid becoming pregnant and use highly effective contraception while on treatment with lenvatinib and for at least one month after finishing treatment. It is currently unknown whether lenvatinib may reduce the effectiveness of hormonal contraceptives, and therefore women using oral hormonal contraceptives should add a barrier method.

Pregnancy

There are no data on the use of lenvatinib in pregnant women. Lenvatinib was embryotoxic and teratogenic when administered to rats and rabbits (see section 5.3).

Lenvatinib should not be used during pregnancy unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the foetus.

Breast-feeding

It is not known whether lenvatinib is excreted in human milk. Lenvatinib and its metabolites are excreted in rat milk (see section 5.3).

A risk to newborns or infants cannot be excluded and, therefore, lenvatinib is contraindicated during breast-feeding (see section 4.3).

Fertility

Effects in humans are unknown. However, testicular and ovarian toxicity has been observed in rats, dogs, and monkeys (see section 5.3).

4.7 Effects on ability to drive and use machines

Lenvatinib has minor influence on the ability to drive and use machines, due to undesirable effects such as fatigue and dizziness. Patients who experience these symptoms should use caution when driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of lenvatinib is based on pooled data from 497 RCC patients treated with lenvatinib in combination with pembrolizumab, including Study 307 (CLEAR); pooled data from 623 RCC patients treated with lenvatinib in combination with everolimus: 458 DTC patients and 496 HCC patients treated with lenvatinib as monotherapy.

Lenvatinib in combination with pembrolizumab in RCC

The safety profile of lenvatinib in combination with pembrolizumab is based on data from 497 RCC patients. The most frequently reported adverse reactions (occurring in ≥30% of patients) were diarrhoea (61.8%), hypertension (51.5%) fatigue (47.1%), hypothyroidism (45.1%), decreased appetite (42.1%), nausea (39.6%), stomatitis (36.6%), proteinuria (33.0%), dysphonia (32.8%), and arthralgia (32.4%).

The most common severe (Grade ≥3) adverse reactions (≥5%) were hypertension (26.2%), lipase increased (12.9%), diarrhoea (9.5%), proteinuria (8.0%), amylase increased (7.6%), weight decreased (7.2%), and fatigue (5.2%).

Discontinuation of lenvatinib, pembrolizumab, or both due to an adverse reaction occurred in 33.4% of patients; 23.7% lenvatinib, and 12.9 % both drugs. The most common adverse reactions (≥1%) leading to discontinuation of lenvatinib, pembrolizumab, or both were myocardial infarction (2.4%), diarrhoea (2.0%), proteinuria (1.8%), and rash (1.4%). Adverse reactions that most commonly led to discontinuation of lenvatinib (≥1%) were myocardial infarction (2.2%), proteinuria (1.8%), and diarrhoea (1.0%).

Dose interruptions of lenvatinib, pembrolizumab, or both due to an adverse reaction occurred in 80.1% of patients; lenvatinib was interrupted in 75.3%, and both drugs in 38.6% of patients. Lenvatinib was dose reduced in 68.4% of patients. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of lenvatinib were diarrhoea (25.6%), hypertension (16.1%), proteinuria (13.7%), fatigue (13.1%), appetite decreased (10.9%), palmar-plantar erythrodysaesthesia syndrome (PPE) (10.7%), nausea (9.7%), asthenia (6.6%), stomatitis (6.2%), lipase increased (5.6%), and vomiting (5.6%).

Lenvatinib in combination with everolimus in RCC

The safety profile of lenvatinib in combination with everolimus is based on data from 623 patients.

The most frequently reported adverse reactions(occurring in ≥30% of patients) were diarrhoea (69.0%), fatigue (41.9%), hypertension (41.7%), decreased appetite (41.6%), stomatitis (40.6%), nausea (38.8%), proteinuria (34.2%), vomiting (32.7%) and weight decreased (31.3%).
The most common severe (Grade ≥3) adverse reactions (≥5%) were hypertension (19.3%), diarrhoea (13.8%), proteinuria (8.8%), fatigue (7.1%), decreased appetite (6.3%) and weight decreased (5.8%).

Discontinuation of lenvatinib, everolimus, or both due to an adverse reaction occurred in 27.0% of patients; 21.7% lenvatinib, and 18.7% both drugs. The most common adverse reactions (≥1%) leading to discontinuation of lenvatinib, everolimus, or both were proteinuria (2.7%), diarrhoea (1.0%) and decreased appetite (1.0%). Adverse reaction that most commonly led to discontinuation of lenvatinib (≥1%) was proteinuria (2.1%).

Dose interruptions of lenvatinib, everolimus, or both due to an adverse reaction occurred in 82.2% of patients; in patients where data on individual drug modifications were collected, lenvatinib was interrupted in 74.3%, and both drugs in 71.9% of patients. The most common adverse reactions (≥5%) resulting in dose reduction or interruption of lenvatinib were diarrhoea (30.4%), fatigue (15.3%), proteinuria (14.7%), appetite decreased (13.4%), stomatitis (13.2%), nausea (10.9%), vomiting (10.2%), hypertension (9.2%), asthenia (7.9%), platelet count decreased (5.7%), and weight decreased (5.1%).

Tabulated list of adverse reactions

Adverse reactions observed in clinical trials and reported from post-marketing use of lenvatinib are listed in Table 4. Adverse reactions known to occur with lenvatinib or combination therapy components given alone may occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical studies with combination therapy.

For additional safety information when lenvatinib is administered in combination, refer to the SmPC for the respective combination therapy components.

Frequencies are defined as:

- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from the available data)

Within each frequency category, adverse reactions are presented in order of decreasing seriousness.

Table 4 Adverse reactions reported in patients treated with lenvatinib[§]

System Organ Class (MedDRA terminology)	**Lenvatinib monotherapy**	**Combination with everolimus**	**Combination with pembrolizumab**
Infections and infestations			
Very common	Urinary tract infection		
Common		Urinary tract infection	Urinary tract infection
Uncommon	Perineal abscess	Perineal abscess	Perineal abscess
Blood and lymphatic disorders			
Very common	Thrombocytopenia[‡] Lymphopenia[‡] Leukopenia[‡] Neutropenia[‡]	Thrombocytopenia[‡] Lymphopenia[‡] Leukopenia[‡] Neutropenia[‡]	Thrombocytopenia[‡] Lymphopenia[‡] Leukopenia[‡] Neutropenia[‡]
Uncommon	Splenic infarction		
Endocrine disorders			
Very common	Hypothyroidism* Increased blood thyroid stimulating hormone*[,‡]	Hypothyroidism* Increased blood thyroid stimulating hormone*[,‡]	Hypothyroidism* Increased blood thyroid stimulating hormone*[,‡]
Common			Adrenal insufficiency
Uncommon	Adrenal insufficiency	Adrenal insufficiency	
Metabolism and nutrition disorders			
Very common	Hypocalcaemia*[,‡] Hypokalaemia[‡] Hypomagnesaemia[‡] Hypercholesterolaemia[‡] Decreased weight Decreased appetite	Hypocalcaemia[‡] Hypokalaemia[‡] Hypomagnesaemia[‡] Hypercholesterolaemia *[,‡] Decreased weight Decreased appetite	Hypocalcaemia[‡] Hypokalaemia[‡] Hypomagnesaemia[‡] Hypercholesterolaemia *[,‡] Decreased weight Decreased appetite
Common	Dehydration	Dehydration	Dehydration
Rare	Tumour lysis syndrome [†]	Tumour lysis syndrome [†]	Tumour lysis syndrome [†]
Psychiatric disorders			
Very common	Insomnia	Insomnia	Insomnia
Nervous system disorders			
Very common	Dizziness Headache Dysgeusia	Headache Dysgeusia	Dizziness Headache Dysgeusia
Common	Cerebrovascular accident[†]	Dizziness	
Uncommon	Posterior reversible encephalopathy syndrome Monoparesis Transient ischaemic attack	Cerebrovascular accident[†] Transient ischaemic attack	Cerebrovascular accident Posterior reversible encephalopathy syndrome Transient ischaemic attack

System Organ Class (MedDRA terminology)	**Lenvatinib monotherapy**	**Combination with everolimus**	**Combination with pembrolizumab**
Cardiac disorders			
Common	Myocardial infarction[a,†] Cardiac failure Prolonged electrocardiogram QT Decreased ejection fraction	Myocardial infarction[a,†] Cardiac failure[†] Prolonged electrocardiogram QT	Myocardial infarction[a] Prolonged electrocardiogram QT
Uncommon		Decreased ejection fraction	Cardiac failure[†] Decreased ejection fraction
Vascular disorders			
Very common	Haemorrhage[b, *, †] Hypertension[c,*] Hypotension	Haemorrhage[b, *, †] Hypertension[c,*]	Haemorrhage[b, *, †] Hypertension[c,*]
Common		Hypotension	Hypotension
Not known	Aneurysms and artery dissections	Aneurysms and artery dissections	Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders			
Very common	Dysphonia	Dysphonia	Dysphonia
Common	Pulmonary embolism[†]	Pulmonary embolism Pneumothorax	Pulmonary embolism
Uncommon	Pneumothorax		Pneumothorax
Gastrointestinal disorders			
Very common	Diarrhoea* Gastrointestinal and abdominal pains[d] Vomiting Nausea Oral inflammation[e] Oral pain[f] Constipation Dyspepsia Dry mouth Increased lipase[‡] Increased amylase[‡]	Diarrhoea* Gastrointestinal and abdominal pains[d] Vomiting Nausea Oral inflammation[e] Oral pain[f] Constipation Dyspepsia Increased lipase[‡] Increased amylase[‡]	Diarrhoea* Gastrointestinal and abdominal pains[d] Vomiting Nausea Oral inflammation[e] Oral pain[f] Constipation Dyspepsia Dry mouth Increased lipase[‡] Increased amylase[‡]
Common	Anal fistula Flatulence Gastrointestinal perforation	Dry mouth Flatulence Gastrointestinal perforation	Pancreatitis[g] Colitis Flatulence Gastrointestinal perforation
Uncommon	Pancreatitis[g] Colitis	Pancreatitis[g] Anal fistula Colitis	Anal fistula

System Organ Class (MedDRA terminology)	**Lenvatinib monotherapy**	**Combination with everolimus**	**Combination with pembrolizumab**
Hepatobiliary disorders			
Very common	Increased blood bilirubin*, ‡ Hypoalbuminaemia*, ‡ Increased alanine aminotransferase*, ‡ Increased aspartate aminotransferase*, ‡ Increased blood alkaline phosphatase‡ Increased gamma-glutamyltransferase‡	Hypoalbuminaemia*, ‡ Increased alanine aminotransferase‡ Increased aspartate aminotransferase‡ Increased blood alkaline phosphatase‡	Increased blood bilirubin ‡ Hypoalbuminaemia‡ Increased alanine aminotransferase‡ Increased aspartate aminotransferase‡ Increased blood alkaline phosphatase‡
Common	Hepatic failure[h], † Hepatic encephalopathy[i], † Cholecystitis Abnormal hepatic function	Cholecystitis Abnormal hepatic function Increased gamma-glutamyltransferase Increased blood bilirubin*, ‡	Cholecystitis Abnormal hepatic function Increased gamma-glutamyltransferase
Uncommon	Hepatocellular damage/hepatitis[j]	Hepatic failure[h], † Hepatic encephalopathy[i]	Hepatic failure[h], † Hepatic encephalopathy[i] Hepatocellular damage/hepatitis[j]
Skin and subcutaneous tissue disorders			
Very common	Palmar-plantar erythrodysaesthesia syndrome Rash Alopecia	Palmar-plantar erythrodysaesthesia syndrome Rash	Palmar-plantar erythrodysaesthesia syndrome Rash
Common	Hyperkeratosis	Alopecia	Hyperkeratosis Alopecia
Uncommon		Hyperkeratosis	
Musculoskeletal and connective tissue disorders			
Very common	Back pain Arthralgia Myalgia Pain in extremity Musculoskeletal pain	Back pain Arthralgia	Back pain Arthralgia Myalgia Pain in extremity Musculoskeletal pain
Common		Myalgia Pain in extremity Musculoskeletal pain	
Uncommon	Osteonecrosis of the jaw	Osteonecrosis of the jaw	
Renal and urinary disorders			
Very common	Proteinuria* Increased blood creatinine‡	Proteinuria* Increased blood creatinine‡	Proteinuria* Increased blood creatinine‡
Common	Renal failure[k], *, † Renal impairment* Increased blood urea	Renal failure[k], *, † Renal impairment* Increased blood urea	Renal failure[k], * Increased blood urea
Uncommon	Nephrotic syndrome		Nephrotic syndrome Renal impairment*

System Organ Class (MedDRA terminology)	Lenvatinib monotherapy	Combination with everolimus	Combination with pembrolizumab
General disorders and administration site conditions			
Very common	Fatigue Asthenia Oedema peripheral	Fatigue Asthenia Oedema peripheral	Fatigue Asthenia Oedema peripheral
Common	Malaise	Malaise	Malaise
Uncommon	Impaired healing	Impaired healing Non-gastrointestinal fistula[l]	Impaired healing Non-gastrointestinal fistula[l]
Not known	Non-gastrointestinal fistula[l]		

§: Adverse reaction frequencies presented in Table 4 may not be fully attributable to lenvatinib alone but may contain contributions from the underlying disease or from other medicinal products used in a combination.
*: See section 4.8 Description of selected adverse reactions for further characterisation.
†: Includes cases with a fatal outcome.
‡: Frequency based on laboratory data.
The following terms have been combined:
a: Myocardial infarction includes myocardial infarction and acute myocardial infarction.
b: Includes all haemorrhage terms:
Haemorrhage terms that occurred in 5 or more patients with RCC in lenvatinib plus pembrolizumab were: epistaxis, haematuria, contusion, gingival bleeding, rectal haemorrhage, haemoptysis, ecchymosis, and haematochezia.
c: Hypertension includes: hypertension, hypertensive crisis, increased blood pressure diastolic, orthostatic hypertension and increased blood pressure.
d: Gastrointestinal and abdominal pain includes: abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort, and gastrointestinal pain.
e: Oral inflammation includes: aphthous stomatitis, aphthous ulcer, gingival erosion, gingival ulceration, oral mucosal blistering, stomatitis, glossitis, mouth ulceration, and mucosal inflammation.
f: Oral pain includes: oral pain, glossodynia, gingival pain, oropharyngeal discomfort, oropharyngeal pain and tongue discomfort.
g: Pancreatitis includes: pancreatitis and acute pancreatitis.
h: Hepatic failure includes: hepatic failure, acute hepatic failure and chronic hepatic failure.
i: Hepatic encephalopathy includes: hepatic encephalopathy, coma hepatic, metabolic encephalopathy and encephalopathy.
j: Hepatocellular damage and hepatitis includes: drug-induced liver injury, hepatic steatosis, and cholestatic liver injury.
k: Renal failure includes: acute prerenal failure, renal failure, renal failure acute, acute kidney injury, and renal tubular necrosis.
l: Non-gastrointestinal fistula includes cases of fistula occurring outside of the stomach and intestines such as tracheal, tracheo-oesophageal, oesophageal, cutaneous fistula and female genital tract fistula.

Description of selected adverse reactions

Hypertension (see section 4.4)

In CLEAR (see section 5.1), hypertension was reported in 56.3% of patients in the lenvatinib plus pembrolizumab-treated group and 42.6% of patients in the sunitinib-treated group. The exposure-adjusted frequency of hypertension was 0.65 episodes per patient year in the lenvatinib plus pembrolizumab-treated group and 0.73 episodes per patient year in the sunitinib-treated group. The median time to onset in lenvatinib plus pembrolizumab-treated patients was 0.7 months. Reactions of Grade 3 or higher occurred in 28.7% of lenvatinib plus pembrolizumab-treated group compared with 19.4% of the sunitinib-treated group. 16.8% of patients with hypertension had dose modifications of lenvatinib (9.1% dose interruption and 11.9% dose reduction). In 0.9% of patients, hypertension led to permanent treatment discontinuation of lenvatinib.

In the pooled RCC population treated with lenvatinib and everolimus, hypertension was reported in 42.5% of patients (the incidence of Grade 3 or Grade 4 hypertension was 19.7%). In patients where data on individual drug modifications were collected, 9.8% of patients with hypertension had dose modifications of lenvatinib (5.3% dose reduction and 6.2% dose interruption) and led to permanent treatment discontinuation in 0.9% of patients. The median time to onset of hypertension events in lenvatinib plus everolimus treated patients was 0.5 months.

Proteinuria (see section 4.4)

In the pooled RCC population treated with lenvatinib and everolimus, proteinuria was reported in 34.8% of patients (9.0% were Grade ≥3). In patients where data on individual drug modifications were collected, 15.1% of patients with proteinuria had dose modifications of lenvatinib (9.6% reduction and 9.8% interruption) and led to permanent treatment discontinuation in 2.1% of patients. The median time to onset of proteinuria events in lenvatinib plus everolimus treated patients was 1.4 months.

Renal failure and impairment (see section 4.4)

In the pooled RCC population treated with lenvatinib and everolimus, 1.3% of patients developed renal failure (0.6% were Grade ≥3) and 5.3% developed acute kidney injury (2.7% were Grade ≥3). Renal events were reported in 17.2% of patients (4.3% were Grade ≥3). In patients where data on individual drug modifications were collected, 5.5% of patients with renal events had dose modifications of lenvatinib (2.3% reduction and 4.0% interruption) and led to permanent treatment discontinuation in 1.9% of patients. The median time to onset of renal events in lenvatinib plus everolimus treated patients was 3.5 months.

Cardiac dysfunction (see section 4.4)

In the pooled RCC population treated with lenvatinib and everolimus, cardiac dysfunction events were reported in 3.5% of patients (1.8% were Grade ≥3). In patients where data on individual drug modifications were collected, 0.9% of patients with cardiac dysfunction events had dose modifications of lenvatinib (0.4% reduction and 0.8% interruption) and led to permanent treatment discontinuation in 0.6% of patients. The median time to onset of cardiac dysfunction events in lenvatinib plus everolimus treated patients was 3.6 months.

Posterior reversible encephalopathy syndrome (PRES) / Reversible posterior leucoencephalopathy syndrome (RPLS) (see section 4.4)

In the pooled RCC population treated with lenvatinib and everolimus, there was 1 event of PRES reported (Grade 2), occurring after 1.3 months of treatment for which no dose modifications or discontinuation were required.

Hepatotoxicity (see section 4.4)

In CLEAR (see section 5.1), the most commonly reported liver-related adverse reactions in the lenvatinib plus pembrolizumab-treated group were elevations of liver enzyme levels, including increases in alanine aminotransferase (11.9%), aspartate aminotransferase (11.1%) and blood bilirubin (4.0%). Similar events occurred in the sunitinib-treated group at rates of 10.3%, 10.9% and 4.4% respectively. The median time to onset of liver events was 3.0 months (any grade) in the lenvatinib plus pembrolizumab-treated group and 0.7 months in the sunitinib-treated group. The exposure-adjusted frequency of hepatoxicity events was 0.39 episodes per patient year in the lenvatinib plus pembrolizumab-treated group and 0.46 episodes per patient year in the sunitinib-treated group. Grade 3 liver-related reactions occurred in 9.9% of lenvatinib plus pembrolizumab-treated patients and 5.3% of sunitinib-treated patients. Liver-related reactions led to dose interruptions and reductions of lenvatinib in 8.5% and 4.3% of patients, respectively, and to permanent discontinuation of lenvatinib in 1.1% of patients.

In the pooled RCC population treated with lenvatinib and everolimus, the most commonly reported liver-related adverse reactions were elevations of liver enzyme levels, including increases in alanine aminotransferase (11.9%), aspartate aminotransferase (11.4%) and gamma-glutamyltransferase increased (2.7%). Grade 3 liver related reactions occurred in 6.1% of lenvatinib plus everolimus treated patients. In patients where data on individual drug modifications were collected, 6.0% of patients with hepatotoxicity events had dose modifications of lenvatinib (2.8% reduction and 4.2% interruption) and led to permanent treatment discontinuation in 0.9% of patients. The median time to onset of liver-related reactions in lenvatinib plus everolimus treated patients was 1.8 months.

Arterial thromboembolisms (see section 4.4)

In CLEAR (see section 5.1), 5.4% of patients in the lenvatinib plus pembrolizumab-treated group reported arterial thromboembolic events (of which 3.7% were Grade ≥ 3) compared with 2.1% of patients in the sunitinib-treated group (of which 0.6% were Grade ≥ 3). No events were fatal. The exposure-adjusted frequency of arterial thromboembolic event episodes was 0.04 episodes per patient year in the lenvatinib plus pembrolizumab-treated group and 0.02 episodes per patient year in the sunitinib-treated group. The most commonly reported arterial thromboembolic event in the lenvatinib plus pembrolizumab-treated group was myocardial infarction (3.4%). One event of myocardial infarction (0.3%) occurred in the sunitinib-treated group. The median time to onset of arterial thromboembolic events was 10.4 months in the lenvatinib plus pembrolizumab-treated group.

In the pooled RCC population treated with lenvatinib and everolimus, arterial thromboembolic events were reported in 2.7% of patients (2.2% were Grade ≥3). In patients where data on individual drug modifications were collected, 0.6% of patients with arterial thromboembolic events had dose modifications of lenvatinib (0.6% interruption) and led to permanent treatment discontinuation in 1.5% of patients. The most commonly reported arterial thromboembolic event in the lenvatinib plus everolimus-treated group was myocardial infarction (1.3%). The median time to onset of arterial thromboembolic events in lenvatinib plus everolimus treated patients was 6.8 months.

Haemorrhage (see section 4.4)

In the pooled RCC population treated with lenvatinib and everolimus, haemorrhage events were reported in 28.6% of patients (3.2% were Grade ≥3). In patients where data on individual drug modifications were collected, 4.9% of patients with haemorrhage events had dose modifications of lenvatinib (4.2% interruption and 0.8% reduction) and led to permanent treatment discontinuation in 0.6% of patients. The most commonly reported haemorrhage events in the lenvatinib plus everolimus-treated group were epistaxis (19.4%) and haematuria (4.2%). The median time to onset of haemorrhage events in lenvatinib plus everolimus treated patients was 1.9 months.

Hypocalcaemia (see section 4.4, QT interval prolongation)

In the pooled RCC population treated with lenvatinib and everolimus, hypocalcaemia was reported in 4.8% of patients (1.1% were Grade ≥3). In patients where data on individual drug modifications were collected, 0.8% of patients with hypocalcaemia had dose modifications of lenvatinib (0.6% dose interruption and 0.4% dose reduction) and led to permanent treatment discontinuation in no patients. The median time to onset of hypocalcaemia events in lenvatinib plus everolimus-treated patients was 2.9 months.

Gastrointestinal perforation and fistula formation (see section 4.4)

In the pooled RCC population treated with lenvatinib and everolimus, GI perforation events were reported in 3.7% of patients (2.9% were Grade ≥3). In patients where data on individual drug modifications were collected, 2.1% of patients with GI perforations had dose modifications of lenvatinib (1.5% interruption and 0.6% reduction) and led to permanent treatment discontinuation in 1.1% of patients. The median time to onset of GI perforation events in lenvatinib plus everolimus-treated patients was 3.6 months.

In the pooled RCC population treated with lenvatinib and everolimus, fistula formation events were reported in 1.0% of patients (0.5% were Grade ≥3). In patients where data on individual drug modifications were collected, 0.8% of patients with GI perforations had dose modifications of lenvatinib (0.8% interruption) and led to permanent treatment discontinuation in 0.4% of patients. The median time to onset of fistula formation events in lenvatinib plus everolimus-treated patients was 3.7 months.

Non-Gastrointestinal fistulae (see section 4.4)
Lenvatinib use has been associated with cases of fistulae including reactions resulting in death. Reports of fistulae that involve areas of the body other than stomach or intestines were observed across various indications. Reactions were reported at various time points during treatment ranging from two weeks to greater than 1 year from initiation of lenvatinib, with a median latency of about 3 months.

QT interval prolongation (see section 4.4)

In the pooled RCC population treated with lenvatinib and everolimus, QTcF interval increases greater than 60 ms were reported in 9.8% of patients in the lenvatinib plus everolimus-treated group. The incidence of QTc interval greater than 500 ms was 3.3% in the lenvatinib plus everolimus-treated group. The median time to onset of QT prolongation events in lenvatinib plus everolimus-treated patients was 3.0 months.

Blood thyroid stimulating hormone increased/hypothyroidism (see section 4.4)

In CLEAR (see section 5.1), hypothyroidism occurred in 47.2% of patients in the lenvatinib plus pembrolizumab-treated group and 26.5% of patients in the sunitinib-treated group. The exposure-adjusted frequency of hypothyroidism was 0.39 episodes per patient year in the lenvatinib plus pembrolizumab-treated group and 0.33 episodes per patient year in the sunitinib-treated group. In general, the majority of hypothyroidism events in the lenvatinib plus pembrolizumab-treated group were of Grade 1 or 2. Grade 3 hypothyroidism was reported in 1.4% of patients in the lenvatinib plus pembrolizumab-treated group versus none in the sunitinib-treated group. At baseline, 90.0% of patients in the lenvatinib plus pembrolizumab-treated group and 93.1% of patients in the sunitinib-treated group had baseline TSH levels ≤ upper limit of normal. Elevations of TSH > upper limit of normal were observed post baseline in 85.0% of lenvatinib plus pembrolizumab-treated patients versus 65.6% of sunitinib-treated patients. In lenvatinib plus pembrolizumab-treated patients, hypothyroidism events resulted in dose modification of lenvatinib (reduction or interruption) in 2.6% patients and discontinuation of lenvatinib in 1 patient.

In the pooled RCC population treated with lenvatinib and everolimus, hypothyroidism occurred in 24.1% of patients. In general, the majority of hypothyroidism events were of Grade 1 or 2. Grade 3 hypothyroidism was reported in 0.3% of patients in the lenvatinib plus everolimus-treated patients. The median time to onset of hypothyroidism events in lenvatinib plus everolimus-treated patients was 2.7 months. At baseline, 83.0% of patients in the lenvatinib plus everolimus-treated group had TSH levels ≤ upper limit of normal. Elevations of TSH > upper limit of normal were observed post-baseline in 71.3% of lenvatinib plus everolimus-treated patients. In patients where data on individual drug modifications were collected, hypothyroidism events resulted in dose modification of lenvatinib (0.4% dose reduction or 0.9% dose interruption) in 1.3% of patients. No discontinuations were reported.

Diarrhoea (see section 4.4)

In the pooled RCC population treated with lenvatinib and everolimus, diarrhoea was reported in 69.0% of patients (13.8% were Grade ≥3). In patients where data on individual drug modifications were collected, 30.4% of patients had dose modifications of lenvatinib (17.7% interruptions and 19.6% reductions) and led to permanent treatment discontinuation in 0.6% of patients.

Paediatric population

In the paediatric Studies 216 and 231 (see section 5.1), the overall safety profile of lenvatinib as a single agent or in combination with everolimus was consistent with that observed in adults treated with lenvatinib.

In Study 216, pneumothorax was reported in 3 patients (4.7%) with Ewing sarcoma, rhabdomyosarcoma (RMS) and Wilms tumour; all 3 patients had lung metastases at baseline. In Study 231, pneumothorax was reported in 8 patients (6.3%) with spindle cell sarcoma, undifferentiated

sarcoma, RMS, malignant peripheral nerve sheath tumour, synovial sarcoma, spindle cell carcinoma, and malignant fibromyxoid ossifying tumour; all 8 patients had lung metastases or primary disease in the chest wall or pleural cavity at baseline. For Study 216, no patient discontinued study treatment due to pneumothorax; in Study 231, one patient discontinued study treatment due to pneumothorax (for additional paediatric information see also Lenvima SmPC section 4.8).

In Phase 1 (combination dose-finding cohort) of Study 216, the most frequently (≥40%) reported adverse drug reactions were hypertension, hypothyroidism, hypertriglyceridemia, abdominal pain, and diarrhoea; and in Phase 2 (combination expansion cohort), the most frequently reported (≥35%) adverse drug reactions were hypertriglyceridemia, proteinuria, diarrhoea, lymphocyte count decreased, white blood cell count decreased, blood cholesterol increased, fatigue, and platelet count decreased.

In Study 231, the most frequently reported (≥15%) adverse drug reactions were hypothyroidism, hypertension, proteinuria, decreased appetite, diarrhoea, and platelet count decreased.

Other special populations

Elderly

In CLEAR, elderly patients (≥75 years) had a higher (≥ 10% difference) incidence of proteinuria than younger patients (<65 years).

In the pooled RCC population treated with lenvatinib and everolimus, elderly patients (≥75 years) had a higher (≥10% difference) incidence of platelet count decreased, weight decreased, proteinuria and hypertension than younger patients (<65 years).

Gender

In CLEAR, males had a higher (≥ 10% difference) incidence than females of diarrhoea.

In the pooled RCC population treated with lenvatinib and everolimus, females had a higher (≥10% difference) incidence than males of nausea, vomiting, asthenia and hypertension.

Ethnic origin

In CLEAR, Asian patients had a higher (≥ 10% difference) incidence than Caucasian patients of palmar-plantar erythrodysaesthesia syndrome, proteinuria and hypothyroidism (including blood thyroid hormone increased) while Caucasian patients had a higher incidence of fatigue, nausea, arthralgia, vomiting, and asthenia.
In the pooled RCC population treated with lenvatinib and everolimus, Asian patients had a higher (≥10% difference) incidence than Caucasian patients of hypothyroidism, stomatitis, platelet count decreased, proteinuria, dysphonia, PPE and hypertension while Caucasian patients had a higher incidence of nausea, asthenia, fatigue and hypercholesterolaemia.

Baseline hypertension

In CLEAR, patients with baseline hypertension had a higher incidence of proteinuria than patients without baseline hypertension.

Baseline diabetes

In the pooled RCC population treated with lenvatinib and everolimus, patients with baseline diabetes had a higher incidence (≥10% difference) of proteinuria than those without baseline diabetes.

Hepatic impairment

There are limited data on patients with hepatic impairment in RCC.

Renal impairment

In RCC patients treated with lenvatinib and everolimus, patients with baseline renal impairment had higher incidence of thrombocytopenia or platelet count decreased compared with patients with normal renal function.

Patients with body weight <60 kg

In RCC patients treated with lenvatinib and everolimus, those with low body weight (<60 kg) had a higher incidence (≥10% difference) of platelet count decreased and hypertension.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The highest doses of lenvatinib studied clinically were 32 mg and 40 mg per day. Accidental medication errors resulting in single doses of 40 to 48 mg have also occurred in clinical trials. The most frequently observed adverse drug reactions at these doses were hypertension, nausea, diarrhoea, fatigue, stomatitis, proteinuria, headache, and aggravation of PPE. There have also been reports of overdose with lenvatinib involving single administrations of 6 to 10 times the recommended daily dose. These cases were associated with adverse reactions consistent with the known safety profile of lenvatinib (i.e., renal and cardiac failure), or were without adverse reactions.

There is no specific antidote for overdose with lenvatinib. In case of suspected overdose, lenvatinib should be withheld and appropriate supportive care given as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01EX08

Mechanism of action

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, the platelet derived growth factor (PDGF) receptor PDGFRα, KIT, and RET. In syngeneic mouse tumour models, lenvatinib decreased tumour-associated macrophages, increased activated cytotoxic T cells, and demonstrated greater antitumour activity in combination with an anti-PD-1 monoclonal antibody compared to either treatment alone.
The combination of lenvatinib and everolimus showed increased antiangiogenic and antitumour activity as demonstrated by decreased human endothelial cell proliferation, tube formation, and VEGF signalling in vitro and tumour volume in mouse xenograft models of human renal cell cancer greater than each substance alone.

Although not studied directly with lenvatinib, the mechanism of action (MOA) for hypertension is postulated to be mediated by the inhibition of VEGFR2 in vascular endothelial cells. Similarly, although not studied directly, the MOA for proteinuria is postulated to be mediated by downregulation of VEGFR1 and VEGFR2 in the podocytes of the glomerulus.

The mechanism of action for hypothyroidism is not fully elucidated.

The mechanism of action for the worsening of hypercholesterolaemia with the combination of lenvatinib and everolimus has not been studied directly and is not fully elucidated.

Although not studied directly, the MOA for the worsening of diarrhoea with the combination of lenvatinib and everolimus is postulated to be mediated by the impairment of intestinal function related to the MOAs for the individual agents – VEGF/VEGFR and c-KIT inhibition by lenvatinib coupled with mTOR/NHE3 inhibition by everolimus.

Clinical efficacy and safety

First-line treatment of patients with RCC (in combination with pembrolizumab)

The efficacy of lenvatinib in combination with pembrolizumab was investigated in Study 307 (CLEAR), a multicentre, open-label, randomized trial that enrolled 1069 patients with advanced RCC with clear cell component including other histological features such as sarcomatoid and papillary in the first-line setting. Patients were enrolled regardless of PD-L1 tumour expression status. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by geographic region. (North-America and Western Europe versus "Rest of the World") and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups (favourable, intermediate and poor risk).

Patients were randomized to lenvatinib 20 mg orally once daily in combination with pembrolizumab 200 mg intravenously every 3 weeks (n=355), or lenvatinib 18 mg orally once daily in combination with everolimus 5 mg orally once daily (n=357), or sunitinib 50 mg orally once daily for 4 weeks then off treatment for 2 weeks (n=357). All patients on the lenvatinib plus pembrolizumab arm were started on lenvatinib 20 mg orally once daily. The median time to first dose reduction for lenvatinib was 1.9 months. The median average daily dose for lenvatinib was 14 mg. Treatment continued until unacceptable toxicity or disease progression as determined by the investigator and confirmed by independent radiologic review committee (IRC) using Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1). Administration of lenvatinib with pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. Pembrolizumab was continued for a maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months. Assessment of tumour status was performed at baseline and then every 8 weeks.

The study population (355 patients in the lenvatinib with pembrolizumab arm and 357 in the sunitinib arm) characteristics were: median age of 62 years (range: 29 to 88 years); 41% age 65 or older, 74% male; 75% White, 21% Asian, 1% Black, and 2% other races; 17% and 83% of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively; patient distribution by IMDC (International Metastatic RCC Database Consortium) risk categories was 33% favourable, 56% intermediate and 10% poor, and MSKCC prognostic groups was 27% favourable, 64% intermediate and 9% poor. Metastatic disease was present in 99% of the patients and locally advanced disease was present in 1%. Common sites of metastases in patients were lung (69%), lymph node (46%), and bone (26%).

The primary efficacy outcome measure was progression free survival (PFS) based on RECIST 1.1 per IRC. Key secondary efficacy outcome measures included overall survival (OS) and objective response rate (ORR). Lenvatinib in combination with pembrolizumab demonstrated statistically significant improvements in PFS, OS and ORR compared with sunitinib at the prespecified interim analysis (final analysis for PFS). The median PFS for lenvatinib in combination with pembrolizumab was 23.9 months (95% CI: 20.8, 27.7) compared with 9.2 months (95% CI: 6.0, 11.0) for sunitinib, with HR 0.39 (95% CI: 0.32, 0.49; *P* value <0.0001). For OS, HR was 0.66 (95% CI: 0.49, 0.88; *P* value 0.0049) with the median OS follow-up time of 26.5 months and the median duration of treatment for lenvatinib plus pembrolizumab of 17.0 months. The ORR for lenvatinib in combination with pembrolizumab was 71% (95% CI: 66, 76) vs 36% (95% CI: 31, 41) *P* value <0.0001 for sunitinib. Efficacy results for PFS, OS and ORR at the protocol-specified final analysis (median follow-up time of 49.4 months) are summarised in Table 5, Figure 1 and Figure 2. PFS results were consistent across pre-specified subgroups, MSKCC prognostic groups and PD-L1 tumour expression status. Efficacy results by MSKCC prognostic group are summarised in Table 6.

The final OS analysis was not adjusted to account for subsequent therapies, with 195/357 (54.6%) patients in the sunitinib arm and 56/355 (15.8%) patients in the lenvatinib plus pembrolizumab arm receiving subsequent anti-PD-1/PD-L1 therapy.

Table 5 Efficacy Results in Renal Cell Carcinoma Per IRC in CLEAR

	Lenvatinib 20 mg with Pembrolizumab 200mg N=355	**Sunitinib 50mg N=357**
Progression-Free Survival (PFS)*		
Number of events, n (%)	207 (58%)	214 (60%)
Median PFS in months (95% CI)[a]	23.9 (20.8, 27.7)	9.2 (6.0, 11.0)
Hazard Ratio (95% CI)[b, c]	0.47 (0.38, 0.57)	
P value[c]	<0.0001	
Overall Survival (OS)		
Number of deaths, n (%)	149 (42%)	159 (45%)
Median OS in months (95% CI)[a]	53.7 (48.7, NE)	54.3 (40.9, NE)
Hazard Ratio (95% CI)[b, c]	0.79 (0.63, 0.99)	
P value[c]	0.0424	
Objective Response Rate (Confirmed)		
Objective response rate, n (%)	253 (71.3%)	131 (36.7%)
(95% CI)	(66.6, 76.0)	(31.7, 41.7)
Number of complete responses (CR), n (%)	65 (18.3%)	17 (4.8%)
Number of partial responses (PR), n (%)	188 (53.0%)	114 (32%)
P value[d]	<0.0001	
Duration of Response[a]		
Median in months (range)	26.7 (1.64+, 55.92+)	14.7 (1.64+, 54.08+)

Tumour assessments were based on RECIST 1.1; only confirmed responses are included for ORR.
Data cutoff date (DCO) = 31 July 2022
CI = confidence interval; NE= Not estimable

* The primary analysis of PFS included censoring for new anti-cancer treatment. Results for PFS with and without censoring for new anti-cancer treatment were consistent.

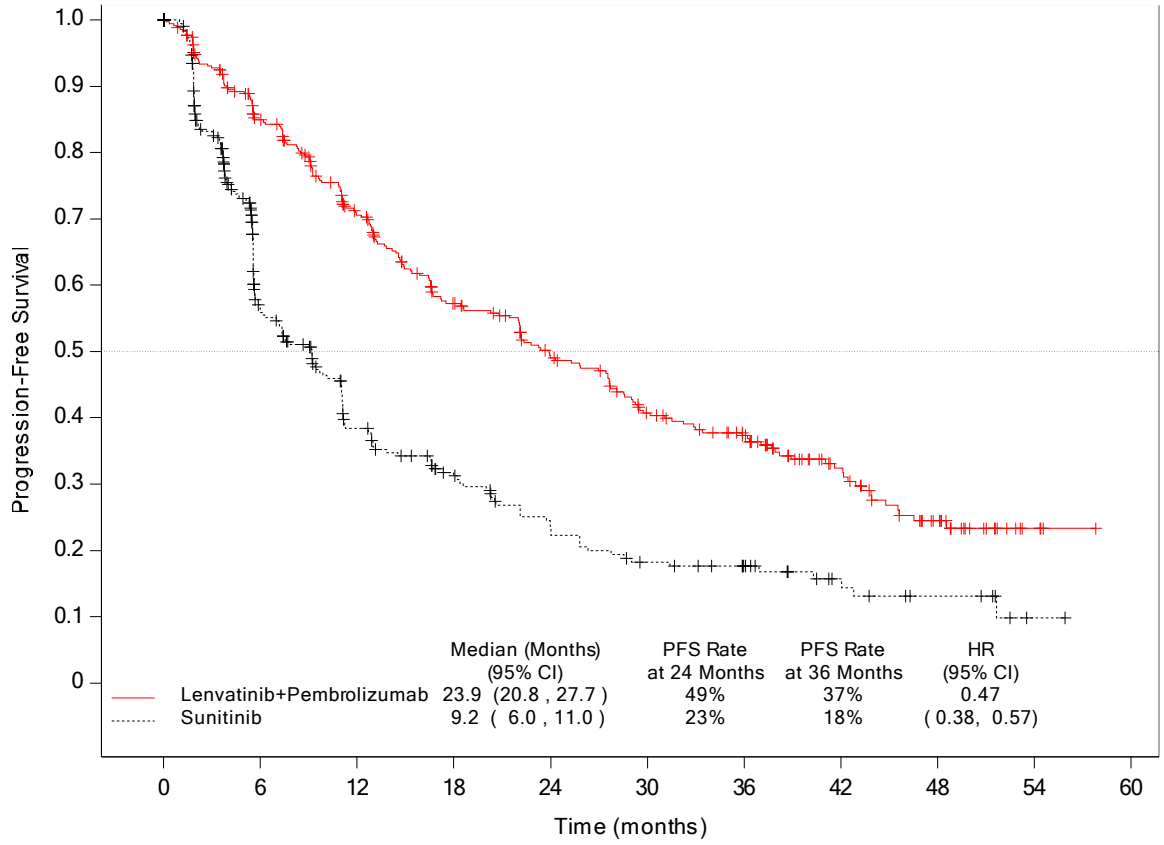
a Quartiles are estimated by Kaplan-Meier method.

b Hazard ratio is based on a Cox Proportional Hazards Model including treatment group as a factor; Efron method is used for ties.

c Stratified by geographic region (Region 1: Western Europe and North America, Region 2: Rest of the World) and MSKCC prognostic groups (favourable, intermediate and poor risk) in IxRS. Nominal two-sided *P* value based on stratified log-rank test.

d Nominal two-sided *P* value based on the stratified Cochran-Mantel-Haenszel (CMH) test. At the earlier pre-specified final analysis of ORR (median follow-up time of 17.3 months), statistically significant superiority was achieved for ORR comparing lenvatinib plus pembrolizumab with sunitinib, (odds ratio: 3.84 (95% CI: 2.81, 5.26), *P* value <0.0001).

Figure 1 Kaplan-Meier Curves for Progression-Free Survival in CLEAR*

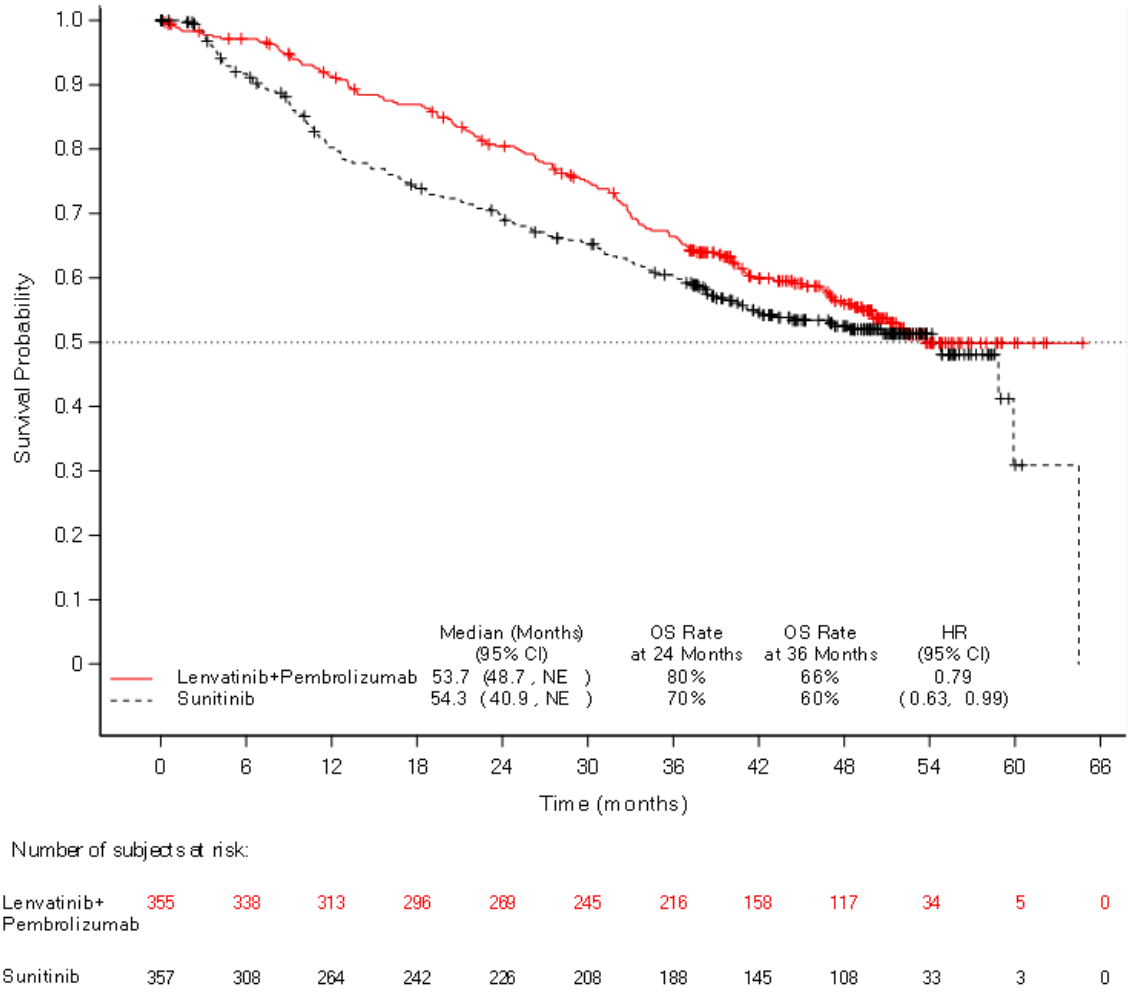


Number of subjects at risk:

Lenvatinib+ Pembrolizumab	355	276	213	161	128	99	81	49	25	4	0
Sunitinib	357	145	85	59	41	30	23	12	7	1	0

DCO: 31 July 2022
*Based on updated PFS analysis conducted at the time of the protocol-specified final OS analysis.

Figure 2 Kaplan-Meier Curves for Overall Survival in CLEAR*



NE = Not estimable.
DCO: 31 July 2022
*Based on the protocol-specified final OS analysis

The CLEAR study was not powered to evaluate efficacy of individual subgroups. Table 6 summarises the efficacy measures by MSKCC prognostic group based on the final OS analysis at a median follow-up of 49.4 months.

Table 6 Efficacy Results in CLEAR by MSKCC Prognostic Group

	Lenvatinib + Pembrolizumab (N=355)		Sunitinib (N=357)		Lenvatinib + Pembrolizumab vs. Sunitinib
	Number of Patients	Number of Events	Number of Patients	Number of Events	
Progression-Free Survival (PFS) by IRC[a]					**PFS HR (95% CI)**
Favourable	96	56	97	65	0.46 (0.32, 0.67)
Intermediate	227	129	228	130	0.51 (0.40, 0.65)
Poor	32	22	32	19	0.18 (0.08, 0.42)
Overall Survival (OS)[a]					**OS HR (95% CI)**
Favourable	96	27	97	31	0.89 (0.53, 1.50)
Intermediate	227	104	228	108	0.81 (0.62, 1.06)
Poor	32	18	32	20	0.59 (0.31, 1.12)

[a] Median follow up 49.4 months (DCO - 31 July 2022)

Open-label, single arm Phase 2 study

Additional data are available from the open-label, single-arm, Phase 2 study KEYNOTE-B61 of lenvatinib (20 mg OD) in combination with pembrolizumab (400 mg every 6 weeks) for the first-line treatment of patients with advanced or metastatic RCC with non-clear cell histology (n=158), including 59% papillary, 18% chromophobe, 4% translocation, 1% medullary, 13% unclassified, and 6% other. The ORR was 50.6% (95% CI (42.6, 58.7)), and the median duration of response was 19.5 months (95% CI 15.3, NR).

Second-line treatment of patients with RCC (in combination with everolimus)

Study 205, a multicentre, randomised, open-label, trial was conducted to determine the safety and efficacy of lenvatinib administered alone or in combination with everolimus in patients with unresectable advanced or metastatic RCC. The study consisted of a Phase 1b dose finding and a Phase 2 portion. The Phase 1b portion included 11 patients who received the combination of 18 mg of lenvatinib plus 5 mg of everolimus. The Phase 2 portion enrolled a total of 153 patients with unresectable advanced or metastatic RCC following 1 prior VEGF-targeted treatment. A total of 62 patients received the combination of lenvatinib and everolimus at the recommended dose. Patients were required, among others, to have histological confirmation of predominant clear cell RCC, radiographic evidence of disease progression according to RECIST 1.1, one prior VEGF-targeted therapy and Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1.

Patients were randomly allocated to one of 3 arms: 18 mg of lenvatinib plus 5 mg of everolimus, 24 mg of lenvatinib or 10 mg of everolimus using a 1:1:1 ratio. Patients were stratified by haemoglobin level (≤13 g/dL vs. >13 g/dL for males and ≤11.5 g/dL vs >11.5 g/dL for females) and corrected serum calcium (≥10 mg/dL vs. <10 mg/dL). The median of average daily dose in the combination arm per patient was 13.5 mg of lenvatinib (75.0% of the intended dose of 18 mg) and 4.7 mg of everolimus (93.6% of the intended dose of 5 mg). The final dose level in the combination arm was 18 mg for 29% of patients, 14 mg for 31% of patients, 10 mg for 23% of patients, 8 mg for 16% of patients and 4 mg for 2% of patients.

Of the 153 patients randomly allocated, 73% were male, the median age was 61 years, 37% were 65 years or older, 7% were 75 years or older, and 97% were Caucasian. Metastases were present in 95% of the patients and unresectable advanced disease was present in 5%. All patients had a baseline ECOG PS of either 0 (55%) or 1 (45%) with similar distribution across the 3 treatment arms. Memorial Sloan Kettering Cancer Centre (MSKCC) poor risk was observed in 39% of patients in the lenvatinib plus everolimus arm, 44% in the lenvatinib arm and 38% in the everolimus arm. International mRCC Database Consortium (IMDC) poor risk was observed in 20% of patients in the lenvatinib plus everolimus arm, 23% in the lenvatinib arm, and 24% in the everolimus arm. The

median time from diagnosis to first dose was 32 months in the lenvatinib plus everolimus-treatment arm, 33 months in the lenvatinib arm and 26 months in the everolimus arm. All patients had been treated with 1 prior VEGF-inhibitor; 65% with sunitinib, 23% with pazopanib, 4% with tivozanib, 3% with bevacizumab, and 2% each with sorafenib or axitinib.

The primary efficacy outcome measure, based on investigator assessed tumour response, was PFS of the lenvatinib plus everolimus arm vs the everolimus arm and of the lenvatinib arm vs the everolimus arm. Other efficacy outcome measures included OS and investigator-assessed ORR. Tumour assessments were evaluated according to RECIST 1.1.

The lenvatinib plus everolimus arm showed a statistically significant and clinically meaningful improvement in PFS compared with the everolimus arm (see Table 7 and Figure 3). Based on the results of a post-hoc exploratory analysis in a limited number of patients per subgroup, the positive effect on PFS was seen regardless of which prior VEGF-targeted therapy was used: sunitinib (Hazard ratio [HR] = 0.356 [95% CI: 0.188, 0.674] or other therapies (HR = 0.350 [95% CI: 0.148, 0.828]). The lenvatinib arm also showed an improvement in PFS compared with the everolimus arm. Overall survival was longer in the lenvatinib plus everolimus arm (see Table 7 and Figure 4). The study was not powered for the OS analysis.

The treatment effect of the combination on PFS and ORR was also supported by a post-hoc retrospective independent blinded review of scans. The lenvatinib plus everolimus arm showed a statistically significant and clinically meaningful improvement in PFS compared with the everolimus arm. Results for ORR were consistent with that of the investigators' assessments, 35.3% in the lenvatinib plus everolimus arm, with one complete response and 17 partial responses; no patient had an objective response in the everolimus arm ($P < 0.0001$) in favour of the lenvatinib plus everolimus arm.

Table 7 Efficacy results following one prior VEGF targeted therapy in RCC Study 205

	lenvatinib 18 mg + everolimus 5 mg (N=51)	**lenvatinib 24 mg (N=52)**	**everolimus 10 mg (N=50)**
Progression-free survival (PFS)[a] by investigator assessment			
Median PFS in months (95% CI)	14.6 (5.9, 20.1)	7.4 (5.6, 10.2)	5.5 (3.5, 7.1)
Hazard Ratio (95% CI)[b] lenvatinib + everolimus vs everolimus	0.40 (0.24, 0.67)	-	-
P value lenvatinib + everolimus vs everolimus	0.0005	-	-
Progression-free survival (PFS)[a] by post-hoc retrospective independent review			
Median PFS in months (95% CI)	12.8 (7.4, 17.5)	9.0 (5.6, 10.2)	5.6 (3.6, 9.3)
Hazard Ratio (95% CI)[b] lenvatinib + everolimus vs everolimus	0.45 (0.26, 0.79)	-	-
P value lenvatinib + everolimus vs everolimus	0.003	-	-
Overall Survival[c]			
Number of deaths, n (%)	32 (63)	34 (65)	37 (74)
Median OS in months (95% CI)	25.5 (16.4, 32.1)	19.1 (13.6, 26.2)	15.4 (11.8, 20.6)
Hazard Ratio (95% CI)[b] lenvatinib + everolimus vs everolimus	0.59 (0.36, 0.97)	-	-

	lenvatinib 18 mg + everolimus 5 mg (N=51)	lenvatinib 24 mg (N=52)	everolimus 10 mg (N=50)
Objective Response Rate n (%) by investigator assessment			
Complete responses	1 (2)	0	0
Partial responses	21 (41)	14 (27)	3 (6)
Objective Response Rate	22 (43)	14 (27)	3 (6)
Stable disease	21 (41)	27 (52)	31 (62)
Duration of response, months, median (95% CI)	13.0 (3.7, NE)	7.5 (3.8, NE)	8.5 (7.5, 9.4)

Tumour assessment was based on RECIST 1.1 criteria. Data cut-off date = 13 Jun 2014
Percentages are based on the total number of patients in the Full Analysis Set within relevant treatment group.
CI = confidence interval, NE = not estimable
[a]Point estimates are based on Kaplan-Meier method and 95% CIs are based on the Greenwood formula using log-log transformation.
[b]Stratified hazard ratio is based on a stratified Cox regression model including treatment as a covariate factor and haemoglobin and corrected serum calcium as strata. The Efron method was used for correction for tied events.
[c]Data cut-off date = 31 Jul 2015

Figure 3 Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment)

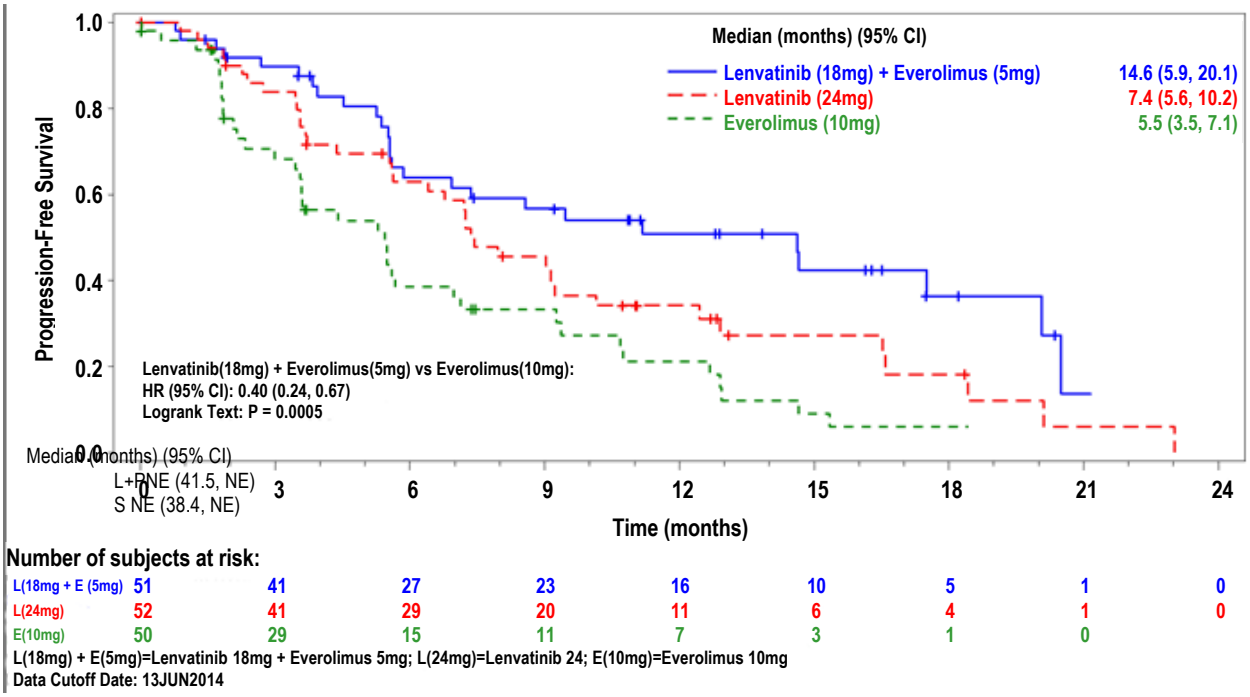
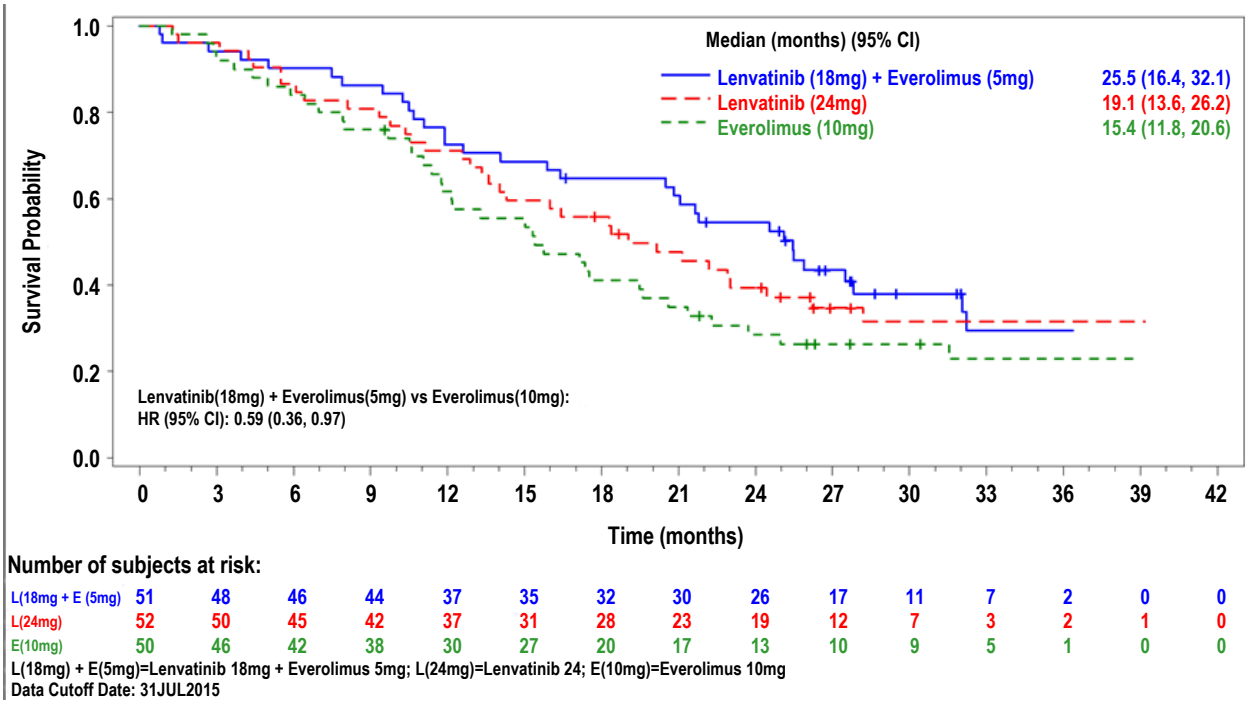


Figure 4 Kaplan-Meier Plot of Overall Survival



Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with lenvatinib in one or more subsets of the paediatric population in the treatment of renal cell carcinoma (RCC) (see section 4.2 for information on paediatric use).

Paediatric studies

The efficacy of lenvatinib was assessed but not established in two open-label studies (for additional paediatric information see also Lenvima SmPC section 5.1):

Study 216 was a multicentre, open-label, single-arm, Phase 1/2 study to determine the safety, tolerability, and antitumour activity of lenvatinib administered in combination with everolimus in paediatric patients (and young adults aged ≤21 years) with relapsed or refractory solid malignancies, including CNS tumours. A total of 64 patients were enrolled and treated. In Phase 1 (combination dose-finding), 23 patients were enrolled and treated: 5 at Dose Level –1 (lenvatinib 8 mg/m^2 and everolimus 3 mg/m2) and 18 at Dose Level 1 (lenvatinib 11 mg/m^2 and everolimus 3 mg/m^2). The recommended dose (RD) of the combination was lenvatinib 11 mg/m^2 and everolimus 3 mg/m^2, taken once daily. In Phase 2 (combination expansion), 41 patients were enrolled and treated at the RD in the following cohorts: Ewing Sarcoma (EWS, n=10), Rhabdomyosarcoma (RMS, n=20), and High-grade glioma (HGG, n=11). The primary efficacy outcome measure was objective response rate (ORR) at Week 16 in evaluable patients based on investigator assessment using RECIST v1.1 or RANO (for patients with HGG). There were no objective responses observed in the EWS and HGG cohorts; 2 partial responses (PRs) were observed in the RMS cohort for an ORR at Week 16 of 10% (95% CI: 1.2, 31.7).

Study 231 is a multicentre, open-label, Phase 2 basket study to evaluate the antitumour activity and safety of lenvatinib in children, adolescents, and young adults between 2 to ≤21 years of age with relapsed or refractory solid malignancies, including EWS, RMS, and HGG. A total of 127 patients were enrolled and treated at the lenvatinib RD (14 mg/m^2) in the following cohorts: EWS (n=9), RMS (n=17), HGG (n=8), and other solid tumours (n=9 each for diffuse midline glioma, medulloblastoma, and ependymoma; all other solid tumours n=66). The primary efficacy outcome measure was ORR at Week 16 in evaluable patients based on investigator assessment using RECIST v1.1 or RANO (for

patients with HGG). There were no objective responses observed in patients with HGG, diffuse midline glioma, medulloblastoma, or ependymoma. Two PRs were observed in both the EWS and RMS cohorts for an ORR at Week 16 of 22.2% (95% CI: 2.8, 60.0) and 11.8% (95% CI: 1.5, 36.4), respectively. Five PRs (in patients with synovial sarcoma [n=2], kaposiform hemangioendothelioma [n=1], Wilms tumour nephroblastoma [n=1], and clear cell carcinoma [n=1]) were observed among all other solid tumours for an ORR at Week 16 of 7.7% (95% CI: 2.5, 17.0).

5.2 Pharmacokinetic properties

Pharmacokinetic parameters of lenvatinib have been studied in healthy adult subjects, adult subjects with hepatic impairment, renal impairment, and solid tumours.

Absorption

Lenvatinib is rapidly absorbed after oral administration with t_{max} typically observed from 1 to 4 hours postdose. Food does not affect the extent of absorption, but slows the rate of absorption. When administered with food to healthy subjects, peak plasma concentrations are delayed by 2 hours. Absolute bioavailability has not been determined in humans; however, data from a mass-balance study suggests that it is in the order of 85%.

Distribution

In vitro binding of lenvatinib to human plasma proteins is high and ranged from 98% to 99% (0.3 - 30 μg/mL, mesilate). This binding was mainly to albumin with minor binding to α1-acid glycoprotein and γ-globulin. A similar plasma protein binding (97% to 99%) with no dependencies on lenvatinib concentrations (0.2 to 1.2 μg/mL) was observed in plasma from hepatically impaired, renally impaired, and matching healthy subjects.
In vitro, the lenvatinib blood-to-plasma concentration ratio ranged from 0.589 to 0.608 (0.1 – 10 μg/mL, mesilate).

In vitro studies indicate that lenvatinib is a substrate for P-gp and BCRP. Lenvatinib shows minimal or no inhibitory activities toward P-gp mediated and BCRP mediated transport activities. Similarly, no induction of P-gp mRNA expression was observed. Lenvatinib is not a substrate for OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, or the BSEP. In human liver cytosol, lenvatinib did not inhibit aldehyde oxidase activity.

In patients, the median apparent volume of distribution (Vz/F) of the first dose ranged from 50.5 L to 92 L and was generally consistent across the dose groups from 3.2 mg to 32 mg. The analogous median apparent volume of distribution at steady-state (Vz/Fss) was also generally consistent and ranged from 43.2 L to 121 L.

Biotransformation

In vitro, cytochrome P450 3A4 was demonstrated as the predominant (>80%) isoform involved in the P450-mediated metabolism of lenvatinib. However, *in vivo* data indicated that non-P450-mediated pathways contributed to a significant portion of the overall metabolism of lenvatinib. Consequently, *in vivo,* inducers and inhibitors of CYP 3A4 had a minimal effect on lenvatinib exposure (see section 4.5).

In human liver microsomes, the demethylated form of lenvatinib (M2) was identified as the main metabolite. M2’ and M3’, the major metabolites in human faeces, were formed from M2 and lenvatinib, respectively, by aldehyde oxidase.

In plasma samples collected up to 24 hours after administration, lenvatinib constituted 97% of the radioactivity in plasma radiochromatograms while the M2 metabolite accounted for an additional 2.5%. Based on $AUC_{(0-inf)}$, lenvatinib accounted for 60% and 64% of the total radioactivity in plasma and blood, respectively.

Data from a human mass balance/excretion study indicate lenvatinib is extensively metabolised in humans. The main metabolic pathways in humans were identified as oxidation by aldehyde oxidase, demethylation via CYP3A4, glutathione conjugation with elimination of the O-aryl group (chlorophenyl moiety), and combinations of these pathways followed by further biotransformations (e.g., glucuronidation, hydrolysis of the glutathione moiety, degradation of the cysteine moiety, and intramolecular rearrangement of the cysteinylglycine and cysteine conjugates with subsequent dimerisation). These *in vivo* metabolic routes align with the data provided in the *in vitro* studies using human biomaterials.

In vitro transporter studies

Please see distribution section.

Elimination

Plasma concentrations decline bi-exponentially following C_{max}. The mean terminal exponential half-life of lenvatinib is approximately 28 hours.

Following administration of radiolabelled lenvatinib to 6 patients with solid tumours, approximately two-thirds and one-fourth of the radiolabel were eliminated in the faeces and urine, respectively. The M3 metabolite was the predominant analyte in excreta (~17% of the dose), followed by M2' (~11% of the dose) and M2 (~4.4 of the dose).

Linearity/non-linearity

Dose proportionality and accumulation

In patients with solid tumours administered single and multiple doses of lenvatinib once daily, exposure to lenvatinib (C_{max} and AUC) increased in direct proportion to the administered dose over the range of 3.2 to 32 mg once-daily.

Lenvatinib displays minimimal accumulation at steady state. Over this range, the median accumulation index (Rac) ranged from 0.96 (20 mg) to 1.54 (6.4 mg).

Special populations

Hepatic impairment

The pharmacokinetics of lenvatinib following a single 10-mg dose were evaluated in 6 subjects each with mild and moderate hepatic impairment (Child-Pugh A and Child-Pugh B, respectively). A 5-mg dose was evaluated in 6 subjects with severe hepatic impairment (Child-Pugh C). Eight healthy, demographically matched subjects served as controls and received a 10-mg dose. The median half-life was comparable in subjects with mild, moderate, and severe hepatic impairment as well as those with normal hepatic function and ranged from 26 hours to 31 hours. The percentage of the dose of lenvatinib excreted in urine was low in all cohorts (<2.16% across treatment cohorts).

Lenvatinib exposure, based on dose-adjusted $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ data, was 119%, 107%, and 180% of normal for subjects with mild, moderate, and severe hepatic impairment, respectively. It has been determined that plasma protein binding in plasma from hepatically impaired subjects was similar to the respective matched healthy subjects and no concentration dependency was observed. See section 4.2 for dosing recommendation.

Renal impairment

The pharmacokinetics of lenvatinib following a single 24-mg dose were evaluated in 6 subjects each with mild, moderate, and severe renal impairment, and compared with 8 healthy, demographically matched subjects. Subjects with end-stage renal disease were not studied.

Lenvatinib exposure, based on $AUC_{(0\text{-inf})}$ data, was 101%, 90%, and 122% of normal for subjects with mild, moderate, and severe renal impairment, respectively. It has been determined that plasma protein binding in plasma from renally impaired subjects was similar to the respective matched healthy subjects and no concentration dependency was observed. See section 4.2 for dosing recommendation.

Age, sex, weight, ethnic origin

Based on a population pharmacokinetic analysis of patients receiving up to 24 mg lenvatinib once daily, age, sex, weight, and race (Japanese vs. other, Caucasian vs. other) had no significant effects on clearance (see section 4.2).

Paediatric population

Based on a population pharmacokinetics analysis in paediatric patients of 2 to 12 years old, which included data from 3 paediatric patients aged 2 to <3 years, 28 paediatric patients aged ≥3 to <6 years and 89 paediatric patients aged 6 to ≤12 years across the lenvatinib paediatric program, lenvatinib oral clearance (CL/F) was affected by body weight but not age. Predicted exposure levels in terms of area under the curve at steady-state (AUCss) in paediatric patients receiving 14 mg/m^2 were comparable to those in adult patients receiving a fixed dose of 24 mg. In these studies, there were no apparent differences in the pharmacokinetics of active substance lenvatinib among children (2 – 12 years), adolescents, and young adult patients with studied tumour types, but data in children are relatively limited to draw definite conclusions (see section 4.2).

5.3 Preclinical safety data

In the repeated-dose toxicity studies (up to 39 weeks), lenvatinib caused toxicologic changes in various organs and tissues related to the expected pharmacologic effects of lenvatinib including glomerulopathy, testicular hypocellularity, ovarian follicular atresia, gastrointestinal changes, bone changes, changes to the adrenals (rats and dogs), and arterial (arterial fibrinoid necrosis, medial degeneration, or haemorrhage) lesions in rats, dogs, and cynomolgus monkeys. Elevated transaminase levels asociated with signs of hepatotoxicity, were also observed in rats, dogs and monkeys. Reversibility of the toxicologic changes was observed at the end of a 4-week recovery period in all animal species investigated.

Genotoxicity

Lenvatinib was not genotoxic.

Carcinogenicity studies have not been conducted with lenvatinib.

Reproductive and developmental toxicity

No specific studies with lenvatinib have been conducted in animals to evaluate the effect on fertility. However, testicular (hypocellularity of the seminiferous epithelium) and ovarian changes (follicular atresia) were observed in repeated-dose toxicity studies in animals at exposures 11 to 15 times (rat) or 0.6 to 7 times (monkey) the anticipated clinical exposure (based on AUC) at the maximum tolerated human dose. These findings were reversible at the end of a 4-week recovery period.

Administration of lenvatinib during organogenesis resulted in embryolethality and teratogenicity in rats (foetal external and skeletal anomalies) at exposures below the clinical exposure (based on AUC) at the maximum tolerated human dose, and rabbits (foetal external, visceral or skeletal anomalies)

based on body surface area; mg/m^2 at the maximum tolerated human dose. These findings indicate that lenvatinib has a teratogenic potential, likely related to the pharmacologic activity of lenvatinib as an antiangiogenic agent.

Lenvatinib and its metabolites are excreted in rat milk.

Juvenile animal toxicity studies

Mortality was the dose-limiting toxicity in juvenile rats in which dosing was initiated on postnatal day (PND) 7 or PND21 and was observed at exposures that were respectively 125- or 12-fold lower compared with the exposure at which mortality was observed in adult rats, suggesting an increasing sensitivity to toxicity with decreasing age. Therefore mortality may be attributed to complications related to primary duodenal lesions with possible contribution from additional toxicities in immature target organs.

The toxicity of lenvatinib was more prominent in younger rats (dosing initiated on PND7) compared with those with dosing initiated on PND21 and mortality and some toxicities were observed earlier in the juvenile rats at 10 mg/kg compared with adult rats administered the same dose level. Growth retardation, secondary delay of physical development, and lesions attributable to pharmacologic effects (incisors, femur [epiphyseal growth plate], kidneys, adrenals, and duodenum) were also observed in juvenile rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Calcium carbonate
Mannitol
Microcrystalline cellulose
Hydroxypropylcellulose
Low-substituted hydroxypropylcellulose
Talc

Capsule shell

Hypromellose
Titanium dioxide (E171)
Yellow iron oxide (E172)
Red iron oxide (E172)

Printing ink

Shellac
Black iron oxide (E172)
Potassium hydroxide
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original blister in order to protect from moisture.

6.5 Nature and contents of container

Polyamide/Aluminium/PVC/Aluminium blisters containing 10 capsules. Each carton contains 30, 60, or 90 hard capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Caregivers should not open the capsule, in order to avoid repeated exposure to the contents of the capsule.

Preparation and administration of suspension:

- The suspension may be prepared using water, apple juice, or milk. If administered via a feeding tube, then the suspension should be prepared using water.
- Place the capsule(s) corresponding to the prescribed dose (up to 5 capsules) in a small container (approximately 20 mL (4 tsp) capacity) or oral syringe (20 mL); do not break or crush the capsules.
- Add 3 mL of liquid to the container or oral syringe. Wait 10 minutes for the capsule shell (outer surface) to disintegrate, then stir or shake the mixture for 3 minutes until the capsules are fully disintegrated.
    - If using an oral syringe, cap the syringe, remove plunger and use a second syringe or calibrated dropper to add the liquid to the first syringe, then replace plunger prior to mixing.
- Administer the entire contents of the container or oral syringe. The suspension may be administered from the container directly into the mouth, or from the oral syringe directly into the mouth or via feeding tube.
- Next, add an additional 2 mL of liquid to the container, or oral syringe using a second syringe or dropper, swirl or shake and administer. Repeat this step at least twice and until there is no visible residue to ensure all of the medication is taken.

Note: Compatibility has been confirmed for polypropylene syringes and for feeding tubes of at least 5 French diameter (polyvinyl chloride or polyurethane tube), at least 6 French diameter (silicone tube) and up to 16 French diameter for polyvinyl chloride, polyurethane, or silicone tubing.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany
E-mail: medinfo_de@eisai.net

8. MARKETING AUTHORISATION NUMBER(S)

Kisplyx 4 mg hard capsules

EU/1/16/1128/001
EU/1/16/1128/003
EU/1/16/1128/004

Kisplyx 10 mg hard capsules

EU/1/16/1128/002
EU/1/16/1128/005
EU/1/16/1128/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 August 2016
Date of latest renewal: 17 June 2021

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (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 European Medicines Agency;
- 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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kisplyx 4 mg hard capsules
lenvatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 4 mg lenvatinib (as mesilate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules
60 hard capsules
90 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Store in the original blister in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1128/001 (Pack size of 30 hard capsules)
EU/1/16/1128/003 (Pack size of 60 hard capsules)
EU/1/16/1128/004 (Pack size of 90 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kisplyx 4 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Kisplyx 4 mg hard capsules
lenvatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Eisai

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kisplyx 10 mg hard capsules
lenvatinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 10 mg lenvatinib (as mesylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules
60 hard capsules
90 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Store in the original blister in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1128/002 (Pack size of 30 hard capsules)
EU/1/16/1128/005 (Pack size of 60 hard capsules)
EU/1/16/1128/006 (Pack size of 90 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kisplyx 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Kisplyx 10 mg hard capsules
lenvatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Eisai

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Kisplyx 4 mg hard capsules
Kisplyx 10 mg hard capsules

lenvatinib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Kisplyx is and what it is used for
2. What you need to know before you take Kisplyx
3. How to take Kisplyx
4. Possible side effects
5. How to store Kisplyx
6. Contents of the pack and other information

1. What Kisplyx is and what it is used for

What Kisplyx is
Kisplyx is a medicine that contains the active substance lenvatinib. It is used in combination with pembrolizumab as the first treatment for adults with advanced kidney cancer (advanced renal cell carcinoma). It is also used in combination with everolimus to treat adults with advanced kidney cancer where other treatments (so-called "VEGF-targeted therapy") have not helped stop the disease.

How Kisplyx works
Kisplyx blocks the action of proteins called receptor tyrosine kinases (RTKs), which are involved in the development of new blood vessels that supply oxygen and nutrients to cells and help them to grow. These proteins can be present in high amounts in cancer cells, and by blocking their action Kisplyx may slow the rate at which the cancer cells multiply and the tumour grows and help to cut off the blood supply that the cancer needs.

2. What you need to know before you take Kisplyx

Do not take Kisplyx if:
- you are allergic to lenvatinib or any of the other ingredients of this medicine (listed in section 6).
- you are breast-feeding (see the section below on Contraception, pregnancy and breast-feeding).

Warnings and precautions
Talk to your doctor before taking Kisplyx if you:
- have high blood pressure
- are a woman able to become pregnant (see the section "Contraception, pregnancy and breast-feeding" below)
- have a history of heart problems or stroke
- have liver or kidney problems
- have had recent surgery or radiotherapy

- need to have a surgical procedure. Your doctor may consider stopping Kisplyx if you will be undergoing a major surgical procedure as Kisplyx may affect wound healing. Kisplyx may be restarted once adequate wound healing is established.
- are over 75 years old
- belong to an ethnic group other than White or Asian
- weigh less than 60 kg
- have a history of abnormal passageways (known as a fistula) between different organs in the body or from an organ to the skin
- If you have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.
- have or have had pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth. You may be advised to have a dental check-up before starting Kisplyx as bone damage in the jaw (osteonecrosis) has been reported in patients treated with Kisplyx. If you need to undergo an invasive dental treatment or dental surgery, tell your dentist that you are being treated with Kisplyx, particularly when you are also receiving or have received injections of bisphosphonates (used to treat or prevent bone disorders).
- are receiving or have received some medicines used to treat osteoporosis (antiresorptive medicines) or cancer medicines which alter formation of blood vessels (so called angiogenesis inhibitors), as the risk of bone damage in the jaw may be increased.

Before taking Kisplyx, your doctor may carry out some blood tests, for example to check your blood pressure and your liver or kidney function and to see if you have low levels of salt and high levels of thyroid stimulating hormone in your blood. Your doctor will discuss the results of these tests with you and decide whether you can be given Kisplyx. You may need to have additional treatment with other medicines, to take a lower dose of Kisplyx, or to take extra care due to an increased risk of side effects.

If you are not sure talk to your doctor before taking Kisplyx.

Conditions you need to look out for
During treatment of your cancer, the breakdown of tumour cells may leak substances into the blood which may lead to a group of complications called tumour lysis syndrome (TLS). This may lead to changes in your kidneys and can be life-threatening. Your doctor will observe and may give you a treatment to reduce the risk. Tell your doctor immediately if you experience signs of TLS (see section 4; Possible side effects).

Children and adolescents
Kisplyx is not currently recommended for use in children and adolescents younger than 18 years old.

Other medicines and Kisplyx
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes herbal preparations and medicines without a prescription.

Contraception, pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
- Use highly effective contraception while taking this medicine, and for at least one month after you finish treatment.
- Do not take Kisplyx if you are planning to become pregnant during your treatment. This is because it may seriously harm your baby.
- If you become pregnant while being treated with Kisplyx, tell your doctor immediately. Your doctor will help you decide whether the treatment should be continued.
- Do not breast-feed if you are taking Kisplyx. This is because the medicine passes into breast milk and may seriously harm your breastfed baby.

Driving and using machines
Kisplyx may cause side effects that can affect your ability to drive or use machines. Avoid driving or using machines if you feel dizzy or tired.

3. How to take Kisplyx

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take

- The recommended daily dose of Kisplyx is 20 mg once a day (two 10-mg capsules) in combination with pembrolizumab either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes.
- The recommended daily dose of Kisplyx is 18 mg once a day (one 10 mg capsule and two 4 mg capsules) in combination with one 5 mg tablet of everolimus once a day.
- If you have severe liver or kidney problems the recommended daily dose of Kisplyx is 10 mg once a day (1 capsule of 10 mg) in combination with one 5 mg tablet of everolimus once a day.
  If you are receiving lenvatinib in combination with pembrolizumab, your doctor or pharmacist will check to see how much pembrolizumab you should receive.
- Your doctor may reduce your dose if you experience side effects.

Taking this medicine

- You can take the capsules with or without food.
- Do not open the capsules to avoid exposure to the contents of the capsule.
- Swallow the capsules whole with water. If you cannot swallow the capsules whole, a liquid mixture can be prepared using water, apple juice, or milk. The liquid mixture may be given by mouth or through a feeding tube. If given through a feeding tube, then the liquid mixture should be prepared using water. If not used at the time of preparation, the liquid mixture may be stored in a covered container and must be refrigerated at 2ºC to 8ºC for a maximum of 24 hours. Shake the liquid mixture for 30 seconds after removing from the refrigerator. If the liquid mixture is not used within 24 hours of preparation, it should be thrown away.
  Preparation and administration of the liquid mixture:
  - Place the whole capsule(s) corresponding to the prescribed dose (up to 5 capsules) in a small container (approximately 20 mL (4 tsp) capacity) or oral syringe (20 mL); do not break or crush capsules.
  - Add 3 mL of liquid to the container or oral syringe. Wait 10 minutes for the capsule shell (outer surface) to dissolve, then stir or shake the mixture for 3 minutes until the capsules are fully dissolved.
    - If liquid mixture is prepared in an oral syringe, cap the syringe, remove plunger and use a second syringe or medicine dropper to add the liquid to the first syringe, then replace plunger prior to mixing.
  - Drink the liquid mixture from the container or use an oral syringe to take directly into the mouth or through a feeding tube.
  - Next, add an additional 2 mL of liquid to the container, or oral syringe using a second syringe or dropper, swirl or shake and take the liquid mixture. Repeat this step at least twice and until there is no visible sign of the mixture to make sure all of the medication is taken.
- Take the capsules at about the same time each day.

How long to take Kisplyx
You will usually carry on taking this medicine as long as you are getting benefit.

If you take more Kisplyx than you should
If you take more Kisplyx than you should, talk to a doctor or pharmacist straight away. Take the medicine pack with you.

If you forget to take Kisplyx

Do not take a double dose (two doses at the same time) to make up for a forgotten dose.

What to do if you forget to take your dose depends on how long it is until your next dose.
- If it is 12 hours or more until your next dose: take the missed dose as soon as you remember. Then take the next dose at the normal time.
- If it is less than 12 hours until your next dose: skip the missed dose. Then take the next dose at the normal time.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine.

Tell your doctor straight away if you notice any of the following side effects - you may need urgent medical treatment:
- feeling numb or weak on one side of your body, severe headache, seizure, confusion, difficulty talking, vision changes or feeling dizzy - these may be signs of a stroke, bleeding in your brain, or the effect on your brain of a severe increase in blood pressure.
- chest pain or pressure, pain in your arms, back, neck or jaw, being short of breath, rapid or irregular heart rate, coughing, bluish colour to lips or fingers, feeling very tired – these may be signs of a heart problem a blood clot in your lung or a leak of air from your lung into your chest so your lung cannot inflate.
- severe pain in your belly (abdomen) - this may be due to a hole in the wall of your gut or a fistula (a hole in your gut which links through a tube-like passage to another part of your body or skin).
- black, tarry, or bloody stools, or coughing up of blood - these may be signs of bleeding inside your body.
- diarrhoea, feeling and being sick - these are very common side effects that can become serious if they cause you to become dehydrated, which can lead to kidney failure. Your doctor can give you medicine to reduce these side effects.
- pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth - these could be signs of bone damage in the jaw (osteonecrosis).
- nausea, shortness of breath, irregular heartbeat, muscular cramps, seizure, clouding of urine and tiredness. These symptoms may be complications due to the breakdown products of dying cancer cells and known as tumour lysis syndrome (TLS).

Tell your doctor straight away if you notice any of the side effects below.

The following side effects may happen with this medicine when given alone:

Very common (may affect more than 1 in 10 people)
- low levels of platelets in the blood which may lead to bruising and difficulty in wound healing
- decrease in the number of white blood cells
- underactive thyroid (tiredness, weight gain, constipation, feeling cold, dry skin) and changes in blood test results for thyroid stimulating hormone (high)
- changes in blood test results for potassium levels (low) and calcium levels (low)
- changes in blood test results for magnesium (low) and cholesterol (high)
- loss of appetite or weight loss
- trouble sleeping
- feeling dizzy
- headache
- bleeding (most commonly nose bleeds, but also other types of bleeding such as blood in the urine, bruising, bleeding from the gums or gut wall)
- high or low blood pressure

- hoarse voice
- feeling sick (nausea) and being sick (vomiting), constipation, diarrhoea, abdominal pain, indigestion
- dry, sore, or inflamed mouth, odd taste sensation
- increase in lipase and amylase (enzymes involved in digestion)
- changes in blood test results for liver function
- redness, soreness and swelling of the skin on the hands and feet (palmar-plantar erythrodysaesthesia)
- rash
- hair loss
- back pain
- joint or muscle pain
- changes in urine tests for protein (high) and urinary infections (increased frequency in urination and pain in passing urine)
- changes in blood test results for kidney function and kidney failure
- feeling very tired or weak
- swelling of the legs

Common (may affect up to 1 in 10 people)
- loss of body fluids (dehydration)
- signs of a stroke, including feeling numb or weak on one side of your body, severe headache, seizure, confusion, difficulty talking, vision changes or feeling dizzy
- heart palpitations
- heart problems or blood clots in the lungs (difficulty breathing, chest pain) or other organs which may include chest pain or pressure, pain in your arms, back, neck or jaw, being short of breath, rapid or irregular heart rate, coughing, bluish colour to lips or fingers, and feeling very tired
- anal fistula (a small channel that forms between the anus and the surrounding skin)
- feeling bloated or having excess wind
- liver failure
- drowsiness, confusion, poor concentration, loss of consciousness that may be signs of liver failure
- inflammation of the gallbladder
- dry skin, thickening and itching of the skin
- feeling unwell
- a hole (perforation) in the stomach or intestines

Uncommon (may affect up to 1 in 100 people)
- painful infection or irritation near the anus
- severe pain in the upper left part of the belly (abdomen) which may be associated with fever, chills, nausea and vomiting (splenic infarction)
- mini-stroke
- severe difficulty breathing and chest pain, caused by a leak of air from your lung into your chest so your lung cannot inflate
- inflammation of the pancreas
- inflammation of the colon (colitis)
- liver damage
- bone damage in the jaw (osteonecrosis)
- wound healing problems
- decreased secretion of hormones produced by adrenal glands

Rare (may affect up to 1 in 1,000 people)
- Tumour lysis syndrome (TLS)

Not Known (the following side effects have been reported since the marketing of Kisplyx but the frequency for them to occur is not known)

- an enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections).
- other types of fistulae (an abnormal connection between different organs in the body or between the skin and an underlying structure such as throat and windpipe). Symptoms depend on where the fistula is located. Talk to your doctor if you experience any new or unsual symptoms such as coughing when swallowing.

The following side effects may happen with this medicine when given in combination with everolimus:

Very common (may affect more than 1 in 10 people)

- low levels of platelets in the blood which may lead to bruising and difficulty in wound healing
- decrease in the number of white blood cells
- underactive thyroid (tiredness, weight gain, constipation, feeling cold, dry skin) and changes in blood test results for thyroid stimulating hormone (high)
- changes in blood test results for potassium levels (low) and calcium levels (low)
- changes in blood test results for magnesium (low) and cholesterol (high)
- loss of appetite or weight loss
- trouble sleeping
- headache
- bleeding (most commonly nose bleeds, but also other types of bleeding such as blood in the urine, bruising, bleeding from the gums or gut wall)
- high blood pressure
- hoarse voice
- feeling sick (nausea) and being sick (vomiting), constipation, diarrhoea, abdominal pain, indigestion
- sore, or inflamed mouth, odd taste sensation
- increase in lipase and amylase (enzymes involved in digestion)
- changes in blood test results for liver function
- redness, soreness and swelling of the skin on the hands and feet (palmar-plantar erythrodysaesthesia)
- rash
- back pain
- joint or muscle pain
- changes in urine tests for protein (high)
- changes in blood test results for kidney function and kidney failure
- feeling very tired or weak
- swelling of the legs

Common (may affect up to 1 in 10 people)

- urinary infections (increased frequency in urination and pain in passing urine)
- loss of body fluids (dehydration)
- feeling dizzy
- heart palpitations
- heart problems or blood clots in the lungs (difficulty breathing, chest pain) or other organs which may include chest pain or pressure, pain in your arms, back, neck or jaw, being short of breath, rapid or irregular heart rate, coughing, bluish colour to lips or fingers, and feeling very tired
- low blood pressure
- severe difficulty breathing and chest pain, caused by a leak of air from your lung into your chest so your lung cannot inflate
- dry mouth
- feeling bloated or having excess wind

- inflammation of the gallbladder
- hair loss
- feeling unwell
- a hole (perforation) in the stomach or intestines

Uncommon (may affect up to 1 in 100 people)
- painful infection or irritation near the anus
- signs of a stroke, including feeling numb or weak on one side of your body, severe headache, seizure, confusion, difficulty talking, vision changes or feeling dizzy
- mini-stroke
- inflammation of the pancreas
- anal fistula (a small channel that forms between the anus and the surrounding skin)
- inflammation of the colon (colitis)
- liver failure or signs of liver damage, including yellow skin or yellowing of the whites of the eyes (jaundice) or drowsiness, confusion, poor concentration
- bone damage in the jaw (osteonecrosis)
- dry skin, thickening and itching of the skin
- wound healing problems
- other types of fistulae (an abnormal connection between different organs in the body or between the skin and an underlying structure such as throat and windpipe). Symptoms depend on where the fistula is located. Talk to your doctor if you experience any new or unsual symptoms such as coughing when swallowing.
- decreased secretion of hormones produced by adrenal glands

Rare (may affect up to 1 in 1,000 people)
- Tumour lysis syndrome (TLS)

Not Known (the following side effects have been reported since the marketing of Kisplyx but the frequency for them to occur is not known)
- an enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections).

The following side effects may happen with this medicine when given in combination with pembrolizumab:

Very common (may affect more than 1 in 10 people)
- low levels of platelets in the blood which may lead to bruising and difficulty in wound healing
- decrease in the number of white blood cells
- underactive thyroid (tiredness, weight gain, constipation, feeling cold, dry skin) and changes in blood test results for thyroid stimulating hormone (high)
- changes in blood test results for potassium levels (low) and calcium levels (low)
- changes in blood test results for magnesium (low) and cholesterol (high)
- loss of appetite or weight loss
- trouble sleeping
- feeling dizzy
- headache
- bleeding (most commonly nose bleeds, but also other types of bleeding such as blood in the urine, bruising, bleeding from the gums or gut wall)
- high blood pressure
- hoarse voice
- feeling sick (nausea) and being sick (vomiting), constipation, diarrhoea, abdominal pain, indigestion
- dry, sore, or inflamed mouth, odd taste sensation
- increase in lipase and amylase (enzymes involved in digestion)
- changes in blood test results for liver function

- redness, soreness and swelling of the skin on the hands and feet (palmar-plantar erythrodysaesthesia)
- rash
- back pain
- joint or muscle pain
- changes in urine tests for protein (high)
- changes in blood test results for kidney function and kidney failure
- feeling very tired or weak
- swelling of the legs

Common (may affect up to 1 in 10 people)
- urinary infections (increased frequency in urination and pain in passing urine)
- loss of body fluids (dehydration)
- heart palpitations
- heart problems or blood clots in the lungs (difficulty breathing, chest pain) or other organs which may include chest pain or pressure, pain in your arms, back, neck or jaw, being short of breath, rapid or irregular heart rate, coughing, bluish colour to lips or fingers, and feeling very tired
- low blood pressure
- inflammation of the pancreas
- inflammation of the colon (colitis)
- feeling bloated or having excess wind
- inflammation of the gallbladder
- dry skin, thickening and itching of the skin
- hair loss
- feeling unwell
- decreased secretion of hormones produced by adrenal glands
- a hole (perforation) in the stomach or intestines

Uncommon (may affect up to 1 in 100 people)
- painful infection or irritation near the anus
- signs of a stroke, including feeling numb or weak on one side of your body, severe headache, seizure, confusion, difficulty talking, vision changes or feeling dizzy
- mini-stroke
- severe difficulty breathing and chest pain, caused by a leak of air from your lung into your chest so your lung cannot inflate
- anal fistula (a small channel that forms between the anus and the surrounding skin)
- liver failure or signs of liver damage, including yellow skin or yellowing of the whites of the eyes (jaundice) or drowsiness, confusion, poor concentration
- wound healing problems
- other types of fistulae (an abnormal connection between different organs in the body or from the skin to an underlying structure such as throat and windpipe). Symptoms would depend on where the fistula is located. Talk to your doctor if you experience any new or unsual symptoms such as coughing when swallowing.

Rare (may affect up to 1 in 1,000 people)
- Tumour lysis syndrome (TLS)

Not Known (the following side effects have been reported since the marketing of Kisplyx but the frequency for them to occur is not known)
- an enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Kisplyx

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and blister after 'EXP'. The expiry date refers to the last day of that month.
- Do not store above 25°C. Store in the original blister in order to protect from moisture.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Kisplyx contains
- The active substance is lenvatinib.
  - Kisplyx 4 mg hard capsules: - Each hard capsule contains 4 mg of lenvatinib (as mesilate).
  - Kisplyx 10 mg hard capsules: - Each hard capsule contains 10 mg of lenvatinib (as mesilate).

- The other ingredients are calcium carbonate, mannitol, microcrystalline cellulose, hydroxypropylcellulose, low-substituted hydroxypropyl cellulose, talc. The capsule shell contains hypromellose, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172). The printing ink contains shellac, black iron oxide (E172), potassium hydroxide, propylene glycol.

What Kisplyx looks like and contents of the pack
- Kisplyx 4 mg hard capsule: yellowish red body and yellowish red cap, approximately 14.3 mm in length, marked in black ink with "Є" on the cap, and "LENV 4 mg" on the body.
- Kisplyx 10 mg hard capsule: yellow body and yellowish red cap, approximately 14.3 mm in length, marked in black ink with "Є" on the cap, and "LENV 10 mg" on the body.
- The capsules come in blisters with a push through aluminium foil lidding in cartons of 30, 60 or 90 hard capsules. Not all pack sizes may be marketed.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.