PRESCRIBING INFORMATION *Kisplyx® (lenvatinib)*

Please refer to the Summary of Product Characteristics (SPC) before prescribing. ***Presentation:*** 4mg and 10mg hard capsules. ***Indication:*** Used in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy. ***Dose and administration:*** For oral use. Should be initiated and supervised by a health care professional experienced in the use of anticancer therapies. 18 mg lenvatinib once daily in combination with 5 mg everolimus once daily at about the same time each day, with or without food. Swallow the capsules whole with water or dissolve in water or apple juice without breaking or crushing - see SPC for guidelines. If dose missed, and it cannot be taken within 12 hours, skip dose and take next dose at normal time. Continue treatment as long as clinical benefit observed or unacceptable toxicity occurs. Initiate medical management for nausea, vomiting, and diarrhoea prior to interruption or dose reduction. Actively treat GI toxicity to reduce risk of renal impairment or failure. ***Dose adjustment:*** Mild to moderate adverse reactions (e.g., Grade 1 or 2) generally do not warrant interruption of the combination, unless intolerable to the patient despite optimal management. Severe (e.g., Grade 3) or intolerable adverse reactions require interruption of the combination of medicines until improvement of the reaction to Grade 0-1 or baseline. For toxicities thought to be related to lenvatinib, upon resolution/improvement of an adverse reaction to Grade 0-1 or baseline, resume treatment at a reduced dose of lenvatinib: First dose reduction 14 mg once daily; second dose reduction 10 mg once daily; third dose reduction 8 mg once daily. For toxicities thought to be related to everolimus, interrupt the treatment, reduce to alternate day dosing, or discontinue (see the everolimus SPC). For toxicities thought to be related to both lenvatinib and everolimus, reduce lenvatinib dose prior to reducing everolimus. Discontinue treatment in case of life-threatening reactions (e.g., Grade 4) except if laboratory abnormalities judged to be non-life-threatening, then manage as severe reactions (e.g., Grade 3). ***Special populations:*** *Patients with hypertension:* Control blood pressure prior to treatment and monitor regularly during treatment. *Patients with hepatic impairment:* No data with the combination. No adjustment of starting dose of the combination required in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. In patients with severe (Child-Pugh C) hepatic impairment, lenvatinib starting dose is 10 mg once daily in combination with everolimus dose for patients with severe hepatic impairment in the everolimus SPC. Adjust dose further based on individual tolerability. Combination should be used in patients with severe hepatic impairment only if the anticipated benefit exceeds the risk. *Patients with renal impairment:* No adjustment of starting dose is required in patients with mild or moderate renal impairment. In patients with severe renal impairment starting dose is 10 mg of lenvatinib with 5 mg of everolimus once daily. Adjust dose further based on individual tolerability. Use of lenvatinib in patients with end-stage renal disease is not recommended. *Elderly population:* No adjustment of starting dose is required. *Paediatric population:* No data in children aged 2 to <18 years. Do not use in children <2 years due to safety concerns identified in animal studies. Race: No adjustment of starting dose is required. *Body weight below 60 kg:* No adjustment of starting dose is required. *Patients with high ECOG performance status:* Benefit-risk in these patients has not been evaluated. ***Contra-Indications:*** Hypersensitivity to active substance or any of the excipients. Breast-feeding. ***Special warnings and precautions:*** Control blood pressure prior to treatment with lenvatinib and, if patients are known to be hypertensive, control with stable dose of antihypertensive therapy for at least 1 week prior to treatment with lenvatinib. Start antihypertensive agents as soon as elevated blood pressure is confirmed. Monitor blood pressure after 1 week of treatment with lenvatinib, then every 2 weeks for the first 2 months and monthly thereafter. When necessary, manage hypertension as recommended in SPC. Consider risk of aneurysms and artery dissections prior to treatment in patients with risk factors such as hypertension or history of aneurysm. Women of childbearing potential must use highly effective contraception while taking lenvatinib and for one month after stopping treatment. Monitor urine protein regularly. Interrupt, adjust or discontinue dose if urine dipstick proteinuria ≥2+ detected. Discontinue in the event of nephrotic syndrome. Interrupt, adjust or discontinue dose in patients receiving agents acting on the renin-angiotensin aldosterone system due to a potentially higher risk for acute renal failure with the combination treatment. Monitor for clinical symptoms or signs of cardiac decompensation, dose interruption, adjustment or discontinuation may be necessary. Dose interruption, adjustment or discontinuation may be necessary in patients with signs or symptoms of PRES. Monitor liver function tests before starting treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. In the case of hepatotoxicity, bleeding, gastrointestinal perforation or fistula, dose interruptions, adjustments, or discontinuation may be necessary. Use lenvatinib with caution in patients who have had an arterial thromboembolism within the previous 6 months. Discontinue following an arterial thrombotic event. Do not start lenvatinib in patients with fistulae to avoid worsening and discontinue permanently in patients with oesophageal or tracheobronchial tract involvement and any Grade 4 fistula. Monitor ECGs in all patients particularly those with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, and those taking medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics. Withhold lenvatinib in QT interval prolongation greater than 500 ms. Resume lenvatinib at a reduced dose when QTc prolongation is resolved to < 480 ms or baseline. Monitor and correct electrolyte abnormalities before starting treatment. Consider periodic monitoring of ECG and electrolytes during treatment. Monitor blood calcium levels at least monthly and replace calcium as necessary during treatment. Interrupt or adjust lenvatinib dose as necessary depending on severity, presence of ECG changes, and persistence of hypocalcaemia. Monitor thyroid function before initiation of, and periodically throughout, treatment with lenvatinib. Monitor TSH levels regularly and adjust thyroid hormone administration as required. Discontinue lenvatinib in the event of persistence of Grade 4 diarrhoea despite medical management. Consider temporary interruption of lenvatinib in patients undergoing major surgical procedures. Consider dental examination and appropriate preventative dentistry prior to lenvatinib initiation. Avoid invasive dental procedures in patients receiving, or previously treated with, intravenous bisphosphonates. Use with caution in elderly or Asian patients due to reduced tolerability to lenvatinib. Consider washout between lenvatinib and other anticancer treatments due to potential risk for additive toxicities. ***Drug Interactions:*** No significant drug-drug interaction expected between lenvatinib and CYP3A4/Pgp substrates. Unknown if lenvatinib reduces effectiveness of hormonal contraceptives. Women using oral hormonal contraceptives should add a barrier method. ***Pregnancy:*** Do not use during pregnancy unless clearly necessary. Women of childbearing potential should avoid becoming pregnant and use highly effective contraception during and for at least one month after treatment. ***Lactation:*** Unknown if excreted in human milk. A risk to newborns or infants cannot be excluded; contraindicated during breast-feeding. ***Fertility:*** Fertility effects in humans are unknown. ***Effects on ability to drive and use machines:*** Use caution when driving or operating machines if experiencing fatigue or dizziness. ***Undesirable effects:*** **Consult the SPC for information on all side effects.** The adverse reactions presented in this section are based on the combined safety data of RCC and differentiated thyroid carcinoma patients. *Very common (≥1/10):* Urinary tract infection, thrombocytopenia, hypothyroidism, blood thyroid stimulating hormone increased, hypocalcaemia, hypercholesterolaemia, hypokalaemia, decreased appetite, weight decreased, insomnia, dizziness, headache, dysgeusia, haemorrhage, hypertension, hypotension, dysphonia, diarrhoea, gastrointestinal and abdominal pains, vomiting, nausea, oral inflammation, oral pain, constipation, dyspepsia, dry mouth, palmar-plantar erythrodysaesthesia syndrome, palmar erythema, rash, alopecia, back pain, arthralgia, myalgia, pain in extremity, musculoskeletal pain, proteinuria, fatigue, asthenia, oedema peripheral. *Common (≥1/100 to <1/10):* Lymphopenia, dehydration, hypomagnesaemia, cerebrovascular accident, myocardial infarction, cardiac failure, electrocardiogram QT prolonged, ejection fraction decreased, pulmonary embolism, anal fistula, flatulence, lipase increased, amylase increased, aspartate aminotransferase increased, hypoalbuminaemia, alanine aminotransferase increased, blood alkaline phosphatase increased, hepatic function abnormal, gamma-glutamyltransferase increased, blood bilirubin increased, cholecystitis, hyperkeratosis, renal failure, renal impairment, blood creatinine increased, blood urea increased, malaise. *Uncommon (≥1/1,000 to <1/100):* Perineal abscess, splenic infarction, posterior reversible encephalopathy syndrome, monoparesis, osteonecrosis of the jaw, transient ischaemic attack, pneumothorax, pancreatitis, hepatocellular damage/hepatitis, nephrotic syndrome, impaired healing. *Frequency not known (cannot be estimated from the available data):* Aneurysms and artery dissections, Non-gastrointestinal fistula. ***Overdose:*** No specific antidote. In case of suspected overdose, lenvatinib should be withheld and appropriate supportive care given as required. ***Legal Category:*** POM ***Cost: UK NHS list price:*** 4mg capsules pack of 30: £1,437.00; 10mg capsules pack of 30: £1,437.00 ***Marketing authorisation (MA) numbers Northern Ireland (NI)/ Republic of Ireland (ROI):*** 4mg capsules: EU/1/16/1128/001; 10mg capsules: EU/1/16/1128/002. ***Great Britain (GB):*** 4mg capsules: PLGB 3967/0007; 10mg capsules: PLGB 3967/0006 ***MA holder:*** Eisai GmbH (NI/ROI); Eisai Europe Ltd (GB) ***Further information from:*** Eisai Ltd., Mosquito Way, Hatfield, Hertfordshire, AL10 9SN, UK ***Date of preparation:*** September 2021. UK-KIS-21-00150

Adverse events should be reported.
Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ or search for the MHRA Yellow Card in the Google Play or Apple App Store, or Republic of Ireland: www.hpra.ie. Adverse events should also be reported to Eisai Ltd on +44 (0)845 676 1400/ +44 (0)208 600 1400 or EUmedinfo@eisai.net