RETSEVMO™

selpercatinib

hard capsules

Summary of Risk Management Plan (RMP)

Summary of the risk management plan (RMP) for Retsevmo (selpercatinib)
The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.
The RMP summary of Retsevmo is a concise document and does not claim to be exhaustive.
As the RMP is an international document, the summary might differ from the „Arzneimittelinformation / Information sur le médicament“ approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Retsevmo in Switzerland is the „Arzneimittelinformation/ Information sur le médicament“(see www.swissmedicinfo.ch) approved and authorized by Swissmedic.
Eli Lilly is fully responsible for the accuracy and correctness of the content of this published summary RMP of Retsevmo.

I. The Medicine and What It Is Used for

Retsevmo as monotherapy is indicated for the treatment of adults with:

- Advanced RET fusion-positive NSCLC in patients who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy
- Advanced RET fusion-positive thyroid cancer in patients who require systemic therapy following prior treatment with sorafenib and/or lenvatinib.

Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET-mutant MTC who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.

See SmPC for full indication information. It contains selpercatinib as the active substance and it is given by oral dosing in the form of a simple blend with excipient capsule in dose strengths of 40 mg or 80 mg.

Further information about the evaluation of Retsevmo’s benefits can be found in Retsevmo’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage.

https://www.ema.europa.eu/en/medicines/human/EPAR/retsevmo

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of selpercatinib, together with measures to minimise such risks and the proposed studies for learning more about selpercatinib’s risks, are outlined below.

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

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

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

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

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

II.A. List of Important Risks and Missing Information

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

List of important risks and missing information	
Important identified risks	None
Important potential risks	Liver injury Cardiac arrhythmia due to QT prolongation Reproductive and developmental toxicities
Missing information	Exposure and safety in patients with severe hepatic impairment Exposure and safety in patients with Cardiac impairment

II.B. Summary of Important Risks

Important Potential Risk 1: Liver Injury	
Evidence for linking the risk to the medicine	In the clinical study, increases of aminotransferases, including ALT and AST, have been observed in patients treated with selpercatinib. Based on the frequency of reported events of aminotransferase increased, and their potential to indicate liver injury, liver injury is considered an important potential risk. Only a few cases of severe increases of aminotransferases and serious hepatic events were reported, no cases of liver failure or Grade 5 liver related events. Therefore, liver injury is considered an

	important potential risk. Generally, these increases were of low severity and manageable by dose reduction or dose omission and resolved upon discontinuation of study treatment. Furthermore, in the majority of cases, no concurrent increase of bilirubin was observed.
Risk factors and risk groups	There are a number of risk factors associated with liver injury including advancing age, female gender, nutritional deficiencies, alcohol consumption, chronic hepatitis B and C, and genetic risk factors (Ingawale et al. 2014). Liver function abnormalities are commonly observed in cancer patient populations and identifying their aetiology is often difficult (Floyd 2006). Potential causes of abnormal liver function in cancer patients include pre-existing medical problems such as hepatic metastases, alcoholism, hepatitis viruses, use of immunosuppression drugs, malnutrition, paraneoplastic syndromes, portal vein thrombosis, infections, hepatic metastasectomy, and blood transfusion (Rodriguez-Frias and Lee 2007). Concomitant medications including nonsteroidal anti-inflammatory drugs (NSAIDS), antiemetic drugs, analgesics, or antibiotics may also be associated with hepatotoxicity due to interaction effects (Rodriguez-Frias and Lee 2007; Ingawale et al. 2014). Idiosyncratic drug-induced liver injury can arise due to the complex interaction between genetic and nongenetic risk factors which can be further subdivided into host susceptibility and environmental factors and include the following: age, sex and other diseases such as chronic liver disease or human immunodeficiency virus infection (Chalasani 2014). Compound-specific risk factors include daily dose, metabolic characteristics, and the propensity for drug interactions (Chalasani and Björnsson, 2010).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.2 and 4.4. **Additional risk minimisation measures:** Not Applicable
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Important Potential Risk 2: Cardiac arrhythmias due to QT

Evidence for linking the risk to the medicine	In the Phase1/2 clinical study, TEAE of QT prolongation was observed in 17.8% of patients treated with selpercatinib. The majority of the events have been Grade 1 (6.7%) or Grade 2 (7.1%) in severity. Grade 3/4 events were observed in 4.0%, with 1 Grade 4 event. No Grade 5 events were reported. To date, there are no cases of arrhythmias or sudden death associated with QT prolongation in the clinical study. The effect of selpercatinib on the QTc interval was evaluated in a thorough QT study in healthy subjects. The largest mean increase in QTc is predicted to be 10.6 msec (upper 90% CI: 12.1 msec) at the mean steady-state C_{max} observed in patients after administration of 160 mg twice daily. The increase in QTc was concentration-dependent
Risk factors and risk groups	Patients at higher risk of QT prolongation include occult congenital long QT syndrome, genetic polymorphisms (reduced repolarized reserve), underlying heart conditions such as bradycardia, myocardial infarction, congenital heart failure or cardiac hypertrophy, female sex, and advanced age (Makkar et al. 1993; Roden 1998; Zeltser et al. 2003; Curigliano et al. 2009; Drew et al. 2010). Certain medications are a common cause of QT prolongation including diuretics, antiarrhythmic drugs, certain antimicrobials such as macrolide and fluoroquinolone antibiotics, and certain gastric motility agents such as cisapride (Viskin 2003; Roden 2004; Curigliano et al. 2009).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections 4.2 and 4.4. **Additional risk minimisation measures:** Not Applicable
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviation: CI = confidence interval; C_{max} = maximum observed drug concentration; QTc = QT interval corrected for heart rate; TEAE = treatment-emergent adverse event.

Important Potential Risk 3: Reproductive and Developmental Toxicities

Evidence for linking the risk to the medicine	Nonclinical data suggest that there is a potential risk for reproductive and developmental toxicities in women exposed to selpercatinib during pregnancy, and a potential risk for reproductive organ injury and fertility effects in men. Accordingly, this has been determined a key safety finding from the nonclinical development program of selpercatinib.
Risk factors and risk groups	Known risk factor on maternal cancer on foetal and infant health may include malnutrition, hypoxia, chronic inflammation, and toxic or teratogenic effects of cancer treatment (Lu et al. 2017). Known risk factor on maternal cancer on foetal and infant health may include malnutrition, hypoxia, chronic inflammation, and toxic or teratogenic effects of cancer treatment (Lu et al. 2017). Other risk factors associated with reproductive and developmental outcomes are listed below: • For maternal and paternal infertility: temporary or permanent amenorrhea and decreased fertility due to chemotherapy in women and gonadal dysfunction due to neoplastic agents such as cisplatin (Ruddy and Partridge 2012). • For spontaneous abortion (miscarriage): for example, previous miscarriage, termination and infertility, assisted conception, regular/high alcohol consumption, feeling stressed, higher maternal and paternal age (Maconochie et al. 2007). • For stillbirth: parity, ethnicity, maternal obesity, smoking, pre-existing diabetes, history of mental health problems, antepartum haemorrhage and foetal growth restriction (Gardosi et al. 2013). • For congenital anomalies and teratogenicity: certain maternal factors such as alcohol consumption, folic acid deficiency, uncontrolled maternal diabetes, or phenylketonuria, obesity, advanced maternal age (Harris 2017); certain medications used to treat cancer (for example, cytarabine, 5-fluorouracil, cyclophosphamide, tamoxifen, and imatinib) (Voulgaris, 2011); or other medical conditions (for example, antiepileptic drugs, folic acid antagonists) (Harris 2017; Sabers 2017).
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.6 **Additional risk minimisation measures:** Not Applicable
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Missing Information 1: Exposure and Safety in patients with Severe Hepatic Impairment	
Risk minimisation measures	**Routine risk minimisation measures:** A clinical pharmacology study assessing the effect of hepatic impairment on the pharmacokinetics of selpercatinib is complete. SmPC is updated based on the safety and pharmacokinetics data **Additional risk minimisation measures:** Not Applicable
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None See Section II.C of this summary for an overview of the postauthorisation development plan.
Important Missing Information 2: Exposure and Safety in patients with Cardiac Impairment	
Risk minimisation measures	**Routine risk minimisation measures:** **None** **Additional risk minimisation measures:** Not Applicable
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None See Section II.C of this summary for an overview of the postauthorisation development plan.

Abbreviation: SmPC = Summary of Product Characteristics.

VI.1.1. II.C. Post-authorisation development plan

VI.1.1.1. II.C.1. Studies that are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Study short name: **LOXO-RET-17001**

Purpose of the study: To determine the RP2D and to assess the antitumour activity of selpercatinib in patients with advanced solid tumours, including *RET* fusion-positive solid tumours, *RET*-mutant MTC, and other tumours with RET activation.

Study short name: **J2G-MC-JZJB**

Purpose of the study: To compare treatment failure-free survival (TFFS), PFS, and other efficacy outcomes of patients with progressive, advanced, kinase inhibitor naïve, *RET*-mutant MTC treated with selpercatinib versus cabozantinib or vandetanib.

Study short name: **J2G-MC-JZJC**

Purpose of the study: To compare PFS and other efficacy outcomes of selpercatinib and platinum-based (carboplatin or cisplatin) and pemetrexed therapy with or without pembrolizumab in patients with advanced or metastatic *RET* fusion-positive NSCLC

Study short name: **LOXO-RET-18036**

Purpose of the study: To determine the ORR and other efficacy outcomes in paediatric patients with advanced cancer harbouring an activating RET alteration following initiation of selpercatinib.

VI.1.1.2. II.C.2. Other studies in the post-authorisation development plan

Study short name: **LOXO-RET-17001**

Purpose of the study: To determine the RP2D and to assess the antitumor activity of selpercatinib in patients with advanced solid tumours, including *RET* fusion-positive solid tumours, *RET*-mutant MTC, and other tumours with RET activation.

Study short name: **J2G-MC-JZJB**

Purpose of the study: To compare TFFS and other efficacy outcomes of patients with progressive, advanced, kinase inhibitor naïve, *RET*-mutant MTC treated with selpercatinib versus cabozantinib or vandetanib.

Study short name: **J2G-MC-JZJC**

Purpose of the study: To compare PFS and other efficacy outcomes of selpercatinib and platinum-based (carboplatin or cisplatin) and pemetrexed therapy with or without pembrolizumab in patients with advanced or metastatic *RET* fusion-positive NSCLC

Study short name: **LOXO-RET-18036**

Purpose of the study: To determine the ORR and other efficacy outcomes in paediatric patients with advanced cancer harbouring an activating RET alteration following initiation of selpercatinib.