# RETSEVMO®

**selpercatinib**

40 mg – 80 mg hard capsules

# Summary of Risk Management Plan (RMP)

## Summary of the risk management plan (RMP) for Retsevmo (selpercatinib)

This is a summary of the RMP for selpercatinib. The RMP details important risks of selpercatinib, how these risks can be minimised, and how more information will be obtained about selpercatinib's risks and uncertainties (missing information).

Selpercatinib's SmPC and its package leaflet give essential information to healthcare professionals and patients on how selpercatinib should be used.

Important new concerns or changes to the current ones will be included in updates of selpercatinib's RMP.

## I. The Medicine and What It Is Used for

See SmPC for full indication information. RETSEVMO contains selpercatinib as the active substance, given orally, in the form of a simple blend with excipient capsule in dose strengths of 40 or 80 mg.

RETSEVMO (selpercatinib) as monotherapy is indicated for the treatment of adults with

- advanced RET fusion-positive NSCLC not previously treated with a RET inhibitor, and
- advanced RET fusion-positive solid tumours, when treatment options not targeting RET provide limited clinical benefit or have been exhausted (see Sections 4.4 and 5.1).

RETSEVMO as monotherapy is indicated for the treatment of adults and adolescents aged 12 years and older with

- advanced RET-fusion-positive TC who are radioactive iodine-refractory (if radioactive iodine is appropriate), and
- advanced *RET*-mutant MTC.

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 in this section.

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 SmPC addressed to patients and healthcare professionals
- important advice on the medicine's packaging
- the authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly, and

- the medicine's legal status — the way a medicine is supplied to the patient, for example, with or without prescription can help to minimise its risks.

Together, these 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' as follows.

## *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, for example, on the long-term use of the medicine.

| **List of important risks and missing information** | |
|---|---|
| **Important identified risks** | None |
| **Important potential risks** | Liver injury<br>Cardiac arrhythmia due to QT prolongation<br>Reproductive and developmental toxicities<br>Growth plate abnormalities in paediatric patients |
| **Missing information** | Exposure and safety in patients with severe hepatic impairment<br>Exposure and safety in patients with cardiac impairment |

## *II.B. Summary of Important Risks*

| **Important Potential Risk 1: Liver injury** | |
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| Evidence for linking the risk to the medicine | In the clinical study LIBRETTO-001, 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. Generally, increases of aminotransferases were of low severity and manageable by dose reduction or dose omission and resolved upon discontinuation of study treatment. |
| 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 et al. 2006). Potential causes of abnormal liver function in patients with cancer include pre-existing medical problems such as hepatic metastases, alcoholism, hepatitis viruses, use of immunosuppression drugs, malnutrition, paraneoplastic syndromes, portal vein thrombosis, infections, hepatic |

| **Important Potential Risk 1: Liver injury** | |
|---|---|
| | metastasectomy, and blood transfusion (Rodriguez-Frias and Lee 2007). Concomitant medications including nonsteroidal anti-inflammatory drugs, 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 non-genetic risk factors which can be further subdivided into host susceptibility and environmental factors and include 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:**<br>SmPC Sections 4.2 and 4.4.<br><br>**Additional risk minimisation measures:**<br>Not applicable |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>None<br>See Section II.C of this summary for an overview of the post-authorisation development plan. |

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; SmPC = summary of product characteristics.

| **Important Potential Risk 2: Cardiac arrhythmias due to QT** | |
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| Evidence for linking the risk to the medicine | In the Phase 1/2 clinical, TEAE of QT prolongation was observed in 21.1% of patients treated with selpercatinib. The majority of the events has been Grade 1 (8.2%) or Grade 2 (8.0%) in severity. Grade 3 events were observed in 5.5% of patients. Fatal events such as sudden death and cardiac arrest were reported in patients with significant cardiac history.<br>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 selpercatinib 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 repolarised 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 et al. 2003; Roden 2004; Curigliano et al. 2009). |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Sections 4.2 and 4.4.<br><br>**Additional risk minimisation measures:**<br>Not applicable |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>None<br>See Section II.C of this summary for an overview of the post-authorisation development plan. |

Abbreviations: CI = confidence interval; $C_{max}$ = maximum observed drug concentration; QTc = corrected time from the start of the Q wave to the end of the T wave interval; SmPC = summary of product characteristics; TEAE = treatment-emergent adverse event.

| **Important Potential Risk 3: Reproductive and developmental toxicities** | |
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| Evidence for linking the risk to the medicine | Non-clinical 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 non-clinical development programme 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 as follows:<br>• 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).<br>• 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).<br>• 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).<br>• 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 et al. 2017); certain medications used to treat cancer (for example, cytarabine, 5-fluorouracil, cyclophosphamide, tamoxifen, and imatinib) (Voulgaris et al. 2011); or other medical conditions (for example, antiepileptic drugs, folic acid antagonists) (Harris et al. 2017; Sabers et al. 2017). |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Section 4.6<br><br>**Additional risk minimisation measures:**<br>Not applicable |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>None<br>See Section II.C of this summary for an overview of the post-authorisation development plan. |

Abbreviation: SmPC = Summary of Product Characteristics

| **Important Potential Risk 4: Growth plate abnormalities in paediatric patients** | |
|---|---|
| Evidence for linking the risk to the medicine | Juvenile and adolescent rats and adolescent minipigs with open growth plates administered selpercatinib, exhibited microscopic changes of hypertrophy, hyperplasia, and dysplasia of growth-plate cartilage (physis). In the juvenile rat study, the skeletal changes were:<br>• irreversible physeal dysplasia at bone growth plates<br>• decreased bone size or geometry, mass, and/or density at both the distal femur metaphysis and femur diaphysis (some findings not reversible), and<br>• decreased femur length (observed at recovery necropsy).<br>The skeletal changes were observed at exposures approximately 1 to 4 times the exposure in adults at the efficacious dose of 160 mg twice daily and are therefore considered potentially relevant to the paediatric patient population. |
| Risk factors and risk groups | Paediatric and adolescent patients with open growth plates, who have not yet obtained full adult height, may be at risk for growth plate abnormalities. The potential impact of which could include decreased longitudinal bone growth.<br><br>Patients with cancer since childhood may have impaired growth before, during, or after treatment for their cancer. A number of factors are responsible for this, including the disease process itself, complications of treatment (infection), direct effects during treatment (anorexia, vomiting), and direct and indirect late effects attributable to therapy. The particular risks of growth impairment for any individual survivor depend upon the cancer type, the treatment given, and the age at presentation. |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Section 4.2<br><br>**Additional risk minimisation measures:**<br>Not applicable |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>None<br>See Section II.C of this summary for an overview of the post-authorisation development plan. |

Abbreviation: SmPC = summary of product characteristics.

| **Important Missing Information 1: Exposure and safety in patients with severe hepatic impairment** | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures:**<br>A clinical pharmacology study assessing the effect of hepatic impairment on the pharmacokinetics of selpercatinib is complete. The respective safety and pharmacokinetic data are described in the SmPC.<br>**Additional risk minimisation measures:**<br>Not applicable. |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>None.<br>See Section II.C of this summary for an overview of the post-authorisation development plan. |
| **Important Missing Information 2: Exposure and safety in patients with cardiac impairment** | |

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|---|---|
| Risk minimisation measures | **Routine risk minimisation measures:**<br>None.<br>**Additional risk minimisation measures:**<br>Not applicable. |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>None.<br>See Section II.C of this summary for an overview of the post-authorisation development plan. |

Abbreviation: SmPC = summary of product characteristics.

## *II.C. Post-authorisation development plan*

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

The following studies are conditions of the marketing authorisation:

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

Purpose of the study: To compare treatment failure-free survival, 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/J2G-OX-JZJJ**

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.

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

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/J2G-OX-JZJJ**

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.