Koselugo®

10 mg and 25 mg, hard capsules

Summary of the Risk Management Plan (RMP) for Koselugo® (Selumetinib)

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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Koselugo® 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 Koselugo® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. AstraZeneca AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Koselugo®.

1. SUMMARY OF THE RISK MANAGEMENT PLAN FOR KOSELUGO® (SELUMETINIB)

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

Selumetinib's Information for Healthcare Professionals and its Patient Information Leaflet give essential information to healthcare professionals and patients on how selumetinib should be used.

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

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

1.1 THE MEDICINE AND WHAT IT IS USED FOR

Selumetinib is indicated for the treatment of children and adolescent patients aged 3 years and above, with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibromas (PN) (see Information for Healthcare Professionals for the full indication). It contains selumetinib sulfate as the active substance and it is given orally (capsule formulation of the hydrogen sulfate salt [selumetinib hydrogen sulfate Hyd-Sulfate] presented in 10 mg and 25 mg strengths).

Further information about the evaluation of selumetinib’s benefits can be found in selumetinib’s SwissPAR, including in its plain-language summary, available on the Swissmedic website**.**

1.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of selumetinib, together with measures to minimise such risks and the proposed studies for learning more about selumetinib'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 Patient Information Leaflet and Information for 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 selumetinib is not yet available, it is listed under 'missing information' below.

1.2.1 List of important risks and missing information

Important risks of selumetinib are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 selumetinib. 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).

Table 1.2-1 List of important risks and missing information

Important identified risks	Left ventricular ejection fraction reduction
Important potential risks	Physeal dysplasia Ocular toxicity Myopathy Hepatotoxicity Choking on the capsule
Missing Information	Long term exposure (including long term safety data on developmental toxicity in children)

1.2.2 Summary of important risks

Table 1.2-2 Important identified risks

Left ventricular ejection fraction reduction	
Evidence for linking the risk to the medicine	In both paediatric and adult populations taking selumetinib, reversible, asymptomatic reductions in LVEF have been recorded in a small number of patients. Left ventricular ejection fraction reduction (corresponding MedDRA PT: ejection fraction decreased) is included as an ADR in Section ”Undesirable Effects” of the Information for Healthcare Professionals for selumetinib.
Risk factors and risk groups	In paediatric patients with NF1, no specific risk factors have been identified to predict which patients might develop LVEF reductions. It could be anticipated that patients with pre-existing impaired left ventricular function may be at greater risk of developing LVEF reductions.
Risk minimisation measures	Routine risk minimisation measures for LVEF reduction (corresponding MedDRA PT: ejection fraction decreased): Information for Healthcare Professionals Sections “Dosage/Administration”, “Warnings and Precautions”, “Undesirable Effects”. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities for LVEF reduction: Post-authorisation safety study to characterise the long-term safety profile of selumetinib among paediatric patients with NF1 related PN in real world clinical practice. See Section 2 of this summary for an overview of the post authorisation development plan.

Table 1.2-3 Important potential risks

Physeal dysplasia	
Evidence for linking the risk to the medicine	Mechanistically there is a plausible rationale for anticipating an effect on bone, and physeal hypertrophy is described pre clinically for the MEK inhibitor trametinib. Preclinical evidence of physeal dysplasia following selumetinib administration has been identified in the rat (however, not in the mouse or monkey).
Risk factors and risk groups	Physeal dysplasia can occur whilst the growth plate remains open and this reflects the period of risk for paediatric patients. In humans the growth plate is open from birth and closure occurs at or prior to adulthood. Limb shortening (dwarfism) and joint pain are common clinical manifestations associated with physeal dysplasia.
Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post-authorisation safety study to characterise the long-term safety profile of selumetinib among paediatric patients with NF1 related PN in real world clinical practice. See Section 2 of this summary for an overview of the post authorisation development plan.

Table 1.2-3 Important potential risks

Ocular toxicity	
Evidence for linking the risk to the medicine	Ocular toxicity is a class effect for MEK inhibitors. Although blurred vision has been reported as a common event and is considered an ADR for selumetinib in the paediatric population, no serious ocular toxicities such as retinal vein occlusion, central serous retinopathy and retinal pigment epithelial detachment were reported for any patient in SPRINT. However, a single event of RPED was reported in a paediatric patient receiving selumetinib monotherapy for pilocytic astrocytoma involving the optic pathway in an externally sponsored paediatric study. In adult patients with advanced cancer, few isolated episodes of ocular toxicity were reported (RVO in 1 patient; chorioretinopathy and RPED in 2 patients each) and for this reason, ocular toxicity is considered to be an important potential risk for the paediatric NF1 population.
Risk factors and risk groups	No case reports of serious ocular toxicities such as retinal vein occlusion, central serous retinopathy and retinal pigment epithelial detachment have been identified in paediatric patients given selumetinib in the SPRINT studies and therefore risk factors have not been identified. Patients were excluded from taking part in the SPRINT studies if they had a range of ophthalmologic conditions that could predispose to ocular toxicities and so it cannot be confirmed if clinically predisposing factors for ocular toxicities result in an increased risk for developing RVO, RPED or chorioretinopathy on treatment with selumetinib. In a retrospective analysis of patients who experienced RVO in a Phase I study with an investigational MEK inhibitor, it was noted that predisposing factors for retinopathy (hypertension, diabetes, hypercholesterolaemia and glaucoma) were noted in all patients with RVO; however, these predisposing factors were not confirmed prospectively. In accordance to the Royal College of Ophthalmologists RVO guidelines 2015, conditions that cause systemic inflammation or hyperviscosity increase the risk of VTE and can rarely which can, rarely, be associated with a retinal vein occlusion.
Risk minimisation measures	Routine risk minimisation measures: Information for Healthcare Professionals Sections “Dosage/Administration”, “Warnings and Precautions”,. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post-authorisation safety study to characterise the long-term safety profile of selumetinib among paediatric patients with NF1 related PN in real world clinical practice. See Section 2 of this summary for an overview of the post-authorisation development plan.
Myopathy	
Evidence for linking the risk to the medicine	CPK increased is listed as a common event in Section ”Undesirable Effects” of selumetinib Information for Healthcare Professionals; however, in the paediatric pool, there was no evidence of muscular AEs such as myalgia or muscular weakness in association with selumetinib-induced CPK increase, with the exception of a small number of reports where other more plausible

Table 1.2-3 Important potential risks

	etiologies were identified. Furthermore, no events of hypocalcaemia were associated with events suggestive of muscle injury. Elevation of CPK, which may accompany and/or herald the onset of myopathy (including the serious outcome of rhabdomyolysis), is a very common event for MEK inhibitors and is considered a class effect although it is usually not associated with any symptoms or clinical consequences. Dropped head syndrome is a rare but distinctive myopathy that has been described with MEK inhibition and is fully reversible with discontinuation of the MEK inhibitor (Chen et al 2012). Rhabdomyolysis is listed as an uncommon ADR for trametinib monotherapy in the Information for Healthcare Professionals.
Risk factors and risk groups	Since no cases of myopathy that appear drug-related have been reported in the paediatric population it is not possible to identify potential risk factors for this occurrence on selumetinib. For drug-induced myopathy in general, many publications report on risk factors for statin induced myopathy which included genetic factors as well as advanced age, small body mass index, female gender, metabolic co-morbidities, and vigorous physical exercise. Age is a particularly strong contributor; however, it is unknown if these risk factors apply to MEK inhibitors and paediatric patients (Feng 2012).
Risk minimisation measures	Routine risk minimisation measures for myopathy: None. Routine risk minimisation measures for increases in CPK: Information for Healthcare Professionals Section ”Undesirable Effects”. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post-authorisation safety study to characterise the long-term safety profile of selumetinib among paediatric patients with NF1 related PN in real world clinical practice. See Section 2 of this summary for an overview of the post-authorisation development plan.
Hepatotoxicity	
Evidence for linking the risk to the medicine	Elevations of ALT and AST have been reported in paediatric patients and are included with a frequency of very common in Section ”Undesirable Effects” of the selumetinib Information for Healthcare Professionals. Transaminase elevations are also very commonly reported events for approved MEK inhibitors. Since the mechanism is poorly understood, it cannot be ruled out that elevated transaminases may be a prelude to more serious hepatoxicity such as liver injury.
Risk factors and risk groups	Since no reports of serious hepatotoxicity such as liver injury (predictable or idiosyncratic) have been received for selumetinib in the paediatric population it’s not possible to state what risk factors or risk groups can be identified. However, it is common for paediatric patients with NF1 to be administered medications such paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) for management of tumour pain that could place them at a higher propensity to develop hepatic events. In the literature, there are a number of risk factors for developing drug induced liver injury (DILI) that have been reported for other drugs including older age, female gender, comorbid disease and concomitant medications as well as genetic polymorphism of enzymes and

Table 1.2-3 Important potential risks

	proteins linked to the metabolism of drugs and overall dose of drug (Harshad Devarbhavi 2012).
Risk minimisation measures	Routine risk minimisation measures for hepatoxicity: None. Routine risk minimisation measures for elevations in ALT and AST: Information for Healthcare Professionals Sections ”Warnings and Precautions”, “Undesirable Effects”. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post-authorisation safety study to characterise the long-term safety profile of selumetinib among paediatric patients with NF1 related PN in real world clinical practice. See Section 2 of this summary for an overview of the post-authorisation development plan.
Choking on the capsule	
Evidence for linking the risk to the medicine	Patients of any age may experience difficulty taking any type of medication for psychological as well as anatomical and developmental reasons. In SPRINT, none of the patients reported an adverse event relating to swallowing or choking, nor were there any diary entries to indicate that choking had been as a result of, or prevented them from taking, their medication.
Risk factors and risk groups	Since no reports that are suggestive of choking have been received for selumetinib in the paediatric population it is not possible to state what risk factors or risk groups can be identified. There is a theoretical risk that patients with large PN in the head and neck region who experience dysphagia may be at increased risk of choking on the capsule. In general, risks relating to choking and adverse swallow events have been shown to be influenced by a child’s demeanour prior to, and at the time of, taking a medicine. In a study of 1677 children (aged 1 year to 4 years and 11 months given albendazole tablets as part of a WHO global programme to eliminate soil-transmitted helminthiasis) by Kernell et al 2018, three key risk factors were identified for choking: non-content child demeanour before administration, child struggling during administration, and the addition of water. The authors went on to demonstrate in a multivariate analysis that child demeanour was the only risk factor that was significantly associated with choking amongst children aged 1 year to 4 years and 11 months.
Risk minimisation measures	Routine risk minimisation measures for choking on the capsule: Information for Healthcare Professionals Section ”Warnings and Precautions”. Routine risk minimisation measures for difficulties with swallowing selumetinib capsules: Information for Healthcare Professionals Section “Dosage/Administration”. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	None.

AE Adverse event; ADR Adverse drug reaction; ALT Alanine aminotransferase; AST Aspartate aminotransferase; CPK Creatine phosphokinase; CSR Central Serious Retinopathy (chorioretinopathy); DILI Drug induced liver injury; EU European Union; LVEF Left ventricular ejection fraction; LVSD Left ventricular systolic dysfunction; MEK Mitogen-activated protein kinase kinase; NF1 Neurofibromatosis type 1; NSAID non-steroidal anti-inflammatory drug; PN Plexiform neurofibromas; RPED Retinal Pigment Epithelial Detachment; RVO Retinal vein occlusion; VTE Venous thromboembolism.

Table 1.2-4 Missing information: Long term exposure (including long term safety data on developmental toxicity in children)

Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post-authorisation safety study to characterise the long-term safety profile of selumetinib among paediatric patients with NF1 related PN in real world clinical practice. See Section 2 of this summary for an overview of the post-authorisation development plan.

EU European Union; NF1 Neurofibromatosis type 1; PN Plexiform neurofibromas.

2. POST-AUTHORISATION DEVELOPMENT PLAN

2.1 Studies which are conditions of the marketing authorisation

Study: Post-authorisation safety study (D1346R00004) to characterise the long-term safety profile of selumetinib among paediatric patients with NF1 related PN in real world clinical practice.
Purpose of the study: To characterise the long-term safety profile of selumetinib among paediatric patients with NF1 related PN in real world clinical practice.

2.2 Other studies in post-authorisation development plan

There are no studies required for selumetinib.