NOVARTIS

Regulatory Affairs

Scemblix®

Summary of the Local Safety Risk Management Plan

Active substance(s) (INN or common name):	*Asciminib*
Product(s) concerned (brand name(s)):	*Scemblix*
Document status:	*Final*
Version number of the RMP Public Summary:	*2.1*
Date of final sign off of the RMP Public Summary	*08-Aug-2024*

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

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Summary of the risk management plan for Scemblix

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

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

I. The medicine and what it is used for

Scemblix is authorized for the treatment of newly diagnosed or previously treated adult patients with Ph+ CML-CP. Scemblix is also authorized for the treatment of adult patients with Ph+ CML-CP previously treated with two or more TKIs and for the treatment of adult patients with Ph+ CML-CP harboring the T315I mutation. It contains asciminib hydrochloride, which is the salt-form of asciminib as the active substance, and it is given orally – in the FCT form and at 20-mg, 40-mg, and 100-mg strengths.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Scemblix, together with measures to minimize such risks and the proposed studies for learning more about Scemblix's risks, are outlined below.

- Specific information, such as warnings, precautions, and advice on correct use, in the CDS addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized 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 (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, 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 Scemblix is not yet available, it is listed under 'missing information' below.

II.A: List of important risks and missing information

Important risks of Scemblix are risks that need special risk management activities to further investigate or minimize 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 Scemblix. 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 (e.g., on the long-term use of the medicine).

Table 1 | List of important risks and missing information

Important identified risks	Acute pancreatitis (including isolated pancreatic enzyme elevations)
	Myelosuppression
	QTc prolongation
Important potential risks	Hepatotoxicity
	Hepatitis B virus infection reactivation
	Reproductive toxicity
Missing information	Long-term safety
	Use in patients with renal impairment
	Use in patients with hepatic impairment

II B: Summary of important risks

Important identified risks

Table 2 | Important identified risk – Acute pancreatitis (including isolated pancreatic enzyme elevations)

Evidence for linking the risk to the medicine	There are very common events of laboratory abnormalities (increased lipase and amylase) and common clinical events (pancreatitis and pancreatitis acute) reported in clinical development program.
Risk factors and risk groups	History of amylase and lipase elevation and pancreatitis.
Risk minimization measures	**Routine risk minimization measures** • CDS Section 4 - Dosage regimen and administration • CDS Section 6 - Warnings and precautions • CDS Section 7 - ADR

	• CDS Section 13 - Non-clinical safety data Legal status: Medical prescription only product **Additional risk minimization measures** None
Additional pharmacovigilance activities	Study CABL001A2301 Study CABL001A2302 Study CABL001A2001B See Section II.C of this summary for an overview of the post-authorization development plan.

Table 3 | Important identified risk – Myelosuppression

Evidence for linking the risk to the medicine	The frequency of the reported events (including grade 3/4 events) was very common; however, these events were manageable with dose modifications and standard clinical practice guidelines. Thrombocytopenia has potential for hemorrhagic events, and neutropenia is a strong risk factor for infections.
Risk factors and risk groups	Low blood cell counts (cytopenia) at the baseline increases the chances of further decrease in these cell counts following asciminib administration.
Risk minimization measures	**Routine risk minimization measures** • CDS Section 4 - Dosage regimen and administration • CDS Section 6 - Warnings and precautions • CDS Section 7 - ADR • CDS Section 13 - Non-clinical safety data Legal status: Medical prescription only product **Additional risk minimization measures** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study CABL001A2301 Study CABL001A2302 Study CABL001A2001B See Section II.C of this summary for an overview of the post-authorization development plan.

Table 4 | Important identified risk – QTc prolongation

Evidence for linking the risk to the medicine	QT prolongation without accompanying arrhythmia has been reported in clinical trials. Dose dependent increase in the QTc interval has also been observed in the concentration dependent analysis.

Risk factors and risk groups	Patients with congenital long QT syndrome, or co-administration of drugs known to cause Torsades de Pointes, or electrolyte abnormalities (hypokalemia/ hypomagnesemia).
Risk minimization measures	**Routine risk minimization measures** • CDS Section 4 - Dosage regimen and administration • CDS Section 6 - Warnings and precautions • CDS Section 7 - ADR • CDS Section 8 - Interactions • CDS Section 11 - Clinical pharmacology • CDS Section 13 - Non-clinical safety data Legal status: Medical prescription only product **Additional risk minimization measures** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study CABL001A2301 Study CABL001A2302 Study CABL001A2001B See Section II.C of this summary for an overview of the post-authorization development plan.

Important potential risks

Table 5 | Important potential risk – Hepatotoxicity

Evidence for linking the risk to the medicine	Current evidence is based on nonclinical studies and the clinical studies. Histopathologically, hepatic changes were characterized by centrilobular hepatocyte hypertrophy, slight bile duct hyperplasia and increased individual hepatocyte necrosis in rats and reversible diffuse hepatocellular hypertrophy in monkeys. These liver changes in rat occurred at exposure equivalent to the human dose of 40 mg b.i.d. or 80 mg q.d. dose. In clinical studies, the majority of the reported events were mild to moderate, reversible hepatic enzyme or bilirubin level abnormalities, with no evidence of irreversible liver damage with the use of asciminib monotherapy for treatment of CML-CP/AP. There was no case related to Hy's law, and none of the reported events were fatal or life-threatening.
Risk factors and risk groups	Unknown.
Risk minimization measures	**Routine risk minimization measures** CDS Section 4 - Dosage regimen and administration CDS Section 7 - ADR CDS Section 11 - Clinical pharmacology

	CDS Section 13 - Non-clinical safety data
	Legal status: Medical prescription only product
	Additional risk minimization measures
	None
Additional pharmacovigilance activities	Additional pharmacovigilance activities:
	Study CABL001A2301
	Study CABL001A2302
	Study CABL001A2001B
	See Section II.C of this summary for an overview of the post-authorization development plan.

Table 6 | Important potential risk – Hepatitis B virus infection reactivation

Evidence for linking the risk to the medicine	Reactivation of HBV has occurred in patients who are chronic carriers of this virus following administration of other BCR::ABL1 TKIs. The reactivation of HBV infection was evaluated as class risk. Nonclinical evidence is not available, and the clinical evidence is limited due to exclusion of such patients from the clinical development program.
Risk factors and risk groups	None identified for HBV infection reactivation.
Risk minimization measures	**Routine risk minimization measures** • CDS Section 4 - Dosage regimen and administration • CDS Section 6 - Warnings and precautions Legal status: Medical prescription only product **Additional risk minimization measures** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study CABL001A2302 Study CABL001A2001B See Section II.C of this summary for an overview of the post-authorization development plan.

Table 7 | Important potential risk – Reproductive toxicity

Evidence for linking the risk to the medicine	Current evidence is based on nonclinical studies and clinical studies. Cardiac malformations along with increased visceral and skeletal variants have been observed in rats. Also, increased incidence of resorptions (embryofetal mortality) and a low incidence of cardiac malformations (dysmorphogenesis) have been observed in rabbits. Reproductive toxicity has not been observed with asciminib with the exclusion of pregnant women and the requirement to use effective contraception methods. Males taking asciminib should not require contraception.
Risk factors and risk groups	Female patients of child-bearing potential receiving asciminib.

Risk minimization measures	**Routine risk minimization measures** • CDS Section 6 - Warnings and precautions • CDS Section 9 - Pregnancy, lactation, females and males of reproductive potential Legal status: Medical prescription only product **Additional risk minimization measures** None

Table 8 | Missing information – Long-term safety

Risk minimization measures	**Routine risk minimization measures** CDS: None **Additional risk minimization measures** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study CABL001A2301 Study CABL001A2302 Study CABL001A2001B See Section II.C of this summary for an overview of the post-authorization development plan.

Table 9 | Missing information – Use in patients with renal impairment

Risk minimization measures	**Routine risk minimization measures** • CDS Section 4 - Dosage regimen and administration • CDS Section 11 - where PK of Scemblix in patients with renal impairment is described **Additional risk minimization measures** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study CABL001A2302 See Section II.C of this summary for an overview of the post-authorization development plan.

Table 10 | Missing information – Use in patients with hepatic impairment

Risk minimization measures	**Routine risk minimization measures** • CDS Section 4 - Dosage regimen and administration • CDS Section 11 - where PK of Scemblix in patients with hepatic impairment is described

	• CDS Section 13 - where hepatic non-clinical findings are described
	Additional risk minimization measures
	None
Additional pharmacovigilance activities	Additional pharmacovigilance activities:
	Study CABL001A2302
	See Section II.C of this summary for an overview of the post-authorization development plan.

II C: Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the Marketing Authorization or specific obligation of Scemblix.

II.C.2. Other studies in post-authorization development plan

Table 11 | Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
Study CABL001A2301: Study of efficacy of CML-CP patients treated with asciminib versus bosutinib, previously treated with 2 or more TKIs.	There remains an unmet need for new compounds in patients with CML who have failed at least 2 prior TKIs. Current practice suggests that a 2G-TKI will have been used for first line therapy for about one half of patients with CML, meaning that most patients who have failed at least two prior TKIs will have failed at least 1 if not 2 2G-TKIs (such as dasatinib and/or nilotinib). Potentially, such patients may also have failed bosutinib and/or ponatinib. Patients having failed at least 2 TKIs may have limited sensitivity to the remaining available agents and, thus, there exists a need for new safe and effective therapy. In addition, mutations will have developed in 21 to 33% of patients that prevent the use of specific TKIs, increasing the need for a better and alternative compound. Omacetaxine, a chemotherapeutic agent, is available for patients who have failed at least 2 prior TKIs under these conditions but only in the US and Canada. This agent is not available for most patients globally, where a bigger unmet medical need is present. Thus, there remains an unmet need for patients with CML who have failed at least 2 prior TKIs despite the existence of multiple agents. Key study objectives include: • To compare the MMR rate at 24 weeks of asciminib vs. bosutinib

	• To compare the safety and tolerability profile of asciminib vs. bosutinib.
Study CABL001A2302: Asciminib treatment optimization in ≥ 3rd line CML-CP	The purpose of the study is to optimize the treatment of asciminib in patients with CML-CP previously treated with 2 or more TKIs. Patients for this study will be identified based on warning criteria and resistance definition following ELN 2020 recommendations. In addition, the study will investigate the use of 2 different posology. For this, patients will be randomized to either receive asciminib 40 mg b.i.d. or of 80 mg q.d. In patients not achieving MMR at 48 weeks or losing the response after the week 48 assessment up to Week 108, asciminib dose may be escalated to 200 mg q.d. if in the investigator's opinion the patient may benefit from the escalation. In addition, there must not be any grade 3 or 4 toxicity while on therapy, or persistent grade 2 toxicity, possibly related to asciminib and unresponsive to optimal management. Key study objectives include: • To estimate the MMR of all the patients at week 48 with CML-CP following 2 or more prior TKI treatments and with no evidence of MMR at baseline.
Study CABL001A2001B: Study to assess long-term safety in patients who have completed a Novartis-sponsored asciminib study and are judged by the investigator to benefit from continued treatment.	The purpose of this study is to assess long term safety of asciminib and to provide continued treatment to participants who have previously participated in an asciminib Novartis sponsored study and who, in the opinion of the investigator, would benefit from continuing treatment, to ensure treatment continuity for participants as in their parent study, or from switching to asciminib, but are unable to access treatment outside of a clinical study. Key study objective includes: • To assess long term safety data and provide continued access to the study treatment received in the parent study protocol.