NOVARTIS

Regulatory Affairs

Scemblix®

Summary of the EU 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: *(aligned with corresponding RMP version)*	*1.0*
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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 (asciminib)

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).

Scemblix's SmPC and its PL give essential information to healthcare professionals and patients on how Scemblix should be used.

This summary of the RMP for Scemblix 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 European Public Assessment Report (EPAR).

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

Asciminib is indicated for the treatment of adult patients with Ph+ CML-CP previously treated with 2 or more TKIs.

Scemblix contains asciminib hydrochloride as the active substance and it is given orally.

Further information about the evaluation of Scemblix's benefits can be found in Scemblix's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage: link to the EPAR summary landing page.

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.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PLand 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 as to ensurethat the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with orwithout 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 andregularly 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 13-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	• Pancreatic toxicity • Myelosuppression • QTc prolongation
Important potential risks	• Hepatotoxicity • Hepatitis B virus infection reactivation • Reproductive toxicity
Missing information	• Long-term safety • Use in pediatric population

II B: Summary of important risks

13.2.1 Important identified risks

Table 13-2 Important identified risk – Pancreatic toxicity

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. Adverse events of pancreatitis/ pancreatitis acute were reported in 9 patients (2.6%) in asciminib monotherapy (all doses) pool, of which 3 patients were taking asciminib 40 b.i.d. for treatment of CML-CP/AP (all reported from Study X2101). Additionally, the events, lipase increased and amylase increased were reported in 65 patients (18.3%) and 38 patients (10.7%); 8 patients (5.1%) and 9 patients (5.8%), in Safety Pool (comprising all the patients taking asciminib monotherapy for CML- CP/AP) and the patients taking in Study A2301, respectively.
Risk factors and risk groups	History of amylase and lipase elevation and pancreatitis.
Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.2 where posology and method of administration are described.

	SmPC Section 4.4 where description of the risk along with monitoring and treatment guidance are added. SmPC Section 4.8 where the adverse reactions related to pancreatic toxicity are listed. PL Section 2 where precautions, monitoring and treatment are described. PL Section 4 where possible side effects of asciminib are described. Legal status: Medical prescription only product **Additional risk minimization measures** None

Table 13-4 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** SmPC Section 4.2 where posology and method of administration are described.
	SmPC Section 4.4 where description of the risk along with monitoring and treatment guidance are added. SmPC Section 4.5 where precaution while administrating asciminib with CYP3A4 substrates is added. SmPC Section 4.8 where adverse reactions related to QTc prolongation are listed. SmPC Section 5.1 where effect of asciminib in cardiac electrophysiology is described. PL Section 2 where precautions, monitoring and treatment are described. PL Section 4 where possible side effects of asciminib are described. Legal status: Medical prescription only product **Additional risk minimization measures** None

Important potential risks

Table 13-5 Important potential risk – Hepatotoxicity

Evidence for linking the risk to the medicine	Current evidence is based on non-clinical 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** SmPC Section 4.2 where posology and method of administration are described. SmPC Section 4.8 where the adverse reactions related to hepatotoxicity are listed. SmPC Section 5.2 where PK of asciminib in patients with hepatic impairment is described. PL Section 4 where possible side effects of asciminib are described. Legal status: Medical prescription only product **Additional risk minimization measures** None

Table 13-6 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-ABL TKIs. The reactivation of HBV infection was evaluated as class risk. The non-clinical evidence is not available, and the clinical evidence is limiteddue 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** SmPC Section 4.4 where description of the risk along with monitoring and treatment guidance are added. PL Section 2 where precautions, monitoring and treatment are described. Legal status: Medical prescription only product **Additional risk minimization measures** None

Table 13-7 Important potential risk – Reproductive toxicity

Evidence for linking the risk to the medicine	Current evidence is based on non-clinical studies and the clinical studies. Cardiac malformations along with increased visceral and skeletal variants have been observed in rats. Also, increased incidence of resorptions (embryo-fetal 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** SmPC Section 4.6 where effects of asciminib in fertility, pregnancy and lactation are described. PL Section 2 where precautions, monitoring and treatment are described. Legal status: Medical prescription only product **Additional risk minimization measures** None

Table 13-8 Missing information – Long-term safety

Risk minimization measures	**Routine risk minimization measures** SmPC: None PL: None **Additional risk minimization measures** None

Table 13-9 Missing information – Use in pediatric population

Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.2 SmPC Section 5.1 PL Section 2 There are no data from the use of asciminib in pediatric population. **Additional risk minimization measures** None

II C: Post-authorization development planII.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

There are no studies required for Scemblix.