Summary of the risk management plan for Scemblix® (asciminib)

This is a summary of the risk management plan (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 summary of product characteristics (SmPC) and its package leaflet (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

Scemblix is indicated for the treatment of adult patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase (CP) previously treated with 2 or more TKIs.

Scemblix contains asciminib hydrochloride, a salt-form of asciminib which is 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: https://www.ema.europa.eu/en/medicines/human/EPAR/scemblix.

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 PL and SmPC 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 as 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

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. 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 mg b.i.d. for treatment of CML-CP/ accelerated phase (AP) (all reported from Study CABL001X2101). 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 CABL001A2301, 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 acute pancreatitis (including isolated pancreatic enzyme elevations) 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
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CABL001X2101 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** 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 myelosuppression 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
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CABL001X2101 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** 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 medicinal products with known risk of torsades de pointes 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
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CABL001X2101 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** 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 pharmacokinetics (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
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CABL001X2101 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 hepatitis B virus (HBV) has occurred in patients who are chronic carriers of this virus following administration of other BCR::ABL tyrosine kinase inhibitors (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** 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
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** 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 8 Missing information – long-term safety

Risk minimization measures	**Routine risk minimization measures** SmPC: None PL: None **Additional risk minimization measures** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study CABL001X2101 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** SmPC Section 4.2 where posology and method of administration are described. SmPC Section 5.2 where PK of asciminib 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** SmPC Section 4.2 where posology and method of administration are described. SmPC Section 5.2 where PK of asciminib in patients with hepatic 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.

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 CABL001X2101: Asciminib dose escalation study	This study is undertaken to provide further information on safety and tolerability in patients with Ph+ CML and Ph+ acute lymphoblastic leukemia. Key study objectives include: • To determine the maximum tolerated dose and/or recommended dose for expansion of asciminib as single agent and in combination with other TKIs (imatinib, nilotinib and dasatinib). • Characterize the safety and tolerability of asciminib as single agent and in combination with other TKIs (imatinib or nilotinib or dasatinib).
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 second generation (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 2 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 United States 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 major molecular response (MMR) rate at 24 weeks of asciminib versus bosutinib. • To compare the safety and tolerability profile of asciminib versus bosutinib.

Study short name	Rationale and study objectives
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 European LeukemiaNet 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 objective includes: • 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.