Summary of the risk management plan for Rydapt (midostaurin)

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

Midostaurin summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how midostaurin should be used.

This summary of the RMP for midostaurin 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 midostaurin RMP.

I. The medicine and what it is used for

Rydapt® contains midostaurin as the active substance, and it is authorised for use in the following indications:

- In combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy and for patients in complete response followed by Rydapt® single agent maintenance therapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive;
- As monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL).

Rydapt® is available as 25 mg soft capsules, and the dosing information is provided below.

For AML: The recommended dose of Rydapt® is 50 mg orally twice daily. Rydapt® is dosed on days 8-21 of induction and consolidation chemotherapy cycles, and then for patients in complete response every day as single agent maintenance therapy until relapse for up to 12 cycles of 28 days each. In patients receiving a haematopoietic stem cell transplant (SCT), Rydapt® should be discontinued 48 hours prior to the conditioning regimen for SCT.

For ASM, SM-AHN and MCL: The recommended starting dose of Rydapt® is 100 mg orally twice daily. Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.

Additional details on the approved indications are available in the SmPC.

Further information about the evaluation of midostaurin's benefits can be found in midostaurin'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/rydapt.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of midostaurin, together with measures to minimise such risks and the proposed studies for learning more about midostaurin 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 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;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. 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, including PSUR, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A: List of important risks and missing information

Important risks of midostaurin 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 midostaurin. 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	None
Important potential risks	• Cardiac dysfunction • Effect of genomic polymorphisms of CYP3A4/CYP3A5 on pharmacokinetics of midostaurin and potential risk of treatment-related toxicity
Missing information	None

II B: Summary of important risks

Table 2 Important potential risk: Cardiac dysfunction

Evidence for linking the risk to the medicine	Current evidence is based on clinical data, literature, and post marketing.
Risk factors and risk groups	The major risk factors for congestive heart failure are total blood cholesterol elevation, hypertension, abnormal lipid profiles, abdominal obesity, alcohol overconsumption, cigarette use, and diabetes. In AML patients, chemotherapy with daunorubicin is a known risk factor for cardiac dysfunction.
Risk minimisation measures	**Routine risk minimisation measures** SmPC Section 4.4 PL Section 2 SmPC Section with specific clinical measure: Section 4.4 **Additional risk minimisation measures** None

Table 3 Important potential risk: Effect of genomic polymorphisms of CYP3A4/CYP3A5 on pharmacokinetics of midostaurin and potential risk of treatment-related toxicity

Evidence for linking the risk to the medicine	Current evidence is based on published literature.
Risk factors and risk groups	Patients with genomic polymorphism of CYP3A4/CYP3A5 and potentially having a reduced CYP3A4/CYP3A5 metabolism activity requiring midostaurin therapy.
Risk minimisation measures	**Routine risk minimisation measures** None SmPC Section with specific clinical measure: None **Additional risk minimisation measures** None
Additional pharmacovigilance activities	Study CPKC412E2301 See section II.C of this summary for an overview of the post-authorisation development plan.

II C: Post-authorisation development plan

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

Table 4 Studies which are conditions of the marketing authorisation

Study short name	Purpose of the study:
Study CPKC412ADE02T	To evaluate the impact of midostaurin given in combination with intensive induction, consolidation including allogeneic hematopoietic stem cell transplantation and single agent maintenance therapy on event-free survival (EFS) in adult patients with AML exhibiting a FLT3-ITD.
Study CPKC412A2408	To further assess the safety of midostaurin in induction, consolidation and maintenance therapy, including, the "7+3" regimen, higher dose of Daunorubicin (60-90mg/m2/day), the substitution of Daunorubicin by Idarubicin and lower dose of Cytarabine (100-200 mg/m2/day) and also allowing the "5+2" reduced dose regimen.
Study CPKC412E2301	To determine if the addition of midostaurin to standard induction and consolidation therapy, followed by single agent maintenance therapy improves EFS not censored for HSCT in patients with newly diagnosed FLT3-WT AML.

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

Table 5 Other studies in the post-authorisation development plan

Study short name	Rationale and study objectives
Study CPKC412E2301	To determine the impact of CYP3A4 and CYP3A5 polymorphisms on the exposure of midostaurin, and on treatment-related toxicity.