Summary of risk management plan for glasdegib (PF-04449913)

This is a summary of the Risk Management Plan (RMP) for glasdegib. The RMP details important risks of glasdegib, how these risks can be minimised, and how more information will be obtained about glasdegib's risks. Routine risk assessment and risk minimisation are considered sufficient to address glasdegib's important risks.

Glasdegib's proposed Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to Healthcare Professionals (HCPs) and patients on how glasdegib should be used.

This summary of the RMP for glasdegib 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 glasdegib's RMP.

I. The Medicine and What It Is Used For

Glasdegib is proposed to be used in combination with Low-Dose Cytarabine (LDAC) for the treatment of newly-diagnosed de novo or secondary Acute Myeloid Leukaemia (AML) in adult patients who are not candidates for standard induction chemotherapy; see the proposed glasdegib SmPC for the full indication. Glasdegib is proposed to be taken orally (PO) once daily (QD) with or without food; the proposed starting dose of glasdegib is 100 mg PO QD. Glasdegib oral, film-coated tablets are proposed to be available containing either 25 mg or 100 mg of glasdegib.

Further information about the evaluation of glasdegib's benefits can be found in glasdegib'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/daurismo

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of glasdegib, together with measures to minimise such 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 PL and SmPC addressed to patients and HCPs;
- 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 public (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 Events (AEs) is collected continuously and regularly analysed 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 a medicinal product are risks that need special risk management activities in order to further investigate or minimise the risk so that the medicinal product can be safely taken. 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 a medicinal product. Potential risks are concerns for which an association with the use of a medicinal product is possible based on available data, but this association has not been established and needs further evaluation.

Missing information refers to information on the safety of a medicinal product that is currently missing and needs to be collected (e.g., the long-term use of the medicine).

Table 1. List of Important Risks and Missing Information of Glasdegib

Important identified risks	None
Important potential risks	Reproductive and Developmental Toxicity (injury to unborn baby/ decreased growth and ability to have children)
	Renal Toxicity (kidney injury)
Missing information	None

II.B. Summary of Important Risks

Table 2. Important Potential Risks of Glasdegib

Important Potential Risk: Reproductive and Developmental Toxicity (injury to unborn baby/ decreased growth and ability to have children)	
Evidence for linking the risk to the medicine:	Glasdegib studies in animals and other drugs in this class (Smoothened [SMO] inhibitor Hedgehog [Hh] pathway inhibitors) Studies in animals treated with glasdegib and other drugs in this class have shown injuries to their unborn; however, there is currently no data on foetal exposure in humans. Glasdegib may cause foetal harm when administered to a pregnant woman.
Risk factors and risk groups:	Risk factors and risk groups include women of childbearing potential, pregnant women, male patients with female partners of childbearing potential, lactating women, and paediatric patients (age: <18 years).
Risk minimisation measures:	<u>Routine risk minimisation measures:</u> SmPC Sections 4.4 (boxed warning), 4.6, 5.1, and 5.3; PL Sections 2 and 4 <u>Additional risk minimisation measures:</u>

Table 2. Important Potential Risks of Glasdegib

	Patient Alert Card for male patients
Additional pharmacovigilance activities:	None proposed
Important Potential Risk: Renal Toxicity (kidney injury)	
Evidence for linking the risk to the medicine:	Glasdegib animal and human studies Studies in animals treated with glasdegib have shown kidney injury. Kidney adverse events have been observed in patients treated with glasdegib, often due to other non-kidney factors or as a result of or made worse by other glasdegib effects (e.g., diarrhoea, vomiting, decreased oral intake); however, an imbalance in evidence of kidney injury (creatinine elevation) was not seen in patients with acute myeloid leukaemia who received glasdegib + low-dose cytarabine (a medicine used to treat cancer) compared to patients with acute myeloid leukaemia who received low-dose cytarabine alone.
Risk factors and risk groups:	Patients with pre-existing or past history of kidney disease and patients receiving potentially kidney-injuring agents may be at a greater risk of developing kidney injury with glasdegib treatment. In addition, older patients, patients with diabetes, patients who smoke, and those who are inactive are at a greater risk of developing kidney dysfunction or of having a more rapid progression of kidney dysfunction.
Risk minimisation measures:	<u>Routine risk minimisation measures:</u> SmPC Sections 4.2, 4.4, and 5.3 <u>Additional risk minimisation measures:</u> None proposed
Additional pharmacovigilance activities:	None proposed

SmPC = Summary of Product Characteristics; PL = Package Leaflet

II.C. Post-Authorisation Development Plan

II.C.1. Studies that are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or that are specific obligations of glasdegib.

II.C.2. Other Studies in Post-Authorisation Development Plan

There are no studies required for glasdegib.