Summary of risk management plan for Mylotarg (GO)

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

Mylotarg's SmPC and its PL give essential information to HCPs and patients on how Mylotarg should be used.

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

I. The Medicine and What It Is Used For

Mylotarg is indicated for combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of patients aged 15 years and older with previously untreated, *de novo* CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia (APL).

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

Important risks of Mylotarg, together with measures to minimise such risks for learning more about Mylotarg's 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 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 patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

If important information that may affect the safe use of Mylotarg is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Mylotarg 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 Mylotarg. 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	Severe (Grade ≥3) and/or serious hepatotoxicity including all VOD/SOS Myelosuppression • Severe (Grade ≥3) and/or serious infection • Haemorrhage Tumour lysis syndrome Infusion-related reactions (including Anaphylaxis) from start of infusion to within 24 hours of end of infusion
Important potential risks	Renal toxicity Reproductive and developmental toxicity (post exposure during pregnancy, including breastfeeding) Neurotoxicity Second primary malignancy Off label use in paediatric patients
Missing information	Use in patients with severe hepatic impairment Use in patients with severe renal impairment

Abbreviations: SOS: Sinusoidal Obstruction Syndrome; VOD: Venoocclusive Disease

II.B. Summary of Important Risks

Table 2. Summary of Important Risks and Missing Information

Important Identified Risk: Severe (Grade ≥3) and/or Serious Hepatotoxicity Including All VOD/SOS	
Evidence for linking the risk to the medicine	Severe and/or serious hepatotoxicity, including severe or fatal hepatic VOD/SOS, has been reported in GO clinical trials and in the postmarketing setting.
Risk factors and risk groups	Based on an analysis across trials, the risk of VOD was higher in adult patients who received higher doses of GO as monotherapy, in patients with moderate or severe hepatic impairment prior to receiving GO, in patients treated with GO after HSCT, and in patients who underwent HSCT after treatment with GO.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, and 4.8; PL sections 2 and 4 Additional risk minimisation measures: None
Important Identified Risk: Myelosuppression	
Evidence for linking the risk to the medicine	In clinical trials, myelosuppression, including neutropenia, thrombocytopenia, anaemia, and pancytopenia, some of which were life-threatening or fatal, were reported in almost 73% of patients receiving GO. Clinical sequelae in the ALFA-0701 study of myelosuppression, including infections and bleeding/haemorrhagic events were reported frequently, some of which were life-threatening or fatal.
Risk factors and risk groups	Patients with previously untreated *de novo* AML may have myelosuppression due to the presence of disease in the bone marrow.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, and 4.8; PL sections 2 and 4 Additional risk minimisation measures: None

Table 2. Summary of Important Risks and Missing Information

Important Identified Risk: Tumour Lysis Syndrome	
Evidence for linking the risk to the medicine	In first relapse GO monotherapy studies, TLS was reported although no events were fatal. Although the frequency was relatively low, fatal reports of TLS complicated by acute renal failure have been reported in the post marketing setting.
Risk factors and risk groups	Patients with AML are at risk of developing TLS. These abnormalities may occur spontaneously before the initiation of chemotherapy due to increased catabolism and the turn-over of leukemic cells, but more frequently TLS is induced by intensive chemotherapy. Additional risk factors include high tumour burden/high WBC count and high sensitivity to chemotherapy.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, and 4.8; PL sections 2 and 4 Additional risk minimisation measures: None
Important Identified Risk: Infusion-Related Reactions (Including Anaphylaxis) From Start of Infusion to Within 24 Hours of End of Infusion	
Evidence for linking the risk to the medicine	In first relapse GO monotherapy studies, infusion related reactions, including anaphylaxis were reported. There have been reports of fatal infusion reactions in the postmarketing setting.
Risk factors and risk groups	Patients with a known hypersensitivity to GO may be at an increased risk of developing an infusion-related reaction related to GO.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, and 4.8; PL sections 2 and 4 Additional risk minimisation measures: None
Important Potential Risk: Renal Toxicity	
Evidence for linking the risk to the medicine	Although Renal Toxicity has not been identified as a risk from clinical trials or in the post-marketing setting, it was observed in non-clinical studies with GO in rats and monkeys.
Risk factors and risk groups	Factors that could potentially be associated with an increased risk of renal toxicity include tumour lysis syndrome in association with treatment of AML, other drugs, advanced age, hemodynamic status, and underlying renal disease.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 5.3 Additional risk minimisation measures: None
Important Potential Risk: Reproductive and Developmental Toxicity (Post Exposure During Pregnancy, Including Breastfeeding)	
Evidence for linking the risk to the medicine	GO was associated with toxicity in embryo-foetal nonclinical studies. GO is genotoxic and can potentially cause foetal harm when administered to a pregnant woman.
Risk factors and risk groups	Based on findings in animals and the known mechanism of action of GO, male and female fertility may be compromised by treatment with GO and GO treatment can cause foetal harm when administered to a pregnant woman. The risks to breastfeeding are not known.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.6 and 5.3; PL section 2 Additional risk minimisation measures: None

Table 2. Summary of Important Risks and Missing Information

Important Potential Risk: Neurotoxicity	
Evidence for linking the risk to the medicine	Nervous system alterations have been identified after repeat doses in non-clinical studies in rats with other antibody-calicheamicin conjugates. Therefore, this important potential risk may represent be a class effect of antibody-drug conjugate drugs, although no risk has been identified in GO clinical studies and in the postmarketing setting.
Risk factors and risk groups	Factors that could potentially be associated with an increased risk of neurotoxicity include chemotherapy, diabetes, drug abuse, heavy metal exposure, pesticides, solvents, organic or organometal compounds, and radiation exposure.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 5.3 Additional risk minimisation measures: None
Important Potential Risk: Second Primary Malignancy	
Evidence for linking the risk to the medicine	In non-clinical studies with GO in rats, microscopic findings included oval cell hyperplasia in the liver that were considered to be preneoplastic in nature. Second primary malignancy has been observed with other antibody-calicheamicin conjugates in non-clinical settings. However, GO related events of second primary malignancy have not been identified in GO clinical studies or in the postmarketing setting.
Risk factors and risk groups	Patients with prior or ongoing malignancies and those exposed to chemotherapy, radiation or other significant immunosuppressive therapies may be at higher risk for development of additional malignancies.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 5.3 Additional risk minimisation measures: None
Important Potential Risk: Off-Label Use in Paediatric Patients	
Evidence for linking the risk to the medicine	There is evidence suggesting that GO may provide benefit to children with AML. Overall, results from the COG AAML 0531 study have shown improvement in event-free survival (EFS) with a similar safety profile as the adult population when GO is combined with intensive first-line therapy at lower doses.
Risk factors and risk groups	No specific group within the paediatric population.
Risk minimisation measures	Routine risk communication: SmPC sections 4.2, 4.8, 5.1, and 5.2; PL section 2 Additional risk minimisation measures: None
Missing Information: Use in patients with severe hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8, and 5.2; PL section 2 Additional risk minimisation measures: None
Missing Information: Use in patients with severe renal impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2 and 5.2 Additional risk minimisation measures: None

II.C. Post-Authorisation Development Plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Mylotarg.

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

There are no studies required for Mylotarg.