PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

BESPONSA (INOTUZUMAB OZOGAMICIN)

Marketing Authorization Number 66022

Powder for concentrate for solution for infusion, 1 mg

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LIST OF ABBREVIATIONS

ALL	Acute lymphoblastic leukaemia
CD	Cluster of differentiation
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FDA	Food and Drug Administration
GI	Gastrointestinal
HSCT	Haematopoietic stem cell transplant
ILD	Interstitial lung disease
PASS	Post-Authorisation Safety Study
PL	Patient Leaflet
Ph+	Philadelphia chromosome-positive
PMR	Post-marketing requirement
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
R/R	Relapsed/refractory
SmPC	Summary Of Product Characteristics
SOS	Sinusoidal obstruction syndrome
TKI	Tyrosine kinase inhibitors
ULN	Upper limit of normal
VOD	Venoocclusive disease

OVERVIEW

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 for Besponsa 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 marketing authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Besponsa in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorised by Swissmedic. Pfizer is fully responsible for the accuracy and correctness of the content of the published RMP summary of Besponsa.

SUMMARY OF RISK MANAGEMENT PLAN

Summary of risk management plan for Besponsa (inotuzumab ozogamicin).

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

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

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

I. The Medicine and What It Is Used For

Besponsa is authorised as monotherapy for the treatment of adults with relapsed or refractory cluster of differentiation-22 (CD22) positive B cell precursor acute lymphoblastic leukaemia (ALL). Adult patients with Philadelphia chromosome positive (Ph+) relapsed or refractory B cell precursor ALL should have failed treatment with at least 1 tyrosine kinase inhibitor (TKI) (see SmPC for the full indication). It contains inotuzumab ozogamicin as the active substance and it is given by infusion.

Further information about the evaluation of Besponsa’s benefits can be found in Besponsa’s EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine’s webpage https://www.ema.europa.eu/en/medicines/human/EPAR/besponsa.

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

Important risks of Besponsa, together with measures to minimise such risks and the proposed studies for learning more about Besponsa '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 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 events is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, 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 Besponsa is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Besponsa 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 Besponsa. 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	Grade ≥3 and/or serious hepatotoxicity, including all VOD/SOS Myelosuppression/cytopenia
Important potential risks	Interstitial lung disease Inflammatory gastrointestinal events Pancreatitis Second primary malignancy Reproductive and developmental toxicity (post exposure during pregnancy and while breast feeding) Neurotoxicity Nephrotoxicity
Missing information	Use in patients with moderate or severe hepatic impairment Use in patients with severe renal impairment Use in Hispanic and Black patients

Abbreviations: SOS=sinusoidal obstruction syndrome; VOD=venoocclusive disease.

II.B. Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Table 2. Important Identified Risk: Grade ≥3 and/or serious hepatotoxicity, including all VOD/SOS

Evidence for linking the risk to the medicine	Inotuzumab ozogamicin clinical and nonclinical studies.
Risk factors and risk groups	Inotuzumab ozogamicin is contraindicated in patients who have experienced prior confirmed severe or ongoing VOD/SOS and patients with serious ongoing hepatic disease (e.g., cirrhosis, nodular regenerative hyperplasia, active hepatitis). In the following subgroups, the reported frequency of VOD/SOS post-haematopoietic stem cell transplant (HSCT) was ≥50%: patients who received a HSCT conditioning regimen containing 2 alkylating agents, patients aged ≥65 years, and patients with a serum bilirubin ≥ upper limit of normal (ULN) prior to HSCT. Based on multivariate analysis in Study 1022, patient factors that were significantly associated with an increased risk of VOD/SOS after a HSCT included the use of HSCT conditioning regimens containing 2 alkylating agents and serum bilirubin ≥ULN prior to HSCT. Based on univariate analysis in Study 1022, other patient factors that appeared to be associated with an increased risk of VOD/SOS after a HSCT include a prior HSCT, age ≥55 years, a history of hepatic disease and/or hepatitis before treatment, later salvage lines, and a greater number of treatment cycles.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.3, 4.4, and 4.8. PL Sections 2, 3 and 4. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	• Study B1931030 (Estimated Study Completion Date: 13 September 2023). This post-authorisation safety study (PASS) is a PMR that was requested by US FDA and is conducted in adults with relapsed/refractory (R/R) B-cell ALL who are eligible for HSCT and who are at higher risk for developing VOD post-HSCT after inotuzumab ozogamicin treatment. See PART II.C of this summary for an overview of the post-authorisation development plan.

Table 3. Important Identified Risk: Myelosuppression/cytopenia

Evidence for linking the risk to the medicine	Inotuzumab ozogamicin clinical and nonclinical studies.
Risk factors and risk groups	In addition to the haematologic abnormalities resulting from relapsed or refractory ALL, such patients may have additional haematopoietic susceptibility to cytotoxic therapies if there is pre-existing bone marrow suppression (e.g., due to prior chemotherapy, prior HSCT, radiation, other therapies), or may experience side effects of other concomitant medications or procedures.
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 4. Important Potential Risk: Interstitial Lung Disease

Evidence for linking the risk to the medicine	Inotuzumab ozogamicin clinical and nonclinical studies.
Risk factors and risk groups	Factors that could potentially be associated with an increased risk of developing interstitial lung disease (ILD)/pneumonitis may include a history of pre-existing pulmonary disease, prior or concomitant treatment with medications with known pulmonary toxicity [antibiotics (e.g., nitrofurantoin, amphotericin B, minocycline); chemotherapy (e.g., bleomycin, methotrexate, cyclophosphamide); antiarrhythmics (e.g., amiodarone), and tamoxifen], and other treatments or circumstances, including radiation therapy, immune suppression resulting in pneumonia (bacterial, viral, fungal, or protozoal), a predisposition to allergic pulmonary disease, autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis, etc.), occupational exposure (e.g., smoke, dust, silicone, asbestos), or other factors.
Risk minimisation measures	Routine and additional risk minimisation measures: None.

Table 5. Important Potential Risk: Inflammatory Gastrointestinal Events

Evidence for linking the risk to the medicine	Inotuzumab ozogamicin clinical and nonclinical studies.
Risk factors and risk groups	Patients receiving therapy for refractory leukaemia, particularly those receiving anti-leukemic therapy, are susceptible to GI inflammation, including gastritis, colitis and/or typhlitis. Factors that could potentially be associated with an increased risk of developing inflammatory GI disease may include a history of pre-existing GI abnormalities, prior cytotoxic chemotherapy, advanced age, chronic illness, and other medications. Of note, ischemic colitis is more likely to occur in older patients, particularly those with comorbidities such as ischemic cardiac disease.
Risk minimisation measures	Routine and additional risk minimisation measures: None.

Table 6. Important Potential Risk: Pancreatitis

Evidence for linking the risk to the medicine	Inotuzumab ozogamicin clinical and nonclinical studies.
Risk factors and risk groups	Factors that could potentially be associated with an increased risk of developing pancreatitis include a variety of medications, (e.g., prior exposure to asparaginase, antibiotics, immunosuppressive agents, anti-hypertensives, aminosalicylates, diuretics, proton-pump inhibitors, steroids, anaesthetics, antibiotics), alcohol abuse, hepatobiliary disorders (e.g., obstruction of the common bile duct, idiopathic biliary sludge, common bile duct tumour infiltration), post-operative trauma and instrumentation (e.g., endoscopic retrograde cholangiopancreatography), hypercalcaemia, parenchymal tumour infiltration, and infection.
Risk minimisation measures	Routine and additional risk minimisation measures: None.

Table 7. Important Potential Risk: Second Primary Malignancy

Evidence for linking the risk to the medicine	Inotuzumab ozogamicin clinical and nonclinical studies.
Risk factors and risk groups	Patients with prior or ongoing malignancies and those exposed to aggressive chemotherapy, radiation or other significant immunosuppressive therapies may be at higher risk for development of additional malignancies.

Table 7. Important Potential Risk: Second Primary Malignancy

Risk minimisation measures	Routine and additional risk minimisation measures: None.

Table 8. Important Potential Risk: Reproductive and Developmental Toxicity (Post Exposure During Pregnancy and While Breast Feeding)

Evidence for linking the risk to the medicine	Inotuzumab ozogamicin nonclinical studies.
Risk factors and risk groups	Based on findings in animals and the known mechanism of action of inotuzumab ozogamicin, male and female fertility may be compromised by treatment with inotuzumab ozogamicin and inotuzumab ozogamicin 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 Sections 2, and 4. Additional risk minimisation measures: None.

Table 9. Important Potential Risk: Neurotoxicity

Evidence for linking the risk to the medicine	Inotuzumab ozogamicin clinical and nonclinical studies.
Risk factors and risk groups	Factors that could potentially be associated with an increased risk of neurotoxicity include chemotherapy, drug abuse, heavy metal exposure, pesticides, solvents, organic or organometal compounds, certain foods and food additives, radiation exposure, and cosmetics.
Risk minimisation measures	Routine and additional risk minimisation measures: None.

Table 10. Important Potential Risk: Nephrotoxicity

Evidence for linking the risk to the medicine	Inotuzumab ozogamicin clinical and nonclinical studies.
Risk factors and risk groups	Factors that could potentially be associated with an increased risk of nephrotoxicity include drugs, advanced age, haemodynamic status, and underlying disease.
Risk minimisation measures	Routine and additional risk minimisation measures: None.

Table 11. Missing Information: Use in Patients with Moderate or Severe Hepatic Impairment

Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, and 5.2. PL Section 2. Additional risk minimisation measures: None.

Table 12. 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.

Table 13. Missing Information: Use in Hispanic and Black patients

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 5.2. Additional risk minimisation measures: None.

II.C. Post-Authorisation Development Plan

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

None.

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

Study B1931030

Purpose of the study: This Phase 4 study is a post-marketing requirement (PMR) that was requested by the United States Food and Drug Administration (US FDA) and is designed to evaluate the safety and efficacy of 2 inotuzumab ozogamicin dose levels in adults with relapsed or refractory B-cell ALL who are eligible for HSCT and who are at higher risk for developing VOD post-HSCT.

Primary objective: To evaluate the rates of VOD and hematologic remission (complete remission/complete remission with incomplete haematologic recovery) for 2 inotuzumab ozogamicin dose levels in adult patients with relapsed or refractory B-cell ALL who are eligible for HSCT and who are at higher risk for developing VOD post-HSCT.

Secondary objective: Safety and efficacy of 2 inotuzumab ozogamicin dose levels.