Summary of risk management plan for Zevalin 1.6 mg/ml kit for radiopharmaceutical preparations for infusion

This is a summary of the risk management plan (RMP) for Zevalin 1.6 mg/ml kit for radiopharmaceutical preparations for infusion (hereinafter referred to as Zevalin). The RMP details important risks of Zevalin, how these risks can be minimised, and how more information will be obtained about Zevalin's risks and uncertainties (missing information).

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

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

I. The medicine and what it is used for

Zevalin is indicated in adults.

[90Y]-radiolabelled Zevalin is indicated as consolidation therapy after remission induction in previously untreated patients with follicular lymphoma.

The benefit of Zevalin following rituximab in combination with chemotherapy has not been established.

[90Y]-radiolabelled Zevalin is indicated for the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma (NHL). (See SmPC for full indications). It contains ibritumomab tiuxetan [^{90}Y] as the active substance and is given intravenously.

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

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

Important risks of Zevalin, together with measures to minimise such risks and the proposed studies for learning more about Zevalin'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 prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about the adverse reactions 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.

II.A List of important risks and missing information

Important risks of Zevalin are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken by the patient. 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 Zevalin. 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).

List of important risks and missing information	
Important identified risks	Carcinogenicity (Second Primary Malignancies, Other than MDS & AML)
	Infection including febrile neutropenia and septic shock
	Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukaemia (AML)
Important potential risks	Congenital anomalies or Reproduction toxicity
Missing information	None

II.B Summary of important risks

Important identified risk information	
Carcinogenicity (Second Primary Malignancies, Other than MDS & AML)	
Evidence for linking the risk to the medicine	Isolated serious adverse event reports
Risk factors and risk groups	Elderly; heavily pre-treated patients (radiation, chemotherapy-like alkylating agents)
Risk minimisation measures	<u>Routine risk minimisation measures:</u> Listings in SmPC section 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects Listings in PIL section of Possible side effects

Additional pharmacovigilance activities	None

Important identified risk information and septic shock	
Infection including febrile neutropenia	
Evidence for linking the risk to the medicine	Updated Integrated Summary of Safety: Additional update of Safety for IDEC-Y2B8, April 5, 2001 Integrated Summary of Dosimetry (Dosimetry Report), July 14, 2000 CSR 304820
Risk factors and risk groups	Patients with neutropenia.
Risk minimisation measures	Routine risk minimisation measures: Listings in SmPC section 4.8 Undesirable effects Listings in PIL section of Possible side effects
Additional pharmacovigilance activities	None

Important identified risk information	
Myelodysplastic Syndrome (MDS) / Acute Myeloid Leukaemia (AML)	
Evidence for linking the risk to the medicine	Clinical trials (Long-term monitoring report, Czuczman 2006) Observational period of study 304820 (NHL FIT) Post-marketing data from safety database
Risk factors and risk groups	Heavily pre-treated patients. Exposure to alkylating agents (chlorambucil, cyclophosphamide), topoisomerase II inhibitors (mitoxantrone, etoposide), external beam-radiation, including total body irradiation. Stem cell transplantation.
Risk minimisation measures	Routine risk minimisation measures Listings in SmPC section 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects Listings in PIL section of Possible side effects
Additional pharmacovigilance activities	None

Important Potential risk information	
Congenital anomalies or Reproduction toxicity	
Evidence for linking the risk to the medicine	Isolated serious adverse event reports
Risk factors and risk groups	Elderly; heavily pre-treated patients (radiation, chemotherapy like alkylating agents)
Risk minimisation measures	<u>Routine risk minimisation measures</u> Listings in SmPC sections of 4.3 Contraindications, 4.6 Fertility, pregnancy and lactation and 4.8 Undesirable effects Listings in PIL of Possible side effects
Additional pharmacovigilance activities	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 Zevalin.

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

There are no studies required for Zevalin.