Part VI: Summary of the risk management plan

Summary of risk management plan for Pixuvri (pixantrone)

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

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

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

I. The medicine and what it is used for

Pixuvri is authorised as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive Non-Hodgkin B cell Lymphomas (NHL) (see SmPC for the full indication). It contains pixantrone as the active substance and it is given by intravenous only.

Further information about the evaluation of Pixuvri's benefits can be found in Pixuvri'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/pixuvri

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

Important risks of Pixuvri, together with measures to minimise such risks and the proposed studies for learning more about Pixuvri'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 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 Pixuvri 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 Pixuvri. 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	• Cardiotoxicity • Myelotoxicity
Important potential risks	None
Missing information	None

II.B Summary of important risks

Important identified risk: Cardiotoxicity	
Evidence for linking the risk to the medicine	**Clinical trials:** Cardiac disorder left ventricular dysfunction, cardiac failure congestive, bundle branch block and tachycardia are considered as common and arrhythmia as uncommon drug-related adverse reactions reported as such during clinical development. The most common related PT is decreased left ventricular ejection fraction, hence the importance of risk **Literature data:** Very few cases of cardiotoxicity have been found in the literature search. For example, only two cases were reported in a study (Dawson 2000); no other real world cases have been reported **Post-marketing data:** In most cases the chronology was suggestive of the role of pixantrone in cardiotoxicity, although for most patients a history of cardiac events or cardiotoxicity is present, and it usually linked to the use of anthracyclines in previous lines of treatment. Most events were considered as serious**.**

Important identified risk: Cardiotoxicity	
Risk factors and risk groups	The patients at highest risk are: - Those with pre-existing cardiac disease, particularly those affecting cardiac function (such as previous myocardial infarction or cardiomyopathy). - Older patients, who may have some degree of subclinical or clinical cardiac dysfunction - Patients who have been previously treated with cardiotoxic drugs (e.g. other anthracyclines, trastuzumab, etc.) - All patients who have had anthracycline therapy are at risk for late onset congestive heart failure. Although pixantrone had substantially less cardiotoxicity than doxorubicin in preclinical studies of mice that had received prior doxorubicin, there is still a potential for enhanced toxicity in humans. - Patients who have received mediastinal radiotherapy - Patients with uncontrolled hypertension - Females have a higher risk for anthracycline induced heart disease than do men
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2, 4.4, 4.8 PL section 2 , 4 Additional risk minimisation measures: None Legal status

Important identified risk: Myelotoxicity	
Evidence for linking the risk to the medicine	**Clinical trials:** Neutropenia, leukopenia, lymphopenia, anaemia, and thrombocytopenia are considered as very common, febrile neutropenia and blood disorders as common and bone marrow failure and eosinophilia as uncommon drug-related adverse reactions reported as such during clinical development. While the most predominant manifestation is neutropenia, the incidence of severe marrow suppression with clinical consequences is relatively low, and patients treated with Pixuvri were closely monitored by frequent blood counts, particularly for neutropenia. **Literature data:** It is well known that bone marrow suppression is an important dose-limiting side effect of chemotherapy for cancer. (Wang 2006). **Post-marketing data:** In most of the cases, the causal role of pixantrone was suspected. While myelotoxicity is an expected side-effect of cytotoxic therapy, the decrease in the white cell counts, particularly neutrophils and lymphocytes, remains the most frequent event in the post-marketing setting.

Important identified risk: Myelotoxicity	
Risk factors and risk groups	People with haematological cancers are more at risk than those with solid tumours, due to decreased bone marrow reserve as a result of the type of and intensity of therapies that they receive. The risk of white blood cell or platelet toxicity increases with: ▪ Combination therapy with other myelotoxic agents, particularly if there has been previous prolonged neutropenia with previous chemotherapy. ▪ Multiple prior regimens ▪ Prior marrow ablative therapy with a stem cell transplant ▪ Increasing age, with elderly patients more likely to develop neutropenic fever ▪ Bone marrow infiltration by lymphoma ▪ Low white blood cell or platelet count at the outset of treatment
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 , 4.3 ,4.8PL section 2 , 4 Additional risk minimisation measures: None Legal status

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 Pixuvri.

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

There are no studies required for Pixuvri.