I. PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR LUMOXITI™

This is a summary of the risk management plan (RMP) for moxetumomab pasudotox (formerly referred to as CAT-8015). The RMP details important risks of moxetumomab pasudotox, and how these risks can be minimised.

The SmPC and its package leaflet for moxetumomab pasudotox give essential information to healthcare professionals and patients on how moxetumomab pasudotox should be used.

This summary of the RMP for moxetumomab pasudotox should be read in the context of all of 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 concerns will be included in updates of the moxetumomab pasudotox RMP.

I.1 THE MEDICINE AND WHAT IT IS USED FOR

Moxetumomab pasudotox is authorised in the European Economic Area (EEA) for the treatment of adult patients with relapsed or refractory HCL after receiving at least 2 prior systemic therapies, including treatment with a PNA. It contains moxetumomab pasudotox as the active substance (1 mg powder for concentrate and solution for solution for infusion) and it is given by IV infusion over 30 minutes on Days 1, 3, and 5 of a 28-day cycle for a maximum of 6 cycles at a dose of 0.04 mg/kg.

Further information about the evaluation of the benefits of moxetumomab pasudotox can be found in the moxetumomab pasudotox 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/lumoxiti

I.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of moxetumomab pasudotox, together with measures to minimise such risks and the proposed studies for learning more about the risks of moxetumomab pasudotox 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 product's Summary of Product Characteristics (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 (eg, 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.

I.2.1 List of important risks and missing information

Important risks of moxetumomab pasudotox 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 moxetumomab pasudotox. 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 (eg, on the long-term use of the medicine).

Table VI-1 List of important risks and missing information

Important identified risks	HUS CLS
Important potential risks	Nephrotoxicity Severe infections Cytokine release syndrome
Missing Information	None

CLS = capillary leak syndrome; HUS = haemolytic uremic syndrome.

I.2.2 Summary of important risks

Table VI-2 Important identified risk: Haemolytic uremic syndrome (HUS)

Evidence for linking the risk to the medicine	While the equivalent of HUS was not established in nonclinical studies with moxetumomab pasudotox, apoptosis of cells of the renal tubular epithelium and tubular necrosis have been observed in toxicity studies with cynomolgus monkeys; these effects were attributed to treatment with an immunotoxin. HUS including "HUS-like" events was observed in clinical HCL trials with moxetumomab pasudotox.
Risk factors and risk groups	Risk factors specific for HUS associated with moxetumomab pasudotox are unknown. In general, HUS can occur as a complication of, or be precipitated by, various diseases, conditions, and treatments, including malignant hypertension, autoimmune diseases, cancers, use of medications or abuse of recreational drugs, hemopoietic stem cell or solid organ transplantation, or infections (Fakhouri et al, 2017). One study suggested that the HLA allele HLA-DRB1*11, which is a known risk factor for acquired TMA, is perhaps a marker for increased susceptibility to HCL (Arons et al, 2014). Other study data support the hypothesis that complement gene variants modify susceptibility to TMA after hemopoietic stem cell transplant among patients with sufficient evidence of vascular injury (often caused by drugs such as chemotherapy or calcineurin inhibitors) in a genetically susceptible host (Jodele et al, 2016).
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 4.8 Additional risk minimisation: None.

HCL = hairy cell leukaemia; HLA = human leukocyte antigen; HUS = haemolytic uremic syndrome; SmPC = Summary of Product Characteristics; TMA = thrombotic microangiopathy.

Table VI-3 Important identified risk: Capillary leak syndrome (CLS)

Evidence for linking the risk to the medicine	There are reports in the literature that in several clinical trials with immunotoxins to treat B-cell malignancies, CLS has been the major dose-limiting pulmonary or renal toxicity observed, characterised by weight gain, increased vascular permeability, recurrent attacks of hypotension, hypoalbuminemia, elevated haematocrit levels, fluid retention, and peripheral oedema or accumulation of fluid in the thoracic cavity (pleural and pericardial effusions) (Sausville et al, 1995; Siegall et al, 1997). CLS has been observed in clinical trials with moxetumomab pasudotox among patients with relapsed/refractory hematologic malignancies, including HCL (see Table II-6). Isolated spontaneous cases of CLS have been also reported in the post-approval setting.
Risk factors and risk groups	While risk factors and risk groups for development of CLS among patients treated with immunotoxins (including patients with HCL treated with moxetumomab pasudotox) have not been clearly established, a few studies suggest that BMT from non-related donor or high-intensity conditioning regimens used in combination with allogeneic BMT, and G-CSF administration have been implicated as the main risk factors for CLS development (Nurnberger et al, 1997; Lucchini et al, 2016).
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 4.8 Additional risk minimisation: None.

BMT = bone marrow transplant; CLS = capillary leak syndrome; G-CSF = granulocyte-colony stimulating factor; HCL = hairy cell leukaemia; SmPC = Summary of Product Characteristics.

Table VI-4 Important potential risk: Nephrotoxicity

Evidence for linking the risk to the medicine	In nonclinical studies with cynomolgus monkeys, the kidney was identified as one of the potential target organs of toxicity, with noted adverse effects of tubular epithelium apoptosis and/or tubular necrosis that were generally reversible. Blood creatinine increased, a common laboratory finding in renal injury, has been observed among moxetumomab pasudotox-treated patients with HUS, CLS, and TLS. In addition to blood creatinine increased events, other events of nephrotoxicity have been reported.
Risk factors and risk groups	Risk factors and risk groups for development of nephrotoxicity in patients treated with moxetumomab pasudotox have not been clearly established. However, patients who develop HUS are at increased risk of developing various degrees of renal impairment. In addition, it is conceivable that elderly patients with HCL have a higher risk of developing nephrotoxicity as literature evidence suggests that risk of renal damage increases with advancing age (Shahinian et al, 2017).
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2 and 4.4 Additional risk minimisation: None.

CLS = capillary leak syndrome; HCL = hairy cell leukaemia; HUS = haemolytic uremic syndrome; SAE = serious adverse event; SmPC = Summary of Product Characteristics; TLS = tumour lysis syndrome.

Table VI-5 Important potential risk: Severe infection

Evidence for linking the risk to the medicine	In addition to the B-cell depleting mechanism of action characteristic for moxetumomab pasudotox, in nonclinical studies with cynomolgus monkeys, reversible decreases in B-cell (CD3-/CD20+) and T-cell (CD3+/CD20-) values were noted at 4 hours after dosing on Days 1 and 22. The possibility that moxetumomab pasudotox administration contributed to exacerbation of malaria infection in 2 of 3 monkeys that tested positive for *Plasmodium* during the dosing phase of the study cannot be excluded. Severe infections (≥ Grade 3) have also been reported in HCL trials with moxetumomab pasudotox. Of note, 19 patients (23.8%) in the pivotal HCL population had a record of active infection at study entry, of whom 4 patients (5.0%) reported treatment-emergent AEs of severe infection. CD4+ T-cell counts assessed in the pivotal HCL study showed a median decrease at Cycle 1 Day 8 with median values at or above baseline at all subsequent time points.
Risk factors and risk groups	Given the small sample size and the relatively low incidence of severe infections in patients with HCL treated with moxetumomab pasudotox, the ability to identify specific risk factors in the target patient population is limited. However, it is conceivable that the pre-existing immunodeficiencies and therapy-induced neutropenia among patients with relapsed/refractory HCL previously treated with myelotoxic and immunosuppressive therapeutic regimens can predispose patients toward a higher risk of severe infections.
Risk minimisation measures	No specific risk minimisation measures.

HCL = hairy cell leukaemia.

Table VI-6 Important potential risk: Cytokine release syndrome

Evidence for linking the risk to the medicine	Cytokine release syndrome associated with immunogenicity in 1 patient was described as dose-limiting toxicity in an early Phase 1 clinical study with the precursor molecule, CAT-3888 (Kreitman, 2009). Cytokine-release syndrome has not been reported in clinical trials with moxetumomab pasudotox, but it is a potential risk associated with a recombinant immunotoxin.
Risk factors and risk groups	Although no specific data were identified for risk factors for cytokine release syndrome in patients with HCL, rituximab, another treatment for HCL, is known to be associated with both infusion reactions and cytokine release syndrome (Thachil et al, 2006; Lee et al, 2014). Given that there have been no reported events of cytokine-release syndrome in patients with HCL who were treated with moxetumomab pasudotox, the ability to identify specific risk factors in the target patient population is limited.
Risk minimisation measures	No specific risk minimisation measures.

HCL = hairy cell leukaemia.

I.2.3 Post-authorisation development plan

I.2.3.1 Studies which are conditions of the marketing authorisation

The following study is a condition of the marketing authorisation.

Study short name

Planned registry study focusing on the collection of safety data as the primary endpoint and efficacy data as a secondary endpoint

Purpose of the study:

Planned registry study to collect safety data for a period of up to 5 years in 50 patients with relapsed or refractory HCL who have received moxetumomab pasudotox and at least 2 prior systemic therapies, including prior treatment with a PNA. The safety outcomes will include important identified risks and important potential risks of moxetumomab pasudotox (CLS, HUS, nephrotoxicity, severe infections, and CRS). In addition, AEs leading to interruption/discontinuation, SAEs, and all deaths will be collected. Efficacy outcomes will include ORR, CR rate, duration of CR, and PFS.

I.2.3.2 Other studies in post-authorisation development plan

There are no other studies required for moxetumomab pasudotox.