ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Lumoxiti 1 mg powder for concentrate and solution for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder for concentrate contains 1 mg moxetumomab pasudotox.

Reconstitution with water for injections results in a final moxetumomab pasudotox vial concentration of 1 mg/mL.

Moxetumomab pasudotox is produced in *Escherichia coli* cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate and solution for solution for infusion.

Powder for concentrate: white to off-white lyophilised powder.

Solution (stabiliser): colourless-to-slightly yellow, clear solution with a pH of 6.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lumoxiti as monotherapy is indicated for the treatment of adult patients with relapsed or refractory hairy cell leukaemia (HCL) after receiving at least two prior systemic therapies, including treatment with a purine nucleoside analogue (PNA).

4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Posology
The recommended dose of Lumoxiti is 0.04 mg/kg administered as a 30-minute intravenous infusion on Days 1, 3, and 5 of each 28-day cycle. Patients should continue treatment for a maximum of 6 cycles, or until disease progression or unacceptable toxicity. Treatment may be stopped at the physician's discretion if complete response (CR) without minimal residual disease (MRD) is achieved prior to the completion of 6 cycles.

Hydration
In patients over 50 kg, 1 L isotonic solution (e.g. dextrose 50 mg/mL [5%] and sodium chloride 9 mg/mL [0.9%] or 4.5 mg/mL [0.45%] solution for injection) should be administered intravenously over 2-4 hours before and after each Lumoxiti infusion. Patients under 50 kg require 0.5 L to be administered.

Patients should be adequately hydrated. Patients are advised to drink 3 L of oral fluids per 24 hours on Days 1 through 8 of each 28-day cycle. In patients under 50 kg, 2 L per day is recommended.

Fluid balance should be monitored to avoid fluid overload (see section 4.4).

Premedication
Premedication is required 30-90 minutes prior to each Lumoxiti infusion with an oral antihistamine (e.g. hydroxyzine or diphenhydramine), an antipyretic (e.g. paracetamol), and a histamine-2 receptor antagonist (e.g. ranitidine, famotidine, or cimetidine).

If a severe infusion related reaction occurs, see section 4.4 for further instructions.

Dose adjustments
Lumoxiti treatment must be withheld and/or discontinued to manage adverse reactions as described below.

Haemolytic uraemic syndrome (HUS) and capillary leak syndrome (CLS) are identified based on clinical presentation (see Table 1).

Table 1 Monitoring for HUS and CLS

	HUS	**CLS**
Monitoring Parameter	Before every infusion, check: • Haemoglobin levels • Platelet count • Serum creatinine • LDH • Indirect bilirubin	Before every infusion, check: • Weight • Blood pressure • Albumin
Assessment	Consider diagnosis of HUS if: • Haemoglobin decreased by 1 g/dL or platelet count <25,000/mm^3 unrelated to the underlying disease, and • Grade 2 creatinine increase (1.5- to 3-times baseline or the upper limit of normal) If HUS is suspected based on the above, promptly check blood LDH, indirect bilirubin and blood smear schistocytes for evidence of haemolysis.	• If weight has increased by ≥10% from Day 1 of the cycle and the patient is hypotensive, promptly check for peripheral oedema, hypoalbuminaemia, and respiratory symptoms, including shortness of breath and cough. • If CLS is suspected, check for a decrease in oxygen saturation and evidence of pulmonary oedema and/or serosal effusions.

Haemolytic uraemic syndrome (HUS)
Patients who experience Grade 2 or higher HUS should receive appropriate supportive measures and fluid replacement, with monitoring of blood chemistry, complete blood counts, and renal function (including monitoring of serum creatinine and/or eGFR) until resolution (see section 4.4).

Table 2 HUS grading and management guidance

HUS grade	Lumoxiti dosing
Grade 2 Evidence of RBC destruction (schistocytosis) and mild renal insufficiency without clinical consequences	Delay dosing until recovery of haemolysis and serum creatinine to Grade 1 or baseline. Discontinue Lumoxiti upon recurrence.
Grade 3 Laboratory findings with clinical consequences (e.g. haemolysis with progressive renal failure, petechiae)	Discontinue Lumoxiti.
Grade 4 Life-threatening consequences (e.g. CNS haemorrhage or thrombosis/embolism or renal failure)	

Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

Capillary leak syndrome (CLS)
Patients who experience Grade 2 or higher CLS should receive appropriate supportive measures including treatment with oral or intravenous corticosteroids, with monitoring of weight, albumin levels, and blood pressure until resolution (see section 4.4).

Table 3 CLS grading and management guidance

CLS grade	Lumoxiti dosing
Grade 2 Symptomatic; intervention indicated	Delay dosing until recovery of symptoms.
Grade 3 Severe symptoms; intervention indicated	Discontinue Lumoxiti.
Grade 4 Life-threatening consequences; urgent intervention indicated	

Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

Increased creatinine
For patients with baseline serum creatinine within normal limits, dosing should be delayed for Grade 2 or higher creatinine increases (greater than 1.5-times baseline or the upper limit of normal). Lumoxiti should be resumed upon recovery to at least Grade 1 (1.0- to 1.5-times baseline, or between the upper limit of normal and 1.5-times the upper limit of normal).

For patients with baseline serum creatinine of Grade 1 or 2, delay dosing for creatinine increases to Grade 3 or higher (greater than 3-times baseline or the upper limit of normal). Lumoxiti should be resumed upon recovery to baseline grade or lower.

Refer to section 4.4 for further monitoring and evaluation information.

Special populations

Elderly
No dose adjustment is required for elderly patients (≥65 years of age) (see Renal function monitoring in section 4.4, and Elderly in sections 4.8 and 5.1).

Renal impairment
No dose adjustment of Lumoxiti is recommended for patients with mild renal impairment. Data supporting use of moxetumomab pasudotox in moderate renal impairment is limited. Moxetumomab pasudotox has not been studied in patients with severe renal impairment (see Renal function monitoring in section 4.4).

Hepatic impairment
No dose adjustment of Lumoxiti is recommended for patients with mild hepatic impairment. Moxetumomab pasudotox has not been studied in patients with moderate or severe hepatic impairment (see section 5.2).

Paediatric population
There is no relevant use of Lumoxiti in children aged 0 to 18 years in the treatment of HCL.

Method of administration
Lumoxiti is for intravenous use.

The diluted solution is administered intravenously over 30 minutes. An infusion set fitted with a sterile, low-protein binding 0.22 micron in-line filter should be used.

After the infusion, the intravenous administration line should be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection at the same rate as the infusion. This ensures the full Lumoxiti dose is delivered.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Haemolytic uraemic syndrome (HUS)
HUS has been reported in patients treated with Lumoxiti and is characterized by the triad of microangiopathic haemolytic anaemia, thrombocytopenia, and progressive renal failure (see section 4.8).

Lumoxiti should be avoided in patients with prior history of severe thrombotic microangiopathy (TMA) or HUS. Prophylactic fluids are recommended during treatment with Lumoxiti (see section 4.2). In Study 1053, patients with a platelet count $\geq$100,000/mm^3 received low-dose acetylsalicylic acid on Days 1 through 8 of each 28-day cycle for prophylaxis of renal insufficiency.

Blood chemistry and complete blood counts should be monitored prior to each dose and as clinically indicated during treatment. Monitoring mid-cycle is also recommended. Diagnosis of HUS should be considered in patients who develop haemolytic anaemia, worsening or sudden onset of thrombocytopenia, worsening of renal function, elevation of bilirubin and/or LDH, and have evidence of haemolysis based on peripheral blood smear schistocytes (see section 4.2).

The events of HUS may be life-threatening if treatment is delayed with increased risk of progressive renal failure requiring dialysis. If HUS is suspected appropriate supportive measures including fluid repletion and haemodynamic monitoring should be initiated, and hospitalisation as clinically indicated should be considered. For Grade 2 HUS, treatment with Lumoxiti should be withheld until resolution, and permanently discontinued for Grade $\geq$3 HUS (see section 4.2).

Capillary leak syndrome (CLS)

CLS has been reported among patients treated with Lumoxiti and is characterized by hypoalbuminaemia, hypotension, symptoms of fluid overload and haemoconcentration (see section 4.8).

Patient weight and blood pressure should be monitored prior to each Lumoxiti infusion and as clinically indicated during treatment. Patients should be assessed for signs and symptoms of CLS including weight gain (≥10% from Day 1 of current cycle), hypotension, peripheral oedema, shortness of breath or cough, and pulmonary oedema and/or serosal effusions. In addition, the following changes in laboratory parameters may help identify CLS: hypoalbuminemia, elevated haematocrit, leucocytosis and thrombocytosis (see section 4.2).

CLS may be life-threatening or fatal if treatment is delayed. Patients should be advised to seek immediate medical attention should signs or symptoms of CLS occur at any time. Patients who develop CLS should receive appropriate supportive measures, including concomitant oral or intravenous corticosteroids, and hospitalisation as clinically indicated. For Grade 2 CLS, treatment with Lumoxiti should be withheld until resolution, and permanently discontinued for Grade ≥3 CLS (see section 4.2).

Renal function monitoring
Patients who experience HUS, those ≥65 years of age, or those with baseline renal impairment may be at increased risk for worsening of renal function following treatment with Lumoxiti (see section 4.8). Treatment with Lumoxiti is not recommended in patients with pre-existing severe renal impairment (creatinine clearance ≤29 mL/min).

Renal function should be monitored prior to each infusion of Lumoxiti, and as clinically indicated throughout treatment. Lumoxiti dosing should be delayed in patients with Grade ≥3 elevations in creatinine, or upon worsening from baseline by 2 or more grades (see section 4.2).

Infusion related reactions
If a severe infusion related reaction occurs, the Lumoxiti infusion should be interrupted and appropriate medical management initiated. An oral or intravenous corticosteroid should be administered approximately 30 minutes before resuming, or before the next Lumoxiti infusion(s). See section 4.2 for information on premedication to reduce risk of infusion related reactions.

Lumoxiti contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say it is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Moxetumomab pasudotox is a recombinant immunotoxin that binds specifically to CD22+ B cells. Based on the mechanism of action of moxetumomab pasudotox, no pharmacokinetic or pharmacodynamic interactions are expected.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception
Women of childbearing potential should use effective contraception during treatment with moxetumomab pasudotox and for at least 30 days after the last dose.

Pregnancy
There are no human or animal data to assess the risk of moxetumomab pasudotox use during pregnancy. Based on its mechanism of action and observed adverse findings of moxetumomab pasudotox in non-pregnant female monkeys including body weight loss, moxetumomab pasudotox may be expected to cause maternal and embryofetal toxicity when administered to a pregnant woman. Moxetumomab pasudotox should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus.

Breast-feeding
There is no information regarding the presence of moxetumomab pasudotox in human milk, the absorption and effects on the breast-fed child, or the effects on milk production. A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Lumoxiti therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
No adverse findings of moxetumomab pasudotox were observed on reproductive organ weights or reproductive organ histopathology following dosing of sexually mature monkeys. There are no data available to directly determine the potential effects on human fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Lumoxiti has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The overall safety profile of Lumoxiti is based on data from 80 patients from Study 1053 (a Phase 3 study).

The most common adverse drug reactions (ADRs) (≥20%) of any grade were oedema (52.5%), nausea (35.0%), infusion related reactions (25.0%), hypoalbuminemia (21.3%), and increased transaminases (21.3%). The most common Grade 3 or 4 ADR was HUS (6.3%).

Adverse reactions resulting in permanent discontinuation of Lumoxiti occurred in 10.0% of patients. The most common adverse reaction leading to Lumoxiti discontinuation was HUS (5.0%). The adverse reaction that most commonly resulted in dose delays was increased serum creatinine (2.5%).

Tabulated list of adverse reactions
ADRs are listed according to system organ class (SOC) in MedDRA. Within each SOC, the ADRs are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, ADRs are presented in order of decreasing seriousness. Frequency category for each ADR is defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000); not known (cannot be estimated from available data).

Table 4 Adverse drug reactions in patients with HCL treated with Lumoxiti (n=80)

SOC	Adverse reactions	Frequency category
Blood and lymphatic system disorders	Haemolytic uraemic syndrome	Common
Metabolism and nutrition disorders	Hypoalbuminaemia[a]	Very common
Vascular disorders	Capillary leak syndrome	Common
Gastrointestinal disorders	Nausea	Very common
General disorders and administration site conditions	Oedema[b]	Very common
Investigations	Transaminases increased[c]	Very common
	Blood creatinine increased	Very common
Injury, poisoning and procedural complications	Infusion related reaction[d]	Very common

[a] Hypoalbuminaemia: includes preferred terms (PTs) of 'hypoalbuminaemia' and 'blood albumin decreased'
[b] Oedema: includes all PTs of 'oedema peripheral,' 'oedema,' 'localized oedema,' 'face oedema,' 'periorbita oedema,' and 'peripheral swelling'

[c] Transaminases increased: includes 'aspartate aminotransferase increased' and/or 'alanine aminotransferase increased'
[d] Infusion related reactions: includes all events regardless of relatedness, as reported by investigator or as retrospectively defined by co-occurrence of 2 or more events of headache, dizziness, hypotension, myalgia, pyrexia, chills, nausea, and/or vomiting on the day of study drug infusion

Description of selected adverse reactions

HUS

In Study 1053 in patients with HCL treated with Lumoxiti, HUS occurred in 8.8% of patients, including Grade 3 in 5.0% and Grade 4 in 1.3%.

The median time to first onset of HUS was 33 days (range: 9-92), and may occur during any cycle of treatment with Lumoxiti. Most cases of HUS occurred in the first 9 days (range: 1-16) of a treatment cycle. The median time to resolution of HUS was 23.5 days (range: 2-44). All cases resolved, including those who discontinued Lumoxiti.

The median end of treatment creatinine clearance (as estimated by Cockcroft-Gault) was higher among patients without HUS (89 mL/min, range 42-195) compared with patients with HUS (76 mL/min, range 19-96).

For clinical management of HUS, see section 4.4.

CLS

In Study 1053 in patients with HCL treated with Lumoxiti, CLS occurred in 8.8% of patients, the majority were Grade 2. There were 2.5% Grade 4 events.

The median time to onset of CLS was 37 days (range: 5-92), and may occur during any cycle of treatment. Most cases of CLS occurred in the first 9 days (range: 1-24) of a treatment cycle. All CLS resolved, with a median time to resolution of 36 days (range: 10-53).

For clinical management of CLS, see section 4.4.

Increase in serum creatinine

In Study 1053, increases in creatinine up to a maximum of 3-times the upper limit of normal were reported in 11.3% of patients. At the end of treatment, serum creatinine levels were within normal limits for the majority (82.5%) of patients. Serum creatinine levels remained elevated above Grade 2 in 5% of patients, two of these patients had Grade 3 or 4 HUS.

Infusion related reactions

Infusion-related reactions as reported by investigator or retrospectively defined as two or more symptoms of headache, dizziness, hypotension, myalgia, pyrexia, chills, nausea, and/or vomiting on the day of treatment with study drug occurred in 25% of patients, including Grade 3 in 2.5% of patients. Infusion related reactions may occur during any cycle of treatment with Lumoxiti (see section 4.2).

Special populations

Elderly

In Study 1053, 39% of patients treated with Lumoxiti were 65 years of age or older. Patients ≥65 years of age had lower median creatinine clearance at baseline and at the end of treatment compared with patients <65 years of age (78 and 69 mL/min versus 114 and 98 mL/min, respectively).

Immunogenicity

In Study 1053, 88% (70/80) of patients were positive for ADA (before or after treatment). Fifty-eight percent (45/77) of patients tested positive for anti-drug antibodies (ADAs) prior to any treatment with moxetumomab pasudotox, and 66% (49/74) of patients tested positive for ADAs whilst on treatment. Neutralising antibodies against moxetumomab pasudotox were detected in 84% of patients (67/80) at

any time. No clinically relevant effects of ADA on safety were identified. See Immunogenicity in section 5.2.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific treatment for moxetumomab pasudotox overdose. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment should be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, other antineoplastic agents, ATC code: L01XC34

Mechanism of action
Moxetumomab pasudotox is a CD22-targeted immunotoxin designed to direct the cytotoxic action of the truncated *Pseudomonas* exotoxin to cells which express the CD22 receptor. CD22 is a B-lymphocyte restricted transmembrane protein with a similar or higher receptor density in HCL cells relative to normal B cells. Nonclinical data indicate that the anticancer activity of moxetumomab pasudotox is due to the binding of the immunotoxin to CD22-expressing tumour cells, followed by internalisation of the Lumoxiti-CD22 complex and processing to release the active PE38 exotoxin. The exotoxin is translocated to the cytosol where it inactivates elongation factor 2 (EF-2), causing inhibition of protein synthesis leading to apoptotic cell death.

Pharmacodynamic effects
In patients with HCL, treatment with Lumoxiti resulted in a reduction of circulating CD19+ B cells. In Study 1053, circulating CD19+ B cells were reduced by 89% from baseline following the first three infusions of Lumoxiti. This reduction was sustained for at least one month post-treatment.

Clinical efficacy and safety
The efficacy and safety of Lumoxiti were evaluated in Study 1053, a multicentre, single-arm, Phase 3 study in patients with relapsed/refractory HCL. Study 1053 was conducted in patients with histologically confirmed HCL or HCL variant who had received prior treatment with at least 2 systemic therapies, including 1 PNA, with a need for therapy based on at least one of the following criteria: neutrophils $<1.0 \times 10^9$/L, platelets $<100 \times 10^9$/L, haemoglobin <10 g/dL or symptomatic splenomegaly.

The study excluded patients who have had chemotherapy, immunotherapy or radiotherapy within 4 weeks of treatment initiation, patients with history of allogeneic bone marrow transplant, patients with known brain metastases, retinal or choroidal detachment, or uncontrolled illness including uncontrolled infection. Further exclusion criteria were a history of thromboembolism, known congenital hypercoagulable conditions, thrombotic microangiopathy/HUS or clinical evidence of severe disseminated intravascular coagulation.

A total of 80 patients were enrolled; 77 with classic HCL and 3 with HCL variant. The median age was 60 (range 34 to 84) years, 79% were male, and 94% were Caucasian at primary analysis. At baseline, 98% of patients had an ECOG performance status of 0 or 1. The median number of prior treatments was 3 (range 2 to 11); all patients received prior PNA therapy, including 29% in combination with rituximab. The most common other prior treatment regimens were rituximab

monotherapy (51%), interferon-alpha (25%), and a BRAF inhibitor (18%). At baseline, 33% (26/80) of patients had low haemoglobin (<10 g/dl), 68% (54/80) of patients had neutropenia (<1.0 x 10^9/L), and 84% (67/80) of patients had baseline platelet counts <100 x 10^9/L. Almost half (48%) of the patients had enlarged spleens at baseline. During screening, 23.8% of patients had an ongoing infection which was adequately controlled or resolved prior to treatment initiation.

Patients received Lumoxiti 0.04 mg/kg as an intravenous infusion over 30 minutes on Days 1, 3, and 5 of each 28-day cycle for a maximum of 6 cycles or until documentation of complete response (CR), disease progression, initiation of alternate therapy, or unacceptable toxicity. Approximately 63% of patients completed 6 cycles and 15% of patients completed treatment earlier than 6 cycles with documentation of minimal residual disease (MRD)-negative CR. An independent review committee (IRC) performed efficacy evaluations using blood, bone marrow, and imaging criteria adapted from previous HCL studies and consensus guidelines.

The major efficacy outcome of Study 1053 was durable CR, as confirmed by maintenance of haematologic remission (haemoglobin ≥11.0 g/dL, neutrophils ≥1.5 x 10^9/L, and platelets ≥100 x 10^9/L without transfusions or growth factor for at least 4 weeks) more than 180 days after IRC-assessed CR.

At the time of final analysis (cut-off date of 29 April 2019), the median follow-up was 24.6 months (range 1 to 72). The efficacy results from Study 1053 are summarised in Table 5.

Table 5 Efficacy results in patients with HCL in study 1053

	Final Analysis
	IRC (N=80)
Durable CR, CR with HR, Duration of HR	
Durable CR (%) [95% CI]	36 [26, 48]
CR with HR ≥360 days, (%) [95% CI]	33 [22, 44]
Duration of HR from onset of CR, median in months [95% CI]	63 [36, 63]
CR and Time to CR	
CR[a] (%) [95% CI]	41 [30, 53]
Time to CR, median in months [95% CI]	6 [5.7, 6.2]
Duration of CR, median in months [95% CI]	63 [36, 63]
HR, Duration of HR and Time to HR	
HR rate (%) [95% CI]	80 [70, 88]
Time to HR, median in months [95% CI]	1 [1.0, 1.2]
Duration of HR from onset of HR, median in months [95% CI]	46 [26, 72]
OR, Time to OR, Duration of OR	
OR rate (%) [95% CI]	75 [64, 84]
Time to OR, median in months [95% CI]	6 [5.7, 5.9]
Duration of OR, median in months [95% CI]	67 [25, 67]
Partial response (PR)[b] (%)	34
Stable disease (SD)[c] (%)	15

IRC = Independent Review Committee-Assessed; HR = Haematologic Remission; CI = Confidence Interval; CR = Complete Response; OR = Overall Response.

[a] CR defined as clearing of the bone marrow of hairy cells by routine Haematoxylin & Eosin stain, radiologic resolution of pre-existing lymphadenopathy and/or organomegaly, and haematologic remission

[b] PR defined as ≥ 50% decrease or normalisation (<500/mm^3) in peripheral blood lymphocyte count, reduction of pre-existing lymphadenopathy and/or organomegaly, and haematologic remission.

[c] SD defined as ≥ 50% decrease of peripheral blood lymphocyte count, reduction of pre-existing lymphadenopathy and/or organomegaly, and haematologic remission or 50% improvement over baseline for haematologic parameters if not meeting haematologic remission criteria.

MRD was evaluated by IRC via immunohistochemistry assessment of bone marrow biopsies. At the time of the final analysis, of the 33 patients who achieved IRC-assessed CR, 82% (27/33) were

MRD-negative and 26 of the 29 patients (89.7%) who achieved a durable CR were MRD-negative. The median duration of CR was 12.0 months for MRD-positive patients (n = 6) and 62.8 months for MRD-negative patients (n = 27).

Pre-specified sub-group analyses of primary and secondary endpoints were performed for the ITT population including age (<65 years, ≥65 years), gender, baseline spleen status (splenectomy, <14 cm, ≥14 cm), number of prior treatments with PNA (1, 2, >2) and HCL histology (classic, variant). The analyses showed that the effect on durable CR rate and CR rate across the majority of sub-groups evaluated were consistent with the results for the ITT population. For subjects ≥65 years, the durable CR rate was 19% (95% CI: 8%, 38%) and the CR rate assessed by IRC was 26% (95% CI: 12%, 47%). Data are limited for the splenectomy and HCL variant subgroups. No CRs were reported; 2 of 4 patients in the splenectomy subgroup and 1 of 3 patients in the HCL variant subgroup achieved a PR.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Lumoxiti in all subsets of the paediatric population in HCL (see section 4.2 for information on paediatric use).

Other information
This medicinal product has been authorised under 'exceptional circumstances'. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of moxetumomab pasudotox was studied in 68 patients with HCL at a dose of 0.04 mg/kg administered intravenously over 30 minutes on Days 1, 3, and 5 of a 28-day cycle. PK exposure increased after subsequent infusions compared with the first infusion, which is likely related to the depletion of malignant B cells after treatment with moxetumomab pasudotox and subsequent reduction of the CD22 sink. All trough concentration levels were negligible, indicating there was no systemic accumulation of moxetumomab pasudotox.

Distribution
Based on noncompartmental PK analysis and consistent with restriction to extracellular fluid, the mean Cycle 1 Day 5 volume of distribution was 6.06 L, with an inter individual variability (CV) of 46.3%.

Biotransformation
The exact pathway through which moxetumomab pasudotox is metabolised has not been characterised. Like other protein therapeutics, moxetumomab pasudotox is expected to undergo proteolytic degradation into small peptides and amino acids via catabolic pathways.

Elimination
Based on noncompartmental PK analysis, moxetumomab pasudotox Cycle 1 Day 5 estimated mean (CV%) systemic clearance was 4.8 L/hr (82.3%) and the mean elimination half-life ($t_{1/2}$) was 2.32 hours (range: 0.17 to 57.4). The elimination half-life following the first dose (Cycle 1 Day 1) could only be estimated in 6 out of 68 patients (mean $t_{1/2}$=0.98 hours).

The primary elimination pathways of moxetumomab pasudotox are assumed to include CD22-mediated internalisation and proteolysis or catabolism. Renal excretion has not been studied for moxetumomab pasudotox. Data from a similar precursor compound indicate that intact protein is excreted into urine. However, renal excretion is not expected to be a major elimination pathway due to the molecular size.

Special populations

Age (34 to 84 years), sex, race, mild hepatic impairment (total bilirubin > ULN to 1.5 x ULN or AST > ULN; n=7), or mild renal impairment (creatinine clearance 60-89 mL/min; n=19), had no clinically meaningful effect on the PK of moxetumomab pasudotox, based on an analysis of noncompartmental PK data by covariates. With body weight dosing, a trend of increased exposure was observed with increasing weight. No dose adjustments are recommended for these demographics.

Moxetumomab pasudotox has not been studied in patients with moderate or severe hepatic impairment (total bilirubin >1.5 ULN or AST = Any) and moderate or severe renal impairment (creatinine clearance <60 mL/min).

Immunogenicity
There is a trend of reduced C_{max} with increased ADA titre at later treatment cycles (Cycle 3 and beyond); however, these results are not conclusive due to the limitation of the bioanalytical method for moxetumomab pasudotox at high ADA titres.

5.3 Preclinical safety data

Carcinogenicity and mutagenicity
No studies have been conducted to assess the carcinogenic or genotoxic potential of moxetumomab pasudotox.

Repeat-dose toxicity
Moxetumomab pasudotox was studied in cynomolgus monkeys for 13 weeks. At doses ≥10-times the human recommended dose, minimal to moderate degeneration of heart tissue was observed microscopically without corresponding changes in ECG. At doses of approximately 34-times the human recommended dose, microscopic evidence of gliosis and axonal degeneration was observed in the brain and spinal cord, respectively, along with observations of body tremors.

Reproductive toxicology
Animal fertility studies have not been conducted with moxetumomab pasudotox. In a 3-month repeat-dose toxicity study using sexually mature cynomolgus monkeys, no adverse findings on male or female reproductive organs were observed at doses approximately 34-times the human recommended dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for concentrate
Sodium dihydrogen phosphate monohydrate
Sucrose
Glycine
Polysorbate 80
Sodium hydroxide

Solution (stabiliser)
Citric acid monohydrate
Sodium citrate
Polysorbate 80
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

No incompatibilities between Lumoxiti and 9 mg/mL (0.9%) sodium chloride in polyvinylchloride or polyolefin intravenous bags have been observed.

Do not co-administer other medicinal products through the same intravenous line.

6.3 Shelf life

Unopened vial
4 years.

Lumoxiti concentrate (i.e. reconstituted Lumoxiti powder for concentrate)
The Lumoxiti concentrate should be immediately further diluted.

From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Lumoxiti solution (i.e. diluted Lumoxiti concentrate in the prepared infusion bag)
Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8°C or 4 hours at room temperature up to 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store and transport refrigerated (2°C - 8°C).
Do not freeze.
Store in the original carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Lumoxiti 1 mg powder for concentrate is provided in a Type 1 glass vial with an elastomeric stopper and a dark blue flip-off aluminium seal.

The 1 mL solution (stabiliser) is provided in a Type 1 glass vial with an elastomeric stopper and a dark grey flip-off aluminium seal.

Each pack contains:
- 2 vials of powder for concentrate and 1 vial of solution (stabiliser) or
- 3 vials of powder for concentrate and 1 vial of solution (stabiliser)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only. Lumoxiti powder for concentrate must be reconstituted and diluted by a healthcare professional using aseptic technique.

Step 1: Calculate dose
- Calculate the dose (mg) and the number of Lumoxiti powder for concentrate vials (1 mg/vial) to be reconstituted.

Number of vials of Lumoxiti powder for concentrate = $\frac{0.04 \text{ mg/kg} \times \text{patient weight (kg)}}{1 \text{ mg/vial}}$

- Do not round down for partial vials. For example, a person whose body weight is 55 kg would need 3 vials of Lumoxiti powder for concentrate.

- Individualise dosing based on the patient's actual body weight prior to the first dose of the first treatment cycle.
  - A change in dose should only be made between cycles when a change in weight of greater than 10% is observed from the weight used to calculate the first dose of the first treatment cycle. No change in dose should be made during a particular cycle.

Step 2: Reconstitute Lumoxiti vials

Lumoxiti powder for concentrate must be reconstituted with water for injections. Water for injections is not provided in the pack.

A solution (stabiliser) is provided inside the Lumoxiti carton and is added to the infusion bag prior to addition of reconstituted powder for concentrate. **Do not use this solution (stabiliser) for reconstitution of the powder for concentrate.**

- Reconstitute each Lumoxiti powder for concentrate vial with 1.1 mL water for injections.
  - Direct the water for injection along the walls of the vial and not directly at the lyophilised powder.
  - The final vial concentration of the reconstituted Lumoxiti powder for concentrate (i.e. Lumoxiti concentrate) is 1 mg/mL.
- Gently swirl the vial until completely dissolved. Invert the vial to ensure all powder in the vial is dissolved. Do not shake.
- Visually inspect that the Lumoxiti concentrate is clear to slightly opalescent, colorless to slightly yellow, and free from visible particles. Do not use if solution is cloudy, discolored, or contains any particles.

Following reconstitution, immediately proceed with the dilution process in Steps 3 and 4. Do not store the Lumoxiti concentrate.

Step 3: Prepare infusion bag

The solution (stabiliser) must be added to the infusion bag only. The solution (stabiliser) must be added to the infusion bag before the Lumoxiti concentrate is added.

Only 1 vial of solution (stabiliser) should be used per infusion bag. Any extra vial(s) of solution (stabiliser) should be discarded.

- Obtain a 50 mL sodium chloride 9 mg/mL (0.9%) solution for injection infusion bag.
- Add 1 mL solution (stabiliser) to the infusion bag.
  - Gently invert the bag to mix the solution. Do not shake.

Step 4: Add Lumoxiti concentrate to infusion bag

Withdraw the required volume (calculated from Step 1) of Lumoxiti concentrate from the reconstituted vial(s).

- Inject Lumoxiti concentrate from the reconstituted vial(s) into the infusion bag containing 50 mL sodium chloride 9 mg/mL (0.9%) solution for injection and 1 mL solution (stabiliser).
- Gently invert the bag to mix the solution. Do not shake.
- Visually inspect the diluted Lumoxiti concentrate (i.e. Lumoxiti solution). Do not use if this solution is cloudy or contains any particles.

Following this dilution step, infuse the Lumoxiti solution (from the final infusion bag) immediately (step 5).

Step 5: Administer Lumoxiti

- Immediately administer the Lumoxiti solution intravenously over 30 minutes. Use an infusion set fitted with a sterile, low-protein binding 0.22 micron in-line filter.
- Do not mix Lumoxiti, or administer as an infusion with other medicinal products.
- After the infusion, flush the intravenous administration line with sodium chloride 9 mg/mL (0.9%) solution for injection at the same rate as the infusion. This ensures the full Lumoxiti dose is delivered.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1522/001 2 vials + 1 vial
EU/1/20/1522/002 3 vials + 1 vial

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Boehringer Ingelheim RCV GmbH & Co KG
Dr, Boehringer-Gasse 5-11
A-1121 Vienna
Austria

Name and address of the manufacturer responsible for batch release

MedImmune Pharma B.V.
Lagelandseweg 78
Nijmegen
6545CG
Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
Non-interventional PASS : In order to further evaluate the safety and efficacy of moxetumomab pasudotox under routine clinical practice for the treatment of patients with relapsed or refractory HCL (who have received at least 2 prior systemic therapies, including prior treatment with a PNA), the MAH should conduct and submit the results of a study based on data from a disease registry in HCL patients according to an agreed protocol.	Annually as part of the annual reassessment

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Lumoxiti 1 mg powder for concentrate and solution for solution for infusion
moxetumomab pasudotox

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 1 mg moxetumomab pasudotox.
After reconstitution with water for injections each vial contains 1 mg/mL moxetumomab pasudotox.

3. LIST OF EXCIPIENTS

Excipients:

Powder for concentrate
Sodium dihydrogen phosphate monohydrate
Sucrose
Glycine
Polysorbate 80
Sodium hydroxide

Solution (stabiliser)
Citric acid monohydrate
Sodium citrate
Polysorbate 80
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate and solution for solution for infusion
2 vials of powder for concentrate
3 vials of powder for concentrate
1 vial of solution (stabiliser) - add to the sodium chloride bag only

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution and dilution
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport refrigerated (2°C - 8°C).
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1522/001 2 vials + 1 vial
EU/1/20/1522/002 3 vials + 1 vial

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Lumoxiti 1 mg powder for concentrate
moxetumomab pasudotox
IV after reconstitution and dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

AstraZeneca

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLUTION (STABILISER) VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solution (stabiliser)
Lumoxiti

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

Add to the sodium chloride bag only
AstraZeneca

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Lumoxiti 1 mg powder for concentrate and solution for solution for infusion
moxetumomab pasudotox

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start being given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Lumoxiti is and what it is used for

What Lumoxiti is
Lumoxiti contains the active substance moxetumomab pasudotox.

What Lumoxiti is used for
Lumoxiti is used on its own to treat a rare cancer called hairy cell leukaemia (HCL) in which the bone marrow makes abnormal white blood cells. It is intended for use in adults when:
- the cancer has come back or
- previous treatment has not worked.

Lumoxiti is for patients who have received at least 2 other treatments for their HCL, including a type of medicine called purine nucleoside analogue.

How Lumoxiti works
Lumoxiti acts by attaching to cells that have a protein called CD22. HCL cells have this protein. After attaching to the HCL cells, the medicine delivers a substance into the cells that causes the HCL cell to die.

2. What you need to know before you are given Lumoxiti

Do not use Lumoxiti:
- if you are allergic to moxetumomab pasudotox or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Lumoxiti if you:
- have had a blood vessel and kidney disease called haemolytic uraemic syndrome (HUS). HUS is a serious side effect of Lumoxiti (see section 4).

- have had clots forming in small blood vessels due to a condition called severe thrombotic microangiopathy (TMA).
- have had a condition whereby fluid leaks from your small blood vessels into your body called capillary leak syndrome (CLS). CLS is a serious side effect of Lumoxiti (see section 4).
- have kidney problems.

Patients who have previously experienced any of the above conditions may be at greater risk of experiencing them again whilst undergoing treatment with Lumoxiti. If you think any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before using this medicine.

Tests and checks
Before and during treatment with Lumoxiti, your doctor may check your blood pressure and weight and carry out some tests. For example, blood tests and urine samples may be required to check how well your kidneys are working.

Children and adolescents
Lumoxiti should not be used in children and adolescents because it has not been studied in patients with HCL aged less than 18 years due to extreme rareness of HCL in these age groups.

Other medicines and Lumoxiti
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Contraception, pregnancy and breast-feeding
Contraception
You must use effective birth control if you are a woman who could become pregnant while you are being treated with Lumoxiti. You must continue using birth control for at least 30 days after your last dose. Discuss with your doctor the most appropriate methods of birth control.

Pregnancy
Tell your doctor if you are pregnant, think you may be pregnant or are planning to have a baby. This is because Lumoxiti may harm your unborn baby.
- Do not use Lumoxiti during pregnancy - unless you and your doctor agree that it is the best option.
- If you become pregnant during Lumoxiti treatment - inform your doctor or nurse immediately.

Breast-feeding
Tell you doctor if you are breast-feeding or plan to breast-feed. It is not known if Lumoxiti passes into your breast milk.
- You and your doctor should decide what is best for you and for your baby.
- This may mean that you will not breast-feed and receive Lumoxiti or that you will breast-feed and not receive Lumoxiti.

Driving and using machines
Lumoxiti is unlikely to affect your ability to drive and use machines. However, if you feel you are not able to concentrate well enough and react quickly, be careful when driving or using machines.

Lumoxiti contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say it is essentially 'sodium-free'.

3. How Lumoxiti will be given

This medicine must be reconstituted and diluted by a healthcare professional. Lumoxiti will be given to you in a hospital or clinic by an experienced doctor or nurse.

The doctor will work out the dose that is right for you based on your weight.

Your doctor or nurse will give you Lumoxiti through an infusion (drip) into your vein (intravenous) over 30 minutes on days 1, 3, and 5 of each 28-day treatment cycle. You may receive up to 6 treatment cycles. Your doctor will decide how many treatment cycles you need.

Before each Lumoxiti infusion, you will be given other medicines to help reduce side effects including reactions related to the infusion (see section 4).

You will be given fluids by infusion before and after each Lumoxiti infusion to help prevent HUS. HUS is a serious side effect of this medicine (see section 4). It is important to drink 2 to 3 litres of fluids every day for the first 8 days of each 28-day treatment cycle as recommended by your doctor.

If you miss an appointment to get Lumoxiti

Call your doctor right away to reschedule your appointment. It is very important that you do not miss a dose of this medicine.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Lumoxiti can cause some serious side effects. Tell your doctor or nurse immediately if you have any of the following side effects because they may need to be treated and your treatment with Lumoxiti may need to be delayed or stopped:

- Bloody diarrhoea, stomach pain, vomiting, fever, feeling tired, confusion, decrease in the amount of urine or dark urine or unusual bleeding or bruising. This may be symptoms of a blood vessel and kidney disease called haemolytic uraemic syndrome (HUS) (**common**, may affect up to 1 in 10 people).
- Fast weight gain, low blood pressure, dizziness or light-headedness, swelling in your arms or legs, shortness of breath, or cough. This may be symptoms of fluid leaking from small blood vessels into your body called capillary leak syndrome (CLS) (**common**, may affect up to 1 in 10 people).
- Reactions during the infusion may occur at any time during your infusion and any cycle of treatment (**very common**, may affect more than 1 in 10 people). Symptoms may be headache, dizziness, low blood pressure, muscle pain, fever, chills, nausea, or vomiting.

Other side effects:

Very common (may affect more than 1 in 10 people):

- swelling of the face, eyes, arms and legs (oedema)
- decreased amount of protein called albumin in the blood
- increased levels of liver enzymes
- increased levels of creatinine in the blood
- nausea

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Lumoxiti

Lumoxiti will be given to you in a hospital or clinic and the healthcare professional will be responsible for its storage. The storage details are as follows:

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and carton after EXP. The expiry date refers to the last day of that month.

Unopened vials:
- Store and transport refrigerated (2°C - 8°C).
- Store in the original carton in order to protect from light.
- Do not freeze.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What Lumoxiti contains
- The active substance is moxetumomab pasudotox. Each vial of powder contains 1 mg of moxetumomab pasudotox. After reconstitution with water for injections, each vial contains 1 mg/mL moxetumomab pasudotox.
- The other ingredients in the powder are sodium dihydrogren phosphate monohydrate, sucrose, glycine, polysorbate 80 and sodium hydroxide (see section 2 'Lumoxiti contains sodium').
- The solution (stabiliser) contains citric acid monohydrate, sodium citrate, polysorbate 80 and water for injections.

What Lumoxiti looks like and contents of the pack

Lumoxiti is a powder for concentrate and solution for solution for infusion.
- The powder is white to off-white.
- The solution (stabiliser) is a colourless-to-slightly yellow, clear solution.

Each Lumoxiti pack contains either:
- 2 vials of powder for concentrate and 1 vial of solution (stabiliser) or
- 3 vials of powder for concentrate and 1 vial of solution (stabiliser)

The powder for concentrate and the solution (stabiliser) are each provided in separate glass vials each with a stopper and an aluminium seal.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
AstraZeneca AB
SE-151 85 Södertälje
Sweden

Manufacturer
MedImmune Pharma B.V.
Lagelandseweg 78
Nijmegen
6545CG
Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

This medicine has been authorised under 'exceptional circumstances'. This means that because of the rarity of this disease it has not been possible to obtain complete information on this medicine. The European Medicines Agency will review any new information which may become available every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

Method of administration
Lumoxiti is for intravenous use.

Lumoxiti powder for concentrate must be reconstituted and diluted by a healthcare professional using aseptic technique.

Step 1: Calculate dose

- Calculate the dose (mg) and the number of Lumoxiti powder for concentrate vials (1 mg/vial) to be reconstituted.

  $$\text{Number of vials of Lumoxiti powder for concentrate} = \frac{0.04\ \text{mg/kg} \times \text{patient weight (kg)}}{1\ \text{mg/vial}}$$

  - Do not round down for partial vials. For example, a person whose body weight is 55 kg would need 3 vials of Lumoxiti powder for concentrate.
- Individualise dosing based on the patient's actual body weight prior to the first dose of the first treatment cycle.
  - A change in dose should only be made between cycles when a change in weight of greater than 10% is observed from the weight used to calculate the first dose of the first treatment cycle. No change in dose should be made during a particular cycle.

Step 2: Reconstitute Lumoxiti vials
Lumoxiti powder for concentrate must be reconstituted with water for injections. Water for injections is not provided in the pack.
A solution (stabiliser) is provided inside the Lumoxiti carton and is added to the infusion bag prior to addition of reconstituted powder for concentrate. **Do not use this solution (stabiliser) for reconstitution of the powder for concentrate.**

- Reconstitute each Lumoxiti powder for concentrate vial with 1.1 mL water for injections.
  - Direct the water for injection along the walls of the vial and not directly at the lyophilised powder.
  - The final vial concentration of the reconstituted Lumoxiti powder for concentrate (i.e. Lumoxiti concentrate) is 1 mg/mL.

- Gently swirl the vial until completely dissolved. Invert the vial to ensure all powder in the vial is dissolved. Do not shake.
- Visually inspect that the Lumoxiti concentrate is clear to slightly opalescent, colorless to slightly yellow, and free from visible particles. Do not use if solution is cloudy, discolored, or contains any particles.

Following reconstitution, immediately proceed with the dilution process in Steps 3 and 4. Do not store the Lumoxiti concentrate.

Step 3: Prepare infusion bag
The solution (stabiliser) must be added to the infusion bag only. The solution (stabiliser) must be added to the infusion bag before the Lumoxiti concentrate is added.
Only 1 vial of solution (stabiliser) should be used per infusion bag. Any extra vial(s) of solution (stabiliser) should be discarded.

- Obtain a 50 mL sodium chloride 9 mg/mL (0.9%) solution for injection infusion bag.
- Add 1 mL solution (stabiliser) to the infusion bag.
    - Gently invert the bag to mix the solution. Do not shake.

Step 4: Add Lumoxiti concentrate to infusion bag
Withdraw the required volume (calculated from Step 1) of Lumoxiti concentrate from the reconstituted vial(s).
- Inject Lumoxiti concentrate from the reconstituted vial(s) into the infusion bag containing 50 mL sodium chloride 9 mg/mL (0.9%) solution for injection and 1 mL solution (stabiliser).
- Gently invert the bag to mix the solution. Do not shake.
- Visually inspect the diluted Lumoxiti concentrate (i.e. Lumoxiti solution). Do not use if this solution is cloudy or contains any particles.

Following this dilution step, infuse the Lumoxiti solution (from the final infusion bag) immediately (step 5).

Step 5: Administer Lumoxiti
Lumoxiti is for intravenous use.
- Immediately administer the Lumoxiti solution intravenously over 30 minutes. Use an infusion set fitted with a sterile, low-protein binding 0.22 micron in-line filter.
- Do not mix Lumoxiti, or administer as an infusion with other medicinal products.
- After the infusion, flush the intravenous administration line with sodium chloride 9 mg/mL (0.9%) solution for injection at the same rate as the infusion. This ensures the full Lumoxiti dose is delivered.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Storage conditions

Store and transport refrigerated (2°C - 8°C).
Do not freeze.
Store in the original carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see below section on shelf life.

Shelf life

Lumoxiti is for single use only.

Unopened vial:
- 4 years.

Lumoxiti concentrate (i.e. reconstituted Lumoxiti powder for concentrate):
- The Lumoxiti concentrate should be immediately further diluted.
- From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Lumoxiti solution (i.e. diluted Lumoxiti concentrate in the prepared infusion bag):
- Following dilution of the Lumoxiti concentrate, infuse the Lumoxiti solution (in the final infusion bag) immediately.
- The total time from initial Lumoxiti powder for concentrate vial reconstitution to the start of the infusion should not exceed 4 hours at room temperature (up to 25°C).
- If the infusion bag is not used immediately, store in a refrigerator (2°C to 8°C) and use within 24 hours of first Lumoxiti powder for concentrate vial puncture. Do not freeze or shake.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Marketing authorisation under exceptional circumstances**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the marketing authorisation under exceptional circumstances as further explained in the European Public Assessment Report.