EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

8 February 2021
EMADOC-1700519818-608352
EMA/OD/0000013333
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted

Lumoxiti (moxetumomab pasudotox, murine anti-CD22 antibody variable region fused to truncated *Pseudomonas* exotoxin 38)
Treatment of hairy cell leukaemia
EU/3/08/592

Sponsor: AstraZeneca AB

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1. Product and administrative information

Product	
Active substances(s) at the time of orphan designation	Murine anti-CD22 antibody variable region fused to truncated *Pseudomonas* exotoxin 38
Other name(s)	CAT-8015; GCR-8015; HA22
International Non-Proprietary Name	Moxetumomab pasudotox
Tradename	Lumoxiti
Orphan condition	Treatment of hairy cell leukaemia
Sponsor's details:	AstraZeneca AB 151 85 Södertälje Sweden
Orphan medicinal product designation procedural history	
Sponsor/applicant	MEDIMMUNE Limited
COMP opinion date	8 October 2008
EC decision date	4 December 2008
EC registration number	EU/3/08/592
Post-designation procedural history	
Transfer of sponsorship	Transfer from MEDIMMUNE Limited to AstraZeneca AB – EC decision of 11 January 2019
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	F. Josephson / B. Bolstad
Applicant	AstraZeneca AB
Application submission date	22 November 2019
Procedure start date	1 February 2020
Procedure number	EMA/H/C/005322
Invented name	Lumoxiti
Proposed therapeutic indication	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). Further information on Lumoxiti can be found in the European public assessment report (EPAR) on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Lumoxiti
CHMP opinion date	10 December 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	K. Penttilä / M. E. Kalland
Sponsor's report submission date	28 February 2020
COMP discussion	3-5 November 2020
COMP opinion date (adoption via written procedure)	14 December 2020

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2008 designation was based on the following grounds:

Whereas the Committee for Orphan Medicinal Products (COMP), having examined the application, concluded:

- hairy cell leukaemia (hereinafter referred to as "the condition") was estimated to be affecting less than 1 in 10,000 persons in the Community, at the time the application was made;
- the condition is life-threatening and chronically debilitating due to poor long-term survival;
- although satisfactory methods of treatment of the condition have been authorised in the Community, justifications have been provided that murine anti-CD22 antibody variable region fused to truncated *Pseudomonas* exotoxin 38 may be of significant benefit to those affected by the condition.

The COMP recommends the designation of this medicinal product, containing murine anti-CD22 antibody variable region fused to truncated *Pseudomonas* exotoxin 38, as an orphan medicinal product for the orphan indication: treatment of hairy cell leukaemia.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Hairy cell leukaemia (HCL) is a chronic and rare indolent B-cell malignancy that account for approximately 2% of all leukaemias (Bouroncle 1994; Kreitman et al 1999). The median age at diagnosis is 52-55 years, and the disease primarily affects men (4-5:1 ratio men vs. women) (Monnereau et al 2014; Robak et al 2015).

The disease is characterised by clonal proliferation of malignant B-cells. Memory B-cells and possibly splenic marginal zone B-cells are considered as the cell of origin for HCL. Patients diagnosed with HCL have abnormal circulating lymphocytes, which are notable for their hairy-like projections visible in light microscope. By flow cytometry, HCL is typically notable for expression of CD11c, CD19, CD22, CD25, CD103 and CD123, and lack of CD5 and CD101. Almost all cases of classical HCL carry a BRAF V600E mutation that leads to upregulation of the MAP kinase/Raf/Mek/Erk pathway, resulting in enhanced cell proliferation and survival. A variant of HCL, called HCL variant, is more aggressive and is classified as a separate disease (WHO classification of lymphoid neoplasms, 2008- revised in 2016) with separate treatment guidelines (ESMO, 2015). HCL variant lack the BRAF V600E mutation and CD25 and CD123 expression, and accounts for approximately 10% of the total HCL population.

The approved therapeutic indication "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)" falls within the scope of the designated orphan condition "treatment of hairy cell leukaemia".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP (see EPAR).

The Applicant proposed a marketing authorisation under exceptional circumstances for moxetumomab pasudotox. This was accepted by the CHMP.

Chronically debilitating and/or life-threatening nature

Most patients with HCL present with splenomegaly and pancytopenia and may have a few circulating neoplastic hairy cells, accompanied with symptoms of fatigue, easy bruising or bleeding, and infection (Jones et al 2012; Chadha et al 2005; Monnereau et al 2014; Grever et al 2017).

Since the time of the initial ODD application in 2008 (at which time PNAs, IFN-α, splenectomy, and off label rituximab were reported as treatment options [BCSH 2000]), the ESMO guideline on treatment of HCL has been published (Robak et al 2015) recommending several further therapies for treatment of HCL in the relapsed or refractory (r/r) setting (as discussed in the section on "Existing methods" below).

HCL is an indolent lymphoproliferative malignancy, which if left untreated, has a median survival of just over 4 years (Golomb et al 1978). Therapies used for the management of HCL in the 1980s (including splenectomy and IFN-α) had limited impact on the life-threatening nature of the disease, as responses to these therapies are generally partial and short-lived (Maevis et al 2014). The majority of patients treated with purine analogues in first- or second-line treatment achieve durable and complete responses to these therapies. However, the small number of patients who relapse and are refractory to purine analogues have limited treatment options.

The condition therefore remains chronically debilitating and life threatening.

Number of people affected or at risk

An updated literature search has been conducted for published studies. 30 years is estimated to be the average survival in patients with HCL based on age of onset and the indolent course of the disease. Based on the published incidence data and disease duration considerations, the total prevalent cases of HCL in EU-28 plus Iceland, Liechtenstein, and Norway in 2020 is estimated to be 1508 × 30 = 45,245 patients, which can be expressed as a prevalence of 0.87 patients per 10,000 population. Previously, the estimate proposed for consideration for the initial orphan designation in 2008 was 0.72 patients per 10,000 population. The slight increase in estimated prevalence is due to refinement of assumptions on which the estimate is based, mainly the incidence used for calculation. Of note, this estimate is double of that reported in the RARECAREnet registry in which prevalence of patients with HCL in the EU-28 as of 01 January 2008 was estimated to be 0.4043 (95% CI: 0.3751, 0.4335) per 10,000 persons (RARECAREnet 2008).

Based on sponsor's estimate the prevalence calculation can be accepted. The COMP concluded that the condition was affecting less than 1 in 10,000 people in the EU, at the time the application was made.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Therapies with regulatory approval in the EU for treatment of HCL include the PNAs (i.e., cladribine and pentostatin) and IFN-α. No changes in authorised treatments have occurred since 2004, prior to submission of the initial orphan designation application for moxetumomab pasudotox in 2008.

The current ESMO guidelines for the treatment of HCL (Robak et al, 2015) recommend that initial 1st-line treatment should consist of PNA monotherapy (cladribine or pentostatin) in young and fit patients presenting with systemic symptoms, splenic discomfort, recurrent infection, or cytopenia. Patients who achieve only partial response to treatment with a PNA monotherapy may be treated with a PNA in combination with rituximab. IFN-α is recommended as a 1st-line option in the event of pregnancy or very severe neutropenia.

The ESMO guidelines for 2nd-line treatment of patients whose disease has relapsed before 12 to 18 months after having attained a CR in the 1st-line setting, recommend re-treatment with PNAs in combination with off-label rituximab. For those whose disease relapses after 12 to 18 months of having attained a CR in the 1st-line setting, re-treatment with the alternative PNA monotherapy is possible (Robak et al 2015). In patients whose disease is refractory to single-agent PNA, 2nd-line treatment may include off label rituximab in combination with a PNA (if rituximab treatment had not previously been administered) or splenectomy.

Beyond this, patients with disease that is refractory to PNAs or who have multiple or early relapses after initial PNA treatment are recommended to be enrolled into clinical trials with new agents, whenever possible. The ESMO treatment algorithm for these patients also includes allogeneic HSCT, vemurafenib and ibrutinib in monotherapy, rituximab in combination with either fludarabine or bendamustine, in addition to moxetumomab pasudotox (the subject of this application) as potential therapy options in this setting. Allogeneic HSCT is mentioned by the ESMO guidelines as having a potential role in younger, heavily pre-treated HCL patients who have had multiple relapses and are refractory to PNAs and rituximab.

None of the medicinal products recommended by the current ESMO guidelines for treatment of r/r disease in the 3rd-line and beyond setting have been granted regulatory approval for treatment of HCL in the EU (Robak et al 2015).

Significant benefit

Of the 4 satisfactory methods for HCL, only IFN-α, splenectomy and allogeneic HSCT are mentioned in the ESMO guidelines as having a potential use in the 3rd-line and beyond setting. PNA monotherapy is not recommended for use after second-line failure due to cumulative myelotoxicity associated with repeated use of these agents.

Moxetumomab pasudotox provides a clinically relevant advantage in terms of improved efficacy compared to existing satisfactory methods recommended by ESMO for treatment of patients with r/r HCL in the 3rd-line and beyond setting, including IFN-α, splenectomy and allogenic HSCT.

Over a third of the patients (36.3%) treated with moxetumomab pasudotox in the pivotal Phase III study (Study CD-ON-CAT-8015-1053) achieved a BICR assessed durable CR (i.e. CR with maintenance of HR for > 180 days). The proportion was similar in patients with PNA-refractory disease (35.9%). Moreover, the effect was long lasting: 32.5% of patients achieved CR (assessed by BICR) and maintained HR for ≥ 360 days; and the median duration of CR (assessed by BICR) was 62.8 months. Although just over a third of the patients achieved a durable CR, the majority of patients (OR by BICR: 75.0%) obtained a clinical benefit in the form of fast and sustained normalisation of haematologic parameters: 80.0% of patients achieved HR, which was achieved within a median of 1.1 months (95% CI: 1.0, 1.2) and was long-lasting with a median duration of 45.8 months (95% CI: 25.9, 71.5 months). Durable HR represents a clinical benefit for patients with HCL, as further therapy is unlikely to be required while patients remain in HR.

As per the ESMO guidelines, IFN-α might be a treatment option for selected patients with r/r HCL who relapse after treatment with PNAs to avoid the immunosuppressive adverse effects of further PNA therapy. However, the evidence supporting its use in the 3rd-line and beyond setting is extremely limited (based on only 4 case reports), and data from studies in earlier lines of the disease suggest that the majority of responses achieved with IFN-α are only partial and of short duration.

As noted in the ESMO guideline, splenectomy may be indicated in patients with massive, resistant and symptomatic splenomegaly. This method resulted in ORR of 60 to 100% as documented in 8 major reports (Habermann and Rai 2011) and achieved median response durations of 5 to 20 months (Mey et al 2003; Golomb 2011). However, the interpretation of these results is complex because standard response criteria, which are now incorporated into the response criteria in malignant disease, were not incorporated in HCL response criteria in splenectomy reports, presumably because splenectomy has no impact on the bone marrow (Habermann 2006). Based on existing knowledge, splenectomy does not improve bone marrow infiltration and fibrosis (Habermann and Rai 2011) and the positive influences of splenectomy with regards to long-term results are uncertain (Maevis et al 2014).

Allogeneic HSCT is included in the ESMO treatment algorithm as a therapeutic option for patients with r/r HCL. The guideline qualifies that this therapy has a potential role in younger, heavily pre-treated HCL patients who have had multiple relapses and are refractory to PNAs and rituximab (Robak et al 2015). This recommendation is based on anecdotal evidence from 2 case reports of patients with refractory HCL treated with allogeneic HSTC in which clinical remission (reduction in hairy cells < 5% with normal haematopoiesis) was ongoing at 21 months in one 32-year-old male (Zinzani et al 2012) and in the second case, complete remission was ongoing at 17 months in a 31-year-old male (Kiyasu et al 2009). Both patients experienced treatment-related toxicities of graft-versus-host disease with skin, eye, and in one case liver involvement. No clinical study data are available to support the efficacy of this therapy in heavily pre-treated r/r HCL patients (Zinzani et al 2012), and the toxicity associated with stem cell transplantation is such that its usage is limited to a rather small group of younger and fit patients.

The COMP considered that the assumption of significant benefit of moxetumomab pasudotox over existing satisfactory methods that are recommended by ESMO for use in the 3rd-line and beyond setting is confirmed. The COMP considered that moxetumomab pasudotox provides a clinically relevant advantage in terms of improved efficacy. In addition, none of the products are authorised products are available in this 3rd-line and beyond setting. Therefore, the criterion of significant benefit may be considered maintained.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 14 December 2020

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of hairy cell leukaemia (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be affecting less than 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening due to reduced survival time and chronically debilitating due to consequences of splenomegaly and pancytopenia, accompanied with symptoms of fatigue, bleeding disorders, and life-threatening infections;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Lumoxiti may be of potential significant benefit to those affected by the orphan condition as defined in the granted therapeutic indication still holds. The sponsor presented data from the clinical trial in patients who were relapsed and refractory to at least two prior lines of treatment showing clinically meaningful rates of durable, complete responses. Moreover, the majority of patients achieved sustained haematological remission, which would obviate the need for additional treatment. This compared favourably to all authorised medicines in this condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Lumoxiti, murine anti-CD22 antibody variable region fused to truncated *Pseudomonas* exotoxin 38, moxetumomab pasudotox for treatment of hairy cell leukaemia (EU/3/08/592) is not removed from the Community Register of Orphan Medicinal Products.