18 January 2019
EMA/25279/2019
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for type II variation application

Blincyto (blinatumomab)
Treatment of acute lymphoblastic leukaemia
EU/3/09/650 (EMEA/OD/029/09)
Sponsor: Amgen Europe B.V.

Note

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

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1. Product and administrative information

Product	
Active substance	Blinatumomab
International Non-Proprietary Name	Blinatumomab
Orphan indication	Treatment of acute lymphoblastic leukaemia
Pharmaceutical form	Powder for solution for infusion
Route of administration	Intravenous use
Pharmaco-therapeutic group (ATC Code)	L01XC0X
Sponsor's details:	Amgen Europe BV Minervum 7061 4817 ZK Breda The Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Micromet AG
COMP opinion date	04/06/2009
EC decision date	24/07/2009
EC registration number	EU/3/09/650
Post-designation procedural history	
Sponsor's name change	From Micromet AG to Micromet GmbH – EC letter of 21/01/2012
Sponsor's name change	From Micromet GmbH to Amgen Research (Munich) GmbH – EC letter 19/06/2012
Transfer of sponsorship	From Amgen Research (Munich) GmbH to Amgen Europe BV – EC letter 13/02/2014
Marketing authorisation type II variation procedural history	
Rapporteur / co-Rapporteur	A. Moreau / D. Melchiorri
Applicant	Amgen Europe BV
Application submission date	8/03/2017
Procedure start date	25/03/2017
Procedure number	EMA/H/C/003731/II/0011
Invented name	Blinatumomab
Therapeutic indication	Blincyto is indicated as monotherapy for the treatment of adults with Philadelphia chromosome negative CD19 positive B-precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%. Further information on Blincyto can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/blincyto
CHMP opinion date	15 November 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	B. Dembowska-Bagińska
Sponsor's report submission date	10/03/2017
COMP discussion	5/12/2018
COMP opinion date	6/12/2018

2. Grounds for the COMP opinion (at the designation stage)

The COMP opinion on the orphan medicinal product designation was based on the following grounds:

- for the purpose of orphan designation, the COMP considered that the indication should be broadened to “treatment of acute lymphoblastic leukaemia”;
- of acute lymphoblastic leukaemia (hereinafter referred to as “the condition”) was estimated to be affecting approximately 1 in 10,000 persons in the Community, at the time the application was made;
- the condition is life-threatening particularly due to the poor long-term prognosis if the disease relapses after systemic therapy;
- although satisfactory methods of treatment of the condition have been authorised in the Community, sufficient justification has been provided that blinatumomab may be of significant benefit to those affected by the condition.

3. Review of criteria for orphan designation at the time of type II variation

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

Acute Lymphoblastic Leukaemia continues to be described in the most recent WHO Classification and ICD codes. ALL represents a biologically and clinically heterogeneous group of B/T-precursor-stage lymphoid cell malignancies arising from genetic insults that block lymphoid differentiation and drive aberrant cell proliferation and survival. In children, ALL is the commonest malignancy accounting for approximately 25 % of childhood cancer and it has 5-year event-free survival rates ranging between 76 % and 86 % in patients receiving protocol-based therapy. In adults, ALL is less common and generally carries a worse prognosis with a long-term survival probability less than 35–40 % (Curr Hematol Malig Rep (2012) 7:133–143). The condition continues to be designated by the COMP as a distinct medical entity.

The approved therapeutic indication “Blincto is indicated as monotherapy for the treatment of adults with Philadelphia chromosome negative CD19 positive B-precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%” falls within the scope of the designated orphan indication “treatment of acute lymphoblastic leukaemia”.

Intention to diagnose, prevent or treat

Based on the positive CHMP benefit-risk assessment, the intention to treat the condition was considered justified.

Chronically debilitating and/or life-threatening nature

ALL is a heterogeneous disease with outcomes dependent on patient age, mutational status and co morbid conditions.

Regardless of prognostic factors, the likelihood of initial remission is ≥ 95% in children and 70 to 90% in adults. About 75% of children and 30 to 40% of adults have continuous disease-free survival for 5 years and appear cured. Patients with ALL refractory to induction or re-induction chemotherapy have poor prognosis if they do not undergo HSCT. With induction therapy, some patients achieve complete remission but the majority of patients relapse. The long-term event-free survival is only 30-35%.

Number of people affected or at risk

The sponsor has submitted a prevalence calculation on data and publications which were from 2012 or older. Data obtained from GLOBOCAN, EUCAN and NORDCAN for Europe were also included. This data is primarily derived from publications released in 2012. The sponsor has also consulted data from SEER. From these sources the sponsor concludes that the prevalence is 1.8 in 10,000 in Europe. The data and the conclusion is in line with the calculation provided in the initial marketing authorisation maintenance report by the sponsor and accepted by the COMP in October 2015.

The COMP considered that the calculation and justification for the prevalence was acceptable.

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

The sponsor has submitted a discussion highlighting that no new products have been authorised since their initial marketing authorisation in 2015. In their report from 2015 the sponsor highlighted that the following products were authorised for the treatment of acute lymphoblastic leukaemia:

INN	Trade name	Member State Where Authorized
Asparaginase	Asparaginase medac	Germany
Clofarabine (2-chloro-9-[2-deoxy-2-fluoro-ß-D arabinofuranosyl]adenine)	Evoltra	European Union
Cyclophosphamide	Cyclophosphamide	United Kingdom
Cytarabine	Cytarabine	United Kingdom
Dasatinib	Sprycel	European Union
Daunorubicin	Daunorubicin	United Kingdom
Dexamethasone	Dexsol 2 mg/5 mL Oral Solution	United Kingdom
Doxorubicin	Doxorubicin	United Kingdom
Idarubicin	Zavedosv	United Kingdom
Imatinib mesylate	Glivec	European Union
Mercaptopurine	Puri-Nethol	United Kingdom
6-Mercaptopurine monohydrate	Xaluprine	European Union
Methotrexate	Methotrexate	United Kingdom
Nelarabine	Atriance	European Union
Prednisone	Prednison HEXAL	Germany
Vincristine	Vincristine Sulphate	United Kingdom

For generic drugs, only 1 representative product is shown.

The sponsor has noted the introduction of a revised ESMO Guideline for Acute Lymphoblastic Leukaemia in 2016 (Hoelzer S. et al).

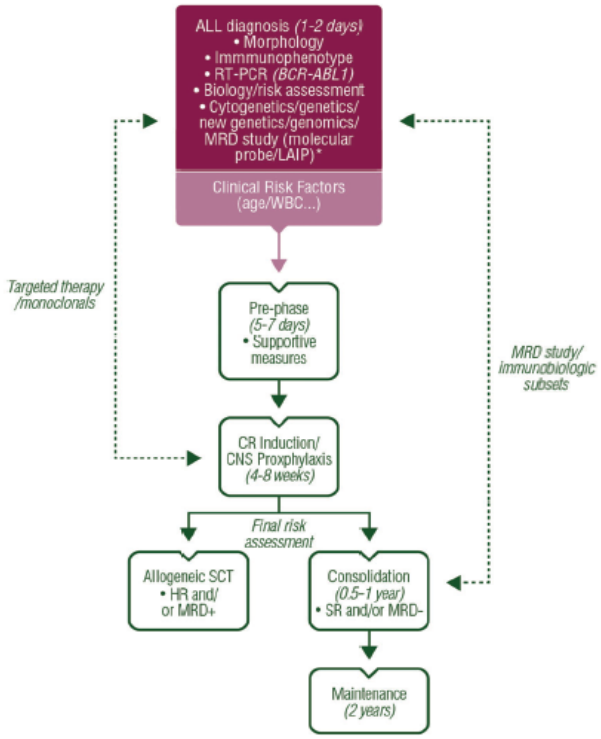
Significant benefit

The sponsor is proposing that blinatumomab will be of significant benefit in patients with minimal residual disease (MRD). This term is used to assess ALL patients and increasingly sought-for prognostic information. It can be obtained through different methodologies and at different treatment times, ranging from pre-phase therapy (prednisone response) to induction day 8-15 (marrow blast cell clearance), end of induction (time to Complete response (CR), MRD) and post-induction phase (MRD).

The CHMP has accepted that MRD identifies a distinct target patient population which can be treated with blinatumumab. It also noted that MRD negativity is an important clinical objective in B-cell precursor ALL patients with residual disease.

It is noted that quantification of MRD is a major and well-established risk factor and should be obtained whenever possible for all patients also outside of clinical trials. Methods of MRD evaluation and standardisation of MRD quantification have been intensively described.

According to the current ESMO view is summarised in the algorithm below:



Diagnosis and risk assessment in adult ALL for achievement of CR and risk-oriented post-remission therapy. Major diagnostic subsets are identified within 1–2 days to allow start of pre-phase therapy, identify cases eligible to targeted therapy (TKI in Ph+ ALL), and set up the MRD study. Pre-phase therapy allows for management/prevention of metabolic/infectious/haemorrhagic complications before start of induction therapy, and checks HLA identity between patient and siblings. Induction/early consolidation therapy (incorporating CNS prophylaxis) aims to induce CR with a deep MRD response, to support subsequent risk and MRD-oriented therapy with/without allogeneic SCT. ALL, acute lymphoblastic leukaemia; RT-PCR, reverse transcriptase polymerase chain reaction; MRD, minimal residual disease; LAIP, leukaemia-associated immunophenotype; WBC, white blood cells; CR, complete remission; CNS, central nervous system; SR, standard risk; HR, high risk; SCT, stem-cell transplantation; TKI, tyrosine kinase inhibitor; Ph+, Philadelphia-positive; HLA, human leucocyte antigen.

The target patient population the sponsor is proposing to treat is associated with the subset identified at the bottom of the algorithm under '*Final risk assessment'* and identified as: *Allogeneic SCT +HR and/or MRD+.* It is noted that there are no authorised or recommended medicines for this subset.

The sponsor has provided data from two single arm trials which they have conducted according to scientific advice given by the CHMP and they have provided one historical comparison.

Study MT103-202 was an exploratory, open-label, multicenter, single-arm, phase 2 study in adult subjects with MRD-positive B-cell precursor ALL. Subjects were ≥ 18 years of age and were in complete hematologic remission with molecular failure or molecular relapse starting any time after consolidation front-line therapy (after at least 3 intense chemotherapy blocks) with GMALL standards or any time outside GMALL standards. Subjects had MRD at a level of ≥ 1 x 10^{-4} in any assay with a minimum sensitivity of 1 x 10^{-4}.

Study MT103-203 is a pivotal, open-label, multicenter, single-arm, phase 2 study in subjects ≥ 18 years of age whose MRD-positive B-cell precursor ALL was in CR as defined by less than 5% blasts in the bone marrow after at least 3 intense chemotherapy blocks. Important exclusion criteria included the presence of circulating blasts or current active extramedullary disease, history of clinically relevant CNS pathology, or any prior allogeneic HSCT.

The COMP noted that patients in complete remission who have minimal residual disease (MRD) have a poor prognosis. The data from study MT103-203 showed that 77.9% of patients recruited and treated with blinatumumab responded. These patients were able to achieve complete molecular remission. Complete molecular remission has been associated with longer survival (with or without allogeneic stem cell transplantation). It was noted that this finding constituted a clinically relevant advantage in the management of the condition.

The use of a historical comparator trial, while not ideal, was considered to be acceptable in the context of this submission as it helped put the efficacy observed in the single arm studies into perspective (*N Gokbuget et al, Blood Cancer Journal (2016) 6, e473*) please see table below:

Table 1. Propensity score analysis of historical data set and blinatumomab clinical trial data: CR and overall survival

End point	Statistic	Historical data set	Blinatumomab trial (MT103-211)
CR/CRh rate	Predicted rate (95% CI)	26.7% (23.4–30.3%)	49.3% (33.4–65.3%)
Overall survival	6-month survival rate (95% CI)	33.4% (31.0–36.1%)	57.6% (54.9–60.4%)
Overall survival	12-month survival rate (95% CI)	17.2% (15.3–19.4%)	39.0% (36.0–42.2%)

The propensity scores estimates vary slightly compared with weighted analysis and blinatumomab clinical trial due to adjustments made with propensity
score modeling. In the weighted analyses, blinatumomab results are not modified and the historical data are weighted to match the distribution of the
blinatumomab trial. In the propensity score analyses, both results are modified to match the distribution of a 'pseudopopulation' in between the blinatumomab and historical control data set.

The COMP acknowledged that recent publications evaluating outcomes in adult patients with MRD ALL after conventional chemotherapy showed that MRD positive status was associated with shorter overall survival and progression free survival. The sponsor's product has been shown to induce complete molecular remission of MRD in the majority of patients treated. . The historical data presented by the sponsor provided acceptable justification for the improvement seen in progression free survival

(remission free survival). This additional time could also be beneficial for treating physicians to prepare patients for allogeneic stem cell transplantation in case it is needed.

It was therefore concluded that the sponsor had provided sufficient data to support the basis of a clinically relevant advantage in a patient population for which there are no currently recommended treatments. A recommendation for maintaining the orphan designation was made.

4. COMP position adopted on 6 December 2018

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.
- the prevalence of acute lymphoblastic leukaemia (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be 1.8 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening particularly due to the poor long-term prognosis if the disease relapses after systemic therapy;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Blincyto is of significant benefit as it improves progression free survival and overall survival in patients with minimal residual disease in acute lymphoblastic leukaemia for which currently there is no authorised treatment.

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 Blincyto, blinatumomab, EU/3/09/650 for acute lymphoblastic leukaemia is not removed from the Community Register of Orphan Medicinal Products.