22 December 2020
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Blincyto (blinatumomab)
Treatment of acute lymphoblastic leukaemia
EU/3/09/650
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 substances(s) at the time of orphan designation	Blinatumomab
International Non-Proprietary Name	Blinatumomab
Tradename	Blincyto
Orphan condition	Treatment of acute lymphoblastic leukaemia
Sponsor's details:	Amgen Europe B.V. Minervum 7061 4817 ZK Breda Noord-Brabant Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Micromet AG
COMP opinion date	2 June 2009
EC decision date	24 July 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
COMP opinion on review of orphan designation at the time of marketing authorisation	8 October 2015
COMP opinion on review of orphan designation at the time of type II variation	6 December 2018
Type II variation procedural history	
Rapporteur / Co-rapporteur	Alexandre Moreau / Daniela Melchiorri
Applicant	Amgen Europe B.V.
Application submission date	31 July 2019
Procedure start date	17 August 2019
Procedure number	EMA/H/C/003731/II/030
Invented name	Blincyto

Proposed therapeutic indication	Blincyto is indicated as monotherapy for the treatment of adults with CD19 positive relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL). Patients with Philadelphia chromosome positive B-precursor ALL should have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options. 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 October 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur	Karri Penttila / Bozenna Dembowska-Baginska
Sponsor's report submission date	21 August 2019
COMP discussion and adoption of list of questions	6-8 October 2020
COMP opinion date	3 December 2020

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

- 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;

2.2. Review of orphan medicinal product designation at the time of marketing authorisation

The COMP opinion on the initial review of the orphan medicinal product designation in 2015 was based on the following grounds:

- 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 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 may be of potential significant benefit to those affected by the orphan condition has been justified with clinical data showing the effectiveness in patients who are negative for the Philadephia gene and for whom there is no effective treatment.

2.3. Review of orphan medicinal product designation at the time type II variation

The COMP opinion on the review of the orphan medicinal product designation at the time of type II variation in 2018 was based on the following grounds:

- 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.

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 CHMP approved extension to the indication (highlighted in the text below)[1] falls within the scope of the designated orphan condition "treatment of acute lymphoblastic leukaemia":

Blincyto is indicated as monotherapy for the treatment of adults with ~~Philadelphia chromosome negative~~ CD19 positive relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL). **Patients with Philadelphia chromosome positive B-precursor ALL should have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options.**

Intention to diagnose, prevent or treat

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

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 conducted a registry and literature search to establish the prevalence of ALL in Europe. Many of the registry sources date from 2012 and earlier. There were however two sources which were more recent, namely the UK's Haematological Malignancy Research Network (HMRN) which was used by Li et al (2016) to estimate total prevalence of ALL in the UK of 1.45 per 10,000 in 2011. The more recent analysis of these data was published by HMRN for data collected up to 2016 and show a 10-year prevalence (standardized to 2013 European population) for B-lymphoblastic leukaemia of 0.6 per 10,000 (HMRN, 2019). NORDCAN which currently provides ALL prevalence estimates for 3 Nordic countries (Denmark, Finland, and Sweden) (NORDCAN, 2019) has also been used. As of 15 March 2019, the overall prevalence of ALL age-standardized to the World Standard Population ranged from 2.8 per 10,000 in Sweden to 3.5 per 10,000 in Finland. When standardized to the European Standard Population (NORDCAN, 2019) it ranged from 2.5 (in Sweden) to 3.2 (in Finland).

The sponsor also provides supporting data from US National Cancer Institute's SEER Cancer Stat Facts, where the total prevalence count of persons with ALL in 2015 was approximately 84,770 (SEER 2019). Using a population estimate for December 1, 2015 (US Census Bureau, 2019) of 321,827,267 persons), this equates to a total prevalence proportion of approximately 2.63 cases per 10,000 persons, which the sponsor says is consistent with prevalence estimates for ALL in Europe.

An analysis of ECIS data was not done and although there isn't a specific domain in ECIS for ALL the exercise could have shed more light on potential changes in Europe like the ones noticed in

[1] New text in bold, removed text as strikethrough

Scandinavia. Finland in particular has a high prevalence of 3.5 in 10,000, and it would be important to understand if there is a similar trend in other European Member States.

It has been noted for example in the publication by Lennmyr E et al, (Eur J Haematology, 2019;103:88-98) that the median age of patients in Sweden was 53 years and that 5-year overall survival in the period from 2007 to 2015 had improved; in patients 18-45yrs from 50% to 65%, 46-65years from 25% to 46% and >65 from 7% to 11%.

The sponsor provided older-, as well as more recent data and concluded on a prevalence of 1.8 in 10,000.

The COMP requested that the sponsor provide a revised estimate for prevalence using more current data as there have been recent reports in the literature indicating better survival and potentially an increase in incidence for the period between 2007 and 2015. These revisions were submitted and discussed during the December COMP plenary.

The revised prevalence estimate was compared to Rarecare data. More current estimates were derived from the following sources data:

- GLOBOCAN (country-specific data)
- NORCAN (data from the Nordic Countries)
- The UK National Cancer Intelligence Network (NCIN)
- The UK Haematological Malignancy Research Network (HMRN)
- The US Surveillance, Epidemiology and End Results (SEER) Program (SEER 18, 2017 5-year prevalence)

Estimated using 2018 SEER data (SEER 18, 2017 data), the proportion of leukaemia patients who had ALL (defined as precursor B-cell, precursor T-cell, lymphoblastic lymphoma and Burkitt's cell leukaemia) was 14%. The sponsor applied the 14% to the figures from the European databases and provided complete prevalences which ranged from 1.98 to 2.57 per 10,000. The sponsor made a comparative analysis of this updated data to those reported using the Rarecare dataset and concluded that the reported value of 1.9 in 10,000 from the application is still relevant. They note that the estimate calculated from RARECARE lies slightly below the lower band of the rang provided but that it may be more valid, as it is based upon data collected across the EU-27. The other estimates (from NORDCAN) are based on data from either single countries, or the whole Nordic Region (Denmark, Finland, Iceland, Norway, Sweden, Faroe Island, and Greenland). The COMP considered this acceptable as there is no conclusive evidence of the percentage of ALL patients in Europe, and therefore the estimate based on Rarecare could be used.

The COMP noted that the data from the separate registries indicated there is an increase in the prevalence albeit difficult to establish due to regional variations and difficulty in establishing the current situation across Europe. The conservative approach proposed by the sponsor appeared to be warranted due to the assumptions made and the use of SEER data in the calculation. The COMP accepted the revision to 1.9 in 10,000 noting that the additional data provided would indicate an increase in the prevalence thus supporting the revision.

Following this the COMP agreed to a prevalence estimate of 1.9 in 10,000.

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 provided a list of products in their submission which primarily focuses on products authorised for the indication they are seeking. As the list is actually broader than this and the list submitted from an earlier report was used for the purpose of completeness as little has changed in the meantime.

Table 1.

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).

Table 2.

Table 4. Recommendations for TKI/chemotherapy combinations in adults with Ph+ ALL

	Recommendation
Adults with Ph+ ALL should be treated front line with a combination of imatinib or second-generation TKI and chemotherapy.	Mandatory
Reduced-intensity chemotherapy may be used in combination with TKI during the first treatment cycles, to minimise early toxicity and mortality.	Recommended
TKI should be administered as continuously as possible, with respect to haematological tolerance.	Recommended
There is no standard post-remission treatment in patients not receiving allogeneic SCT because of no donor or advanced age. Prolonged administration of imatinib/consolidation chemotherapy followed by imatinib maintenance should be applied.	Recommended
Allogeneic SCT in first CR with a standard myeloablative conditioning probably remains the best post-remission option in younger patients with a donor. The role of reduced-intensity conditioning allogeneic SCT remains to be evaluated in this ALL subset.	Recommended
Post-SCT imatinib maintenance is recommended for 1–2 years of duration.	Recommended
Prolonged monitoring of *BCR-ABL1* MRD levels is recommended, associated with resistance mutation screening in patients with persistent MRD detection or re-increasing MRD levels. Results should be used to guide the switch towards a second- or third-generation TKI in these higher risk patients.	Recommended

TKI, tyrosine kinase inhibitor; Ph+, Philadelphia-positive; ALL, acute lymphoblastic leukaemia; SCT, stem-cell transplantation; CR, complete remission; MRD, minimal residual disease.

Table 3.

Table 6. Summary of recommendations for adult ALL

Diagnostic work-up of ALL

- Morphology, immunophenotype and cytogenetics to confirm the diagnosis and ALL subsets are mandatory
- New genetics and molecular genetics are recommended to detect rare subtypes, such as Ph-like ALL, ETP ALL
- Targets for therapy with TKIs or antibodies have to be identified
- Minimal residual disease by immunophenotype or molecular probe at diagnosis, for MRD-based risk classification and treatment algorithm, mandatory

Risk assessment and prognostic factors

- It is essential to stratify patients as standard-risk or high-risk patients
- Risk stratification is currently determined by a combination of prognostic factors at diagnosis and treatment-related parameters, preferentially MRD
- MRD during therapy is now the most relevant prognostic parameter for treatment decisions

Treatment

Treatment algorithm

- Chemotherapy includes induction therapy 1–2 months, consolidation cycles (alternating) 6–8 months and maintenance therapy 2–2.5 years
- Ongoing chemotherapy protocols for AYAs use paediatric-type regimens
- Prophylactic treatment to prevent CNS relapse is mandatory

Antibody therapy

- Anti-CD20 rituximab in combination with a chemotherapy is strongly recommended for Burkitt leukaemia/lymphoma
- Anti-CD22 immunoconjugates directed against CD22 currently under investigation
- Anti-CD19; activation of patients' own T cells directed against CD19
- Bispecific (CD3/CD19) blinatumomab under investigation
- Chimaeric antigen receptor-modified T cells directed against CD19 in early phase

Targeted therapy with TKIs in Ph+ ALL

- A TKI should be combined with chemotherapy in front-line therapy
- The TKI imatinib (400–800 mg/day) should be administered continuously, also post-SCT
- Prolonged monitoring of *BCR-ABL-1* MRD is recommended, as well as resistance mutation screening. In case of persisting MRD, increasing MRD level, or resistance mutation, switch to a second- or third-generation TKI

SCT

- AlloSCT in CR1 significantly improves OS and EFS in high-risk patients/MRD+ patients and is the best post-remission option for Ph+ ALL and *MLL*-rearranged ALL
- Conditioning regimens are age-adapted with full allo versus RIC for elderly patients or patients unfit for full conditioning
- The role of autoSCT should be investigated for MRD-negative patients, in the setting of clinical trials
- All patients in CR ≥2 are candidates for alloSCT

Approach for relapsed/ refractory ALL

- Full diagnostic work-up necessary to exclude/reveal clonal aberrations, and to provide bases for targeted therapies
- Different treatment for patients with short versus long first remission duration (>18/24 months) where re-induction is considered
- Treatment; there is no standard re-induction therapy established, most often used new drugs

ALL, acute lymphoblastic leukaemia; Ph, Philadelphia; ETP, early T-cell precursor; MRD, minimal residual disease; AYAs, adolescents and young adults; CNS, central nervous system; TKI, tyrosine kinase inhibitor; Ph+, Philadelphia-positive; SCT, stem-cell transplantation; alloSCT, allogeneic SCT; CR1, first complete remission; OS, overall survival; EFS, event-free survival; RIC, reduced-intensity conditioning; autoSCT, autologous SCT; CR ≥2, second or later complete remission.

Significant benefit

The sponsor proposes to expand the target patient population who can be treated with Blincyto by including Philadephia chromosome positive B-precursor ALL patients who have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and who have no alternative treatment options.

The CHMP has agreed to this extension to Section 4.1 if the SmPC during their September 2020 plenary.

The data used to support this extension came from Study 20120216: A Phase 2 Single Arm, Multicenter Trial to Evaluate the Efficacy of the BiTE® Antibody Blinatumomab in Adult Subjects with

Relapsed/Refractory Philadelphia Positive B-precursor Acute Lymphoblastic Leukemia (Alcantara Study).

Study 20120216 met its primary objective, showing a 35.6% best CR/CRh* rate within the first 2 cycles of blinatumomab (null hypothesis <10%): a total of 16 patients (in FAS) presented with CR/CRh (35.6%; [21.9%, 51.2%]) within the first 2 cycles of blinatumomab treatment, including 14 with CR (31.1%; [18.2-46.6]). It was noted that CRh would not be sufficient on its own. However, considering observed results, the inclusion of CRh in the primary endpoint had a limited impact on study results since most of responses were CR. A similar trend was noticed in PP analysis. One additional achieved a CR/CRh* after the first 2 cycles. Of note, a total of 40 patients are included in PP in CSR, while 41 are displayed in the clinical summary of efficacy.

The ESMO ALL Guidelines (Ann Oncol (2016) 27 (suppl 5): v69-v82) mentions that: *"Allogeneic hematopoietic stem cell transplantation (HSCT) is recommended in first remission for patients with Philadelphia-positive ALL. Since the introduction of TKIs, the objective response rates are similar between subjects with Philadelphia-negative ALL and subjects with Philadelphia-positive ALL (Thomas et al, 2004; Yanada and Naoe, 2006); however, duration of response and relapse-free survival (RFS) have remained short in ALL Phi+ patients.*

Treatment of Philadelphia-positive ALL patients who are resistant to or relapse after first-line therapy remains challenging.

Recently, 2 non-TKI treatments were approved for the treatment of relapsed or refractory ALL that included Philadelphia-positive ALL subjects in the pivotal trials. Inotuzumab ozogamicin (Besponsa) is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B-cell precursor ALL; adult patients with Philadelphia-positive relapsed or refractory B-cell precursor ALL should have failed treatment with at least 1 TKI. Tisagenlecleucel (Kymriah) is indicated for the treatment of pediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant, or in second or later relapse."

The target patient population as defined in the proposed amendment to Section 4.1 identifies patient where there are no available treatments thus indicating that there is nothing requiring a direct or indirect comparison for the justification of significant benefit.

As there are no satisfactory methods available for this added patient population, the COMP accepted that Blincyto would be of clinically relevant advantage.

4. COMP position adopted on 3 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 acute lymphoblastic leukaemia (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 1.9 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 for the treatment of the condition have been authorised in the European Union, the assumption that Blincyto may be of potential significant benefit in the treatment of patients who are double relapsed and refractory and for whom there are no further treatment options still holds.

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