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| Title of the program | A Medical Need Program of Blinatumomab for the treatment of adults with B-precursor acute lymphoblastic leukemia (ALL) in complete hematological remission defined as less than or equal to 5% blasts in the bone marrow after at least three intense chemotherapy blocks and presence of minimal residual disease (MRD) at a level ≥ $10^{-4}$. |
| Product Name | BLINCYTO® |
| Active substance | Blinatumomab |
| Indication | <u>Intended indication for the Medical Need Program</u><br>Blinatumomab for the treatment of B-precursor acute lymphoblastic leukemia (ALL) in complete hematological remission defined as less than or equal to 5% blasts in the bone marrow after at least three intense chemotherapy blocks and presence of minimal residual disease (MRD) at a level ≥ $10^{-4}$.<br><br><u>Authorized Indication</u><br>Treatment of adults with B-precursor acute lymphoblastic leukemia (ALL) in complete hematological remission defined as less than or equal to 5% blasts in the bone marrow after at least three intense chemotherapy blocks and presence of minimal residual disease (MRD) at a level ≥ $10^{-4}$. |
| In- and exclusion criteria | <u>Inclusion Criteria:</u><br>- Patients with B–precursor ALL in complete hematological remission defined as less than or equal to 5% blasts in the bone marrow after at least three intense* chemotherapy blocks (e.g. GMALL induction I-II/consolidation I, induction/intensification/consolidation or three blocks of Hyper CVAD)<br>- Presence of minimal residual disease (MRD) at a level of ≥ $10^{-4}$ documented after an interval of at least 2 weeks from the last systemic chemotherapy by a validated methodology and test performed in a specialized treatment center with access to laboratory that has expertise in MRD assays<br>- Age ≥ 18 years<br>- Adequate bone marrow function**<br>- Patients cannot be satisfactorily treated with the approved and commercially available alternative treatments, in accordance with clinical guidelines, because of efficacy and/or safety issues<br>- Ability to understand and willingness to sign a written informed consent<br>- Signed and dated written informed consent is available<br><br>* Age appropriate treatment given with the intention to achieve a complete hematological remission and the best long term outcome at the judgment of the treating physician can be considered as intense chemotherapy treatment.<br>** The physician will take into account the degree of hematopoietic recovery from the last previous chemotherapy and decide whether the functional level of bone marrow is adequate or not for blinatumomab use in view of benefits, but also risks.<br><br><u>Exclusion criteria:</u><br>- Presence of circulating blasts or current extra-medullary involvement by ALL<br>- History of relevant CNS pathology or current relevant CNS pathology<br>- Current infiltration of cerebro-spinal fluid by ALL<br>- History of or active relevant autoimmune disease<br>- Eligibility for treatment with TKIs (i.e., Philadelphia chromosome-positive (Ph) patients with no documented treatment failure of or intolerance/contraindication to at least 2 TKIs)<br>- Known hypersensitivity to immunoglobulins or to any other component of the study drug formulation<br>- Breast-feeding<br>- The patient is eligible for a clinical trial running with blinatumomab and/or a clinical trial running in the envisaged indication of this program<br><br>Treatment with blinatumomab should be carefully considered based on individual patient benefit/risk ratio (e.g taking into account age, comorbidity, toxicity, bone marrow function, etc.). |
| Treatment | <u>Treatment</u><br>Blinatumomab is administered as a continuous intravenous infusion delivered at a constant flow rate using an infusion pump, over a period of up to 96 hours. Patients will receive at least one treatment cycle. A single cycle of treatment is 4 weeks of |

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| | continuous infusion. Each cycle of treatment is separated by a 2 week treatment-free interval. Patients not undergoing haematopoietic stem cell transplantation (HSCT) may receive up to 4 cycles of blinatumomab treatment. If patients are suitable for allogeneic HSCT after treatment with at least one treatment cycle of blinatumomab, they may undergo allogeneic HSCT instead of receiving further cycles of blinatumomab.<br><br>The recommended dose of blinatumomab is 28 µg/day for all treatment cycles.<br><br>Dose reduction and stopping rules:<br>- Consideration to discontinue BLINCYTO permanently as appropriate should be made in the case of the following life-threatening (grade 4) toxicities: cytokine release syndrome, tumour lysis syndrome, neurological toxicity, elevated liver enzymes and any other clinically relevant toxicities<br>- Consideration to discontinue BLINCYTO temporarily as appropriate should be made in the case of the following severe (grade 3) : cytokine release syndrome, tumour lysis syndrome, neurological toxicity, elevated liver enzymes and any other clinically relevant toxicities.<br>- If the interruption of treatment after an adverse event is no longer than 7 days, continue the same cycle to a total of 28 days of infusion inclusive of days before and after the interruption in that cycle. If an interruption due to an adverse event is longer than 7 days, start a new cycle. If the toxicity takes more than 14 days to resolve, discontinue BLINCYTO permanently, except if described differently in the SmPC |
| Process to include a patient | Inclusion of a patient<br>The forms are available on request at EU_BE_Blinatumomab@amgen.com<br>1. Completed and signed ICF<br>2. Written request of the treating physician<br>3. Send the request to EU_BE_Blinatumomab@amgen.com<br>4. Review by 3 BHS physicians<br>5. If positive advice: confirmation of enrolment by the responsible physician of the program<br><br>Taken into account the urgency of the disease, all requests will be treated as soon as possible, and at the latest within 1 week after the request.<br><br>Product Supply:<br>- Blinatumomab will be provided for 2 treatment cycles.<br>- The need for up to 2 additional treatment cycles is patient-dependent and will be determined by the treating physician. |
| Duration of the program | This program started on 1st January 2016 and its execution is in line with the legal requirements.<br><br>Blinatumomab will be provided free of charge by Amgen on an individual patient basis following the criteria stated in this program until, in the clinical judgement of the treating physician, the patient is no longer benefiting from continuation of the treatment.<br>Or, until one of the following stopping criteria for ending the CU is met (whichever comes first):<br>- Blinatumomab is reimbursed in the indication of MRD+ B-precursor ALL in Belgium<br>- EMA ultimately decides that the benefit/risk assessment is not supportive of registration of blinatumomab in this indication<br>- Amgen decides to withdraw the registration dossier following an unfavorable benefit/risk profile of blinatumomab in the treatment of MRD+ B-precursor ALL<br>- Amgen decides to stop the development of blinatumomab in this indication.<br>Or at the latest until the first half of 2018.<br><br>The program is reviewed regularly by Amgen, who has the right to stop the program at any time. Patients that were already included in the program will be supported until the end of their treatment. |
| Responsible of the program | Responsible of the program:<br>Amgen N.V. / S.A.<br>Arianelaan 5 |

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| | 1200 Brussels<br>Phone: +32 2 775 27 11<br><br>Responsible physician:<br>Dr. Jo Van der Veken<br><br>Points of contact for this program:<br>- Florence Colliez<br>Regional Medical Liaison<br>+32 (0)472 90 06 51<br>fcolliez@amgen.com<br>- Anke Van den broeck<br>TA Head Oncology Haematology<br>+32 (0) 2 775 27 81<br>+32 (0) 485 41 77 84<br>ankev@amgen.com |
| Modalities for the disposal | Any unused or expired medication needs to be returned to Amgen or destroyed in an appropriate facility as soon as possible after the patient's discontinuation from the compassionate use program. The medication delivered for an individual patient request in the context of a medical need program can only be used for that particular patient. |
| The information for registration of suspected unexpected serious adverse reactions | Physicians are requested to report all adverse events (non-serious and serious), other safety findings and product complaints by OR faxing a completed, signed and dated Safety Report Form to the Amgen – Belgian Safety Department (Safety fax nr: 0800 80 877) within one working day OR mailing a completed, signed and dated Safety Report Form to the email svc-ags-in-be@amgen.com within one working day.<br>The physician may be asked to provide follow-up information on the reported event.<br><br>In case of an adverse event, the treating physician will decide on the further treatment with darbepoetin alfa, and on the actions needed to take. |