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

BLINCYTO 38.5 micrograms powder for concentrate and solution for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 38.5 micrograms blinatumomab.

Reconstitution with water for injections results in a final blinatumomab concentration of 12.5 micrograms/mL.

Blinatumomab is produced in Chinese hamster ovary 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.

BLINCYTO powder (powder for concentrate): White to off-white powder.

Solution (stabiliser): Colourless-to-slightly yellow, clear solution with a pH of 7.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BLINCYTO is indicated for the treatment of adults with Philadelphia chromosome negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL).

4.2 Posology and method of administration

Treatment should be initiated under the direction of and supervised by physicians experienced in the treatment of haematological malignancies.

Hospitalisation is recommended for initiation at a minimum for the first 9 days of the first cycle and the first 2 days of the second cycle.

In patients with a history or presence of clinically relevant central nervous system (CNS) pathology (see section 4.4), hospitalisation is recommended at a minimum for the first 14 days of the first cycle. In the second cycle, hospitalisation is recommended at a minimum for 2 days, and clinical judgment should be based on tolerance to BLINCYTO in the first cycle. Caution should be exercised as cases of late occurrence of first neurological events in the second cycle have been observed.

For all subsequent cycle starts and reinitiation (e.g. if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalisation is recommended.
BLINCYTO infusion bags should be prepared to infuse over 24 hours, 48 hours, 72 hours, or 96 hours. See method of administration.

**Posology**

Patients may receive 2 cycles of treatment. A single cycle of treatment is 28 days (4 weeks) of continuous infusion. Each cycle of treatment is separated by a 14 day (2 week) treatment-free interval.

Patients who have achieved complete remission (CR/CRh*) after 2 treatment cycles may receive up to 3 additional cycles of BLINCYTO consolidation treatment, based on an individual benefits-risks assessment.

**Recommended dose (for patients at least 45 kg in weight):**

<table>
<thead>
<tr>
<th>Cycle 1</th>
<th>2 week-treatment-free interval (Days 29 – 42)</th>
<th>Cycle 2 and subsequent cycles (Days 1 - 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose Days 1 - 7</td>
<td>Subsequent dose Days 8 - 28</td>
<td>28 mcg/day via continuous infusion</td>
</tr>
<tr>
<td>9 mcg/day via continuous infusion</td>
<td>28 mcg/day via continuous infusion</td>
<td></td>
</tr>
</tbody>
</table>

**Premedication and additional medication recommendations**

Dexamethasone 20 mg intravenously should be administered 1 hour prior to initiation of each cycle of BLINCYTO therapy.

Anti-pyretic use (e.g. paracetamol) is recommended to reduce pyrexia during the first 48 hours of each treatment cycle.

Intrathecal chemotherapy prophylaxis is recommended before and during BLINCYTO therapy to prevent central nervous system ALL relapse.

**Pre-phase treatment for patients with high tumour burden**

For patients with ≥ 50% leukaemic blasts in bone marrow or > 15,000/microlitre peripheral blood leukaemic blast counts treat with dexamethasone (not to exceed 24 mg/day).

**Dose adjustments**

Consideration to discontinue BLINCYTO temporarily or permanently as appropriate should be made in the case of the following severe (grade 3) or life-threatening (grade 4) toxicities (see section 4.4): cytokine release syndrome, tumour lysis syndrome, neurological toxicity, elevated liver enzymes and any other clinically relevant toxicities.

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 table below.
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade*</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine release syndrome, tumour lysis syndrome</td>
<td>Grade 3</td>
<td>Interrupt BLINCYTO until resolved, then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Discontinue BLINCYTO permanently.</td>
</tr>
<tr>
<td>Neurological toxicity</td>
<td>Convulsion</td>
<td>Discontinue BLINCYTO permanently if more than one convolution occurs.</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>Interrupt BLINCYTO until no more than grade 1 (mild) and for at least 3 days, then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. For re-initiation, premedicate with a 24 mg dose of dexamethasone. Then reduce dexamethasone step-wise over 4 days. If the toxicity occurred at 9 mcg/day, or if the toxicity takes more than 7 days to resolve, discontinue BLINCYTO permanently.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Discontinue BLINCYTO permanently.</td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td>Grade 3</td>
<td>If clinically relevant, interrupt BLINCYTO until no more than grade 1 (mild), then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Consider discontinuing BLINCYTO permanently.</td>
</tr>
<tr>
<td>Other clinically relevant (as determined by treating physician) adverse reactions</td>
<td>Grade 3</td>
<td>Interrupt BLINCYTO until no more than grade 1 (mild), then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur.</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Consider discontinuing BLINCYTO permanently.</td>
</tr>
</tbody>
</table>

*Based on the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Grade 3 is severe, and grade 4 is life-threatening.

**Special populations**

**Elderly**

No dose adjustment is necessary in elderly patients (≥ 65 years of age), see section 5.1. There is limited experience with BLINCYTO in patients ≥ 75 years of age.

**Renal impairment**

Based on pharmacokinetic analyses, dose adjustment is not necessary in patients with mild to moderate renal dysfunction (see section 5.2). The safety and efficacy of BLINCYTO have not been studied in patients with severe renal impairment.

**Hepatic impairment**

Based on pharmacokinetic analyses, no effect of baseline liver function on blinatumomab exposure is expected and adjustment of the initial dose is not necessary (see section 5.2). The safety and efficacy of BLINCYTO have not been studied in patients with severe hepatic impairment.

**Paediatric population**

The safety and efficacy of BLINCYTO in paediatric patients have not yet been established.
Currently available data are described in section 4.8 but no recommendation on a posology can be made.

**Method of administration**

**Important note:** Do not flush infusion lines into the patient, as it will cause an inadvertent bolus of BLINCYTO to be administered. BLINCYTO should be infused through a dedicated lumen.

For instructions on the handling and preparation of the medicinal product before administration, see section 6.6.

BLINCYTO solution for infusion 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.

The BLINCYTO solution for infusion must be administered using intravenous tubing that contains a sterile, non-pyrogenic, low protein-binding 0.2 micrometre in-line filter.

A therapeutic dose of 9 mcg/day or 28 mcg/day should be administered to the patient by infusing a total of 240 mL BLINCYTO solution for infusion at one of 4 constant infusion rates and associated infusion durations:

- Infusion rate of 10 mL/h for a duration of 24 hours
- Infusion rate of 5 mL/h for a duration of 48 hours
- Infusion rate of 3.3 mL/h for a duration of 72 hours
- Infusion rate of 2.5 mL/h for a duration of 96 hours

The choice of the infusion duration should be made by the treating physician considering the frequency of the infusion bag changes. The target therapeutic dose of BLINCYTO delivered does not change.

**Change of infusion bag**

The infusion bag must be changed at least every 96 hours by a health care professional for sterility reasons.

### 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Breast-feeding (see section 4.6).

### 4.4 Special warnings and precautions for use

**Neurologic events**

Neurologic events including events with a fatal outcome have been observed. Grade 3 (CTCAE version 4.0) or higher (severe or life-threatening) neurologic events following initiation of blinatumomab administration included encephalopathy, seizures, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. Among patients that experienced a neurologic event, the median time to the first event was within the first two weeks of treatment and the majority of events resolved after treatment interruption and infrequently led to BLINCYTO treatment discontinuation.

Elderly patients may be more susceptible to serious neurologic events such as cognitive disorder, encephalopathy, and confusion.

Patients with a medical history of neurologic signs and symptoms (such as dizziness, hypoesthesia, hyporeflexia, tremor, dysaesthesia, paraesthesia, memory impairment) demonstrated a higher rate of
neurologic events (such as tremor, dizziness, confusional state, encephalopathy and ataxia). Among these patients, the median time to the first neurologic event was within the first cycle of treatment.

There is limited experience in patients with a history or presence of clinically relevant central nervous system (CNS) pathology (e.g. epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson’s disease, cerebellar disease, organic brain syndrome, psychosis) as they were excluded from clinical trials. There is a possibility of a higher risk of neurologic events in this population. The potential benefits of treatment should be carefully weighed against the risk of neurologic events and heightened caution should be exercised when administering BLINCYTO to these patients.

There is limited experience with blinatumomab in patients with documented active ALL in the CNS or cerebrospinal fluid (CSF). However patients have been treated with blinatumomab in clinical studies after clearance of CSF blasts with CNS directed therapy (such as intrathecal chemotherapy). Therefore once the CSF is cleared, treatment with BLINCYTO may be initiated.

It is recommended that a neurological examination be performed in patients prior to starting BLINCYTO therapy and that patients be clinically monitored for signs and symptoms of neurologic events (e.g. writing test). Management of these signs and symptoms to resolution may require either temporary interruption or permanent discontinuation of BLINCYTO (see section 4.2). In the event of a seizure, secondary prophylaxis with appropriate anticonvulsant medicinal products (e.g. levetiracetam) is recommended.

**Infections**

In patients receiving blinatumomab, serious infections, including sepsis, pneumonia, bacteraemia, opportunistic infections and catheter site infections have been observed, some of which were life-threatening or fatal. Patients with Eastern Cooperative Oncology Group (ECOG) performance status at baseline of 2 experienced a higher incidence of serious infections compared to patients with ECOG performance status of < 2. There is limited experience with BLINCYTO in patients with an active uncontrolled infection.

Patients receiving BLINCYTO should be clinically monitored for signs and symptoms of infection and treated appropriately. Management of infections may require either temporary interruption or discontinuation of BLINCYTO (see section 4.2).

**Cytokine release syndrome and infusion reactions**

Cytokine release syndrome (CRS) which may be life-threatening or fatal (grade ≥ 4) has been reported in patients receiving BLINCYTO (see section 4.8).

Serious adverse events that may be signs and symptoms of CRS included pyrexia, asthenia, headache, hypotension, total bilirubin increased, and nausea; uncommonly, these events led to BLINCYTO discontinuation. The median time to onset of a CRS event was 2 days. Patients should be closely monitored for signs or symptoms of these events.

Disseminated intravascular coagulation (DIC) and capillary leak syndrome (CLS, e.g. hypotension, hypoalbuminaemia, oedema and haemoconcentration) have been commonly associated with CRS (see section 4.8). Patients experiencing capillary leak syndrome should be managed promptly.

Haemophagocytic histiocytosis/macrophage activation syndrome (MAS) has been uncommonly reported in the setting of CRS.

Infusion reactions may be clinically indistinguishable from manifestations of CRS (see section 4.8). The infusion reactions were generally rapid, occurring within 48 hours after initiating infusion. However some patients reported delayed onset of infusion reactions or in later cycles. Patients should be observed closely for infusion reactions, especially during the initiation of the first and second
treatment cycles and treated appropriately. Anti-pyretic use (e.g. paracetamol) is recommended to help reduce pyrexia during the first 48 hours of each cycle. To mitigate the risk of CRS, it is important to initiate BLINCYTO (cycle 1, days 1-7) at the recommended starting dose in section 4.2.

Management of these events may require either temporary interruption or discontinuation of BLINCYTO (see section 4.2).

Tumour lysis syndrome

Tumour lysis syndrome (TLS), which may be life-threatening or fatal (grade ≥ 4) has been observed in patients receiving BLINCYTO.

Appropriate prophylactic measures including aggressive hydration and anti-hyperuricaemic therapy (such as allopurinol or rasburicase) should be used for the prevention and treatment of TLS during BLINCYTO treatment, especially in patients with higher leukocytosis or a high tumour burden. Patients should be closely monitored for signs or symptoms of TLS, including renal function and fluid balance in the first 48 hours after the first infusion. In clinical studies, patients with moderate renal impairment showed an increased incidence of TLS compared with patients with mild renal impairment or normal renal function. Management of these events may require either temporary interruption or discontinuation of BLINCYTO (see section 4.2).

Neutropenia and febrile neutropenia

Neutropenia and febrile neutropenia, including life-threatening cases, have been observed in patients receiving BLINCYTO. Laboratory parameters (including, but not limited to white blood cell count and absolute neutrophil count) should be monitored routinely during BLINCYTO infusion, especially during the first 9 days of the first cycle, and treated appropriately.

Elevated liver enzymes

Treatment with BLINCYTO was associated with transient elevations in liver enzymes. The majority of the events were observed within the first week of treatment initiation and did not require interruption or discontinuation of BLINCYTO (see section 4.8).

Monitoring of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and total blood bilirubin prior to the start of and during BLINCYTO treatment especially during the first 48 hours of the first 2 cycles should be performed. Management of these events may require either temporary interruption or discontinuation of BLINCYTO (see section 4.2).

Pancreatitis

Pancreatitis, life-threatening or fatal, has been reported in patients receiving BLINCYTO in clinical trials and the post-marketing setting. High-dose steroid therapy may have contributed, in some cases, to the pancreatitis.

Patients should be closely monitored for signs and symptoms of pancreatitis. Patient evaluation may include physical examination, laboratory evaluation for serum amylase and serum lipase, and abdominal imaging, such as ultrasound and other appropriate diagnostic measures. Management of pancreatitis may require either temporary interruption or discontinuation of BLINCYTO (see section 4.2).
Leukoencephalopathy including progressive multifocal leukoencephalopathy

Cranial magnetic resonance imaging (MRI) changes showing leukoencephalopathy have been observed in patients receiving BLINCYTO, especially in patients with prior treatment with cranial irradiation and anti-leukaemic chemotherapy (including systemic high dose methotrexate or intrathecal cytarabine). The clinical significance of these imaging changes is unknown.

Due to the potential for progressive multifocal leukoencephalopathy (PML), patients should be monitored for signs and symptoms. In case of suspicious events consider consultation with a neurologist, brain MRI and examination of cerebral spinal fluid (CSF), see section 4.8.

Immunisations

The safety of immunisation with live viral vaccines during or following BLINCYTO therapy has not been studied. Vaccination with live virus vaccines is not recommended for at least 2 weeks prior to the start of BLINCYTO treatment, during treatment, and until recovery of B lymphocytes to normal ranges following last treatment cycle.

Due to the potential depletion of B-cells in newborns following exposure to blinatumomab during pregnancy, newborns should be monitored for B-cell depletion and vaccinations with live virus vaccines should be postponed until the infant’s B-cell count has recovered (see section 4.6).

Contraception

Women of childbearing potential have to use effective contraception during and for at least 48 hours, after treatment with BLINCYTO (see section 4.6).

Medication errors

Medication errors have been observed with BLINCYTO treatment. It is very important that the instructions for preparation (including reconstitution and dilution) and administration are strictly followed to minimise medication errors (including underdose and overdose) (see section 4.2).

Excipients with known effect

This medicinal product provides less than 1 mmol (23 mg) sodium over a 24 hour infusion i.e. “essentially sodium free”.

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed. Results from an in vitro test in human hepatocytes suggest that blinatumomab did not affect CYP450 enzyme activities.

Initiation of BLINCYTO treatment causes transient release of cytokines during the first days of treatment that may suppress CYP450 enzymes. Patients who are receiving medicinal products that are CYP450 and transporter substrates with a narrow therapeutic index should be monitored for adverse effects (e.g. warfarin) or drug concentrations (e.g. cyclosporine) during this time. The dose of the concomitant medicinal product should be adjusted as needed.
4.6 Fertility, pregnancy and lactation

Pregnancy

Reproductive toxicity studies have not been conducted with blinatumomab. In an embryo-foetal developmental toxicity study conducted in mice, the murine surrogate molecule crossed the placenta and did not induce embryotoxicity, or teratogenicity (see section 5.3). The expected depletions of B and T-cells were observed in the pregnant mice but haematological effects were not assessed in foetuses.

There are no data from the use of blinatumomab in pregnant women.

Blinatumomab should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus.

Women of childbearing potential have to use effective contraception during and for at least 48 hours after treatment with blinatumomab (see section 4.4).

In case of exposure during pregnancy, depletion of B-cells may be expected in newborns due to the pharmacological properties of the product. Consequently, newborns should be monitored for B-cell depletion and vaccinations with live virus vaccines should be postponed until the infant’s B-cell count has recovered (see section 4.4).

Breast-feeding

It is unknown whether blinatumomab or metabolites are excreted in human milk. Based on its pharmacological properties, a risk to the suckling child cannot be excluded. Consequently, as a precautionary measure, breast-feeding is contra-indicated during and for at least 48 hours after treatment with blinatumomab.

Fertility

No studies have been conducted to evaluate the effects of blinatumomab on fertility. No adverse effects on male or female mouse reproductive organs in 13 week toxicity studies with the murine surrogate molecule (see section 5.3).

4.7 Effects on ability to drive and use machines

Blinatumomab has major influence on the ability to drive and use machines. Confusion and disorientation, coordination and balance disorders, risk of seizures and disturbances in consciousness can occur (see section 4.4). Due to the potential for neurologic events, patients receiving blinatumomab should refrain from driving, engaging in hazardous occupations or activities such as driving or operating heavy or potentially dangerous machinery while blinatumomab is being administered. Patients must be advised that they may experience neurologic events.

4.8 Undesirable effects

Summary of the safety profile

The adverse reactions described in this section were identified in the randomised phase III clinical study (N = 267) and in the single-arm phase II study (N = 189) in adults with Philadelphia chromosome negative relapsed or refractory B-precursor ALL.

The most serious adverse reactions that may occur during blinatumomab treatment include: infections (29.6%), neutropenia/febrile neutropenia (11.6%), neurologic events (11.6%), cytokine release syndrome (2.4%), and tumour lysis syndrome (0.9%).
The most common adverse reactions were: infections (63.6%), pyrexia (60.1%), infusion-related reactions (32.0%), headache (31.1%), febrile neutropenia (25.7%), anaemia (24.8%), oedema (24.1%), neutropenia (22.1%), thrombocytopenia (20.4%), increased liver enzymes (16.7%), cough (16.2%) and rash (16.0%).

Tabulated list of adverse reactions

Adverse reactions are presented below by system organ class and frequency category. Frequency categories were determined from the crude incidence rate reported for each adverse reaction in the randomised phase III clinical study (N = 267) and in the single-arm phase II study (N = 189) in adults with Philadelphia chromosome negative relapsed or refractory B-precursor ALL. Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>MedDRA system organ class</th>
<th>Very common (≥ 1/10)</th>
<th>Common (≥ 1/100 to &lt; 1/10)</th>
<th>Uncommon (≥ 1/1,000 to &lt; 1/100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Bacterial infections(^a,b)</td>
<td>Sepsis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fungal infections(^a,b)</td>
<td>Pneumonia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Viral infections(^a,b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infections – pathogen unspecified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Febrile neutropenia(^1)</td>
<td>Leukocytosis(^8)</td>
<td>Histiocytosis</td>
</tr>
<tr>
<td></td>
<td>Anaemia(^1)</td>
<td>Lymphopenia(^10)</td>
<td>haematophagic</td>
</tr>
<tr>
<td></td>
<td>Neutropenia(^11)</td>
<td>Lymphadenopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia(^16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leukopenia(^9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Cytokine release syndrome(^a)</td>
<td>Hypersensitivity</td>
<td>Cytokine storm</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td>Tumour lysis syndrome</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>Confusional state(^a)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Disorientation</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Encephalopathy(^4)</td>
<td>Speech disorder</td>
</tr>
<tr>
<td></td>
<td>Tremor(^a)</td>
<td>Aphasia</td>
<td>Cranial nerve disorder(^b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paraesthesia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seizure</td>
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<tr>
<td></td>
<td></td>
<td>Cognitive disorder</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Memory impairment</td>
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<tr>
<td></td>
<td></td>
<td>Somnolence</td>
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<tr>
<td></td>
<td></td>
<td>Hypoesthesia</td>
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<tr>
<td></td>
<td></td>
<td>Dizziness</td>
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<tr>
<td></td>
<td></td>
<td>Ataxia</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Speech disorder</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cranial nerve disorder</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Tachycardia(^15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypotension(^7)</td>
<td>Hypertension(^6)</td>
<td>Capillary leak syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flushing</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal</td>
<td>Cough</td>
<td>Dyspnoea</td>
<td>Acute respiratory failure</td>
</tr>
<tr>
<td>disorders</td>
<td></td>
<td>Respiratory failure</td>
<td>Dyspnoea exertional</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wheezing</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Productive cough</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash(^14)</td>
<td>Hyperbilirubinaemia(^3)</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue</td>
<td>Back pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>disorders</td>
<td>Pain in extremity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bone pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MedDRA system organ class</td>
<td>Very common (≥ 1/10)</td>
<td>Common (≥ 1/100 to &lt; 1/10)</td>
<td>Uncommon (≥ 1/1,000 to &lt; 1/100)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
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<td>-----------------------------</td>
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</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pyrexia(^1)</td>
<td>Chest pain(^2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oedema(^1)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Chills</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Hepatic enzyme increased(^3), Decreased immunoglobulins(^4)</td>
<td>Blood alkaline phosphatase increased</td>
<td>Weight increased</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Infusion-related reactions(^5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{1}\) Additional information is provided in “Description of selected adverse reactions”.
\(^{2}\) MedDRA high level group terms (MedDRA version 18.1).

Event terms that represent the same medical concept or condition were grouped together and reported as a single adverse reaction in the table above. The terms contributing to the relevant adverse reaction are indicated below:

1. Anaemia includes anaemia and haemoglobin decreased.
2. Chest pain includes chest discomfort, chest pain, musculoskeletal chest pain and non-cardiac chest pain.
3. Decreased immunoglobulins includes blood immunoglobulin G decreased, globulins decreased, hypogammaglobulinaemia, hypoglobulinaemia and immunoglobulins decreased.
4. Hepatic enzyme increased includes alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, hepatic enzyme increased and transaminases increased.
5. Hyperbilirubinaemia includes blood bilirubin increased and hyperbilirubinaemia.
6. Hypertension includes blood pressure increased and hypertension.
7. Hypotension includes blood pressure decreased and hypotension.
8. Leukocytosis includes leukocytosis and white blood cell count increased.
9. Leukopenia includes leukopenia and white blood cell count decreased.
10. Lymphopenia includes lymphocyte count decreased and lymphopenia.
11. Neutropenia includes neutropenia and neutrophil count decreased.
12. Oedema includes face oedema, generalised oedema, oedema and oedema peripheral.
13. Pyrexia includes body temperature increased and pyrexia.
14. Rash includes erythema, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular and rash pruritic.
15. Tachycardia includes sinus tachycardia, supraventricular tachycardia and tachycardia.
16. Thrombocytopenia includes platelet count decreased and thrombocytopenia.
17. Infusion-related reactions is a composite term that includes the term infusion-related reaction and the following events occurring with the first 48 hours of infusion and event lasted <=2 days: pyrexia, cytokine release syndrome, hypotension, myalgia, acute kidney injury, hypertension, and rash erythematous.

Description of selected adverse reactions

Neurologic events

In BLINCYTO-treated patients in the randomised phase III clinical study (N = 267) and the single arm phase II clinical study (N = 189), 66.0% of patients experienced one or more neurologic adverse reactions (including psychiatric disorders), primarily involving the central nervous system. Serious and grade ≥ 3 neurologic adverse reactions were observed in 11.6% and 12.1% of patients respectively, of which the most common serious adverse reactions were encephalopathy, tremor, aphasia, and confusional state. The majority of neurologic events (80.5%) were clinically reversible and resolved following interruption of BLINCYTO. The median time to the first event was within the first two weeks of treatment. One case of fatal encephalopathy has been reported in an earlier phase II clinical single-arm study. For clinical management of neurologic events, see section 4.4.
Infections

Life-threatening or fatal (grade ≥ 4) viral, bacterial and fungal infections have been reported in patients treated with BLINCYTO. In addition, reactivations of virus infection (e.g. Polyoma (BK)) have been observed in the phase II clinical study. Patients with ECOG performance status at baseline of 2 experienced a higher incidence of serious infections compared to patients with ECOG performance status of < 2. For clinical management of infections, see section 4.4.

Cytokine release syndrome (CRS)

In BLINCYTO-treated patients in the randomised phase III clinical study (N = 267) and the single arm phase II clinical study (N = 189), serious CRS reactions were reported in 2.4% of patients with a median time to onset of 2 days. Capillary leak syndrome was observed in 1 patient in the phase II clinical study. For clinical management of CRS, see section 4.4.

Elevated liver enzymes

In BLINCYTO-treated patients in the randomised phase III clinical study (N = 267) and the single arm phase II clinical study (N = 189), 22.4% of patients reported elevated liver enzymes and associated signs/symptoms. Serious and grade ≥ 3 adverse reactions (such as ALT increased, AST increased, and blood bilirubin increased) were observed in 1.5% and 13.6% of patients respectively. The median time to onset to the first event was 4 days from the start of BLINCYTO treatment initiation. The duration of hepatic adverse reactions has generally been brief and with rapid resolution, often when continuing uninterrupted treatment with BLINCYTO. For clinical management of elevated liver enzymes, see section 4.4.

Pancreatitis

Pancreatitis, life-threatening or fatal, has been reported in patients receiving BLINCYTO in the clinical trials and the post-marketing settings. The median time to onset was 7.5 days. For clinical management of pancreatitis, see section 4.4.

Leukoencephalopathy including progressive multifocal leukoencephalopathy

Leukoencephalopathy has been reported. Patients with brain MRI/CT findings consistent with leukoencephalopathy experienced concurrent serious adverse events including confusional state, tremor, cognitive disorder, encephalopathy, and convulsion. Although there is a potential for the development of progressive multifocal leukoencephalopathy (PML), no confirmed case of PML has been reported in the phase III clinical study.

Paediatric population

There is limited experience in paediatric patients. BLINCYTO has been evaluated in paediatric patients with relapsed or refractory B-precursor ALL in a phase I/II dose escalation/evaluation study. At a dose higher than the recommended dose for adult patients, a case of fatal cardiac failure occurred in the setting of life-threatening cytokine release syndrome (CRS) and tumour lysis syndrome (TLS), see section 4.4.

Other special populations

There is limited experience with BLINCYTO in patients ≥ 75 years of age. Generally, safety was similar between elderly patients (≥ 65 years of age) and patients less than 65 years of age treated with BLINCYTO. However, elderly patients may be more susceptible to serious neurologic events such as cognitive disorder, encephalopathy and confusion.

The safety of BLINCYTO has not been studied in patients with severe renal impairment.
Immunogenicity

In clinical studies of adult ALL patients treated with BLINCYTO, less than 3% tested positive for anti-blinatumomab antibodies. Six of those patients had anti-blinatumomab antibodies with in vitro neutralising activity.

If formation of anti-blinatumomab antibodies with a clinically significant effect is suspected, contact the Marketing Authorisation Holder to discuss antibody testing. Contact details are provided in section 6 of the package leaflet.

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

Overdoses have been observed including one patient who received 133-fold the recommended therapeutic dose of BLINCYTO delivered over a short duration. Overdoses resulted in adverse reactions which were consistent with the reactions observed at the recommended therapeutic dose and included fever, tremors, and headache. In the event of overdose, the infusion should be temporarily interrupted and patients should be monitored. Reinitiation of BLINCYTO at the correct therapeutic dose should be considered when all toxicities have resolved and no earlier than 12 hours after interruption of the infusion (see section 4.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other Antineoplastic agents, ATC code: L01XC19.

Mechanism of action

Blinatumomab is a bispecific T-cell engager antibody construct that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T-cells. It activates endogenous T-cells by connecting CD3 in the T-cell receptor (TCR) complex with CD19 on benign and malignant B-cells. The anti-tumour activity of blinatumomab immunotherapy is not dependent on T-cells bearing a specific TCR or on peptide antigens presented by cancer cells, but is polyclonal in nature and independent of human leukocyte antigen (HLA) molecules on target cells. Blinatumomab mediates the formation of a cytolytic synapse between the T-cell and the tumour cell, releasing proteolytic enzymes to kill both proliferating and resting target cells. Blinatumomab is associated with transient upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T-cells, and results in elimination of CD19+ cells.

Pharmacodynamic effects

Consistent immune-pharmacodynamic responses were observed in patients studied. During the continuous intravenous infusion over 4 weeks, the pharmacodynamic response was characterised by T-cell activation and initial redistribution, rapid peripheral B-cell depletion, and transient cytokine elevation.

Peripheral T-cell redistribution (i.e. T-cell adhesion to blood vessel endothelium and/or transmigration into tissue) occurred after start of blinatumomab infusion or dose escalation. T-cell counts initially
declined within 1 to 2 days and then returned to baseline levels within 7 to 14 days in the majority of patients. Increase of T-cell counts above baseline (T-cell expansion) was observed in few patients.

Peripheral B-cell counts decreased rapidly to an undetectable level during treatment at doses \( \geq 5 \text{ mcg/m}^2/\text{day} \) or \( \geq 9 \text{ mcg/day} \) in the majority of patients. No recovery of peripheral B-cell counts was observed during the 2-week treatment-free period between treatment cycles. Incomplete depletion of B-cells occurred at doses of 0.5 mcg/m\(^2\)/day and 1.5 mcg/m\(^2\)/day and in a few non-responders at higher doses.

Cytokines including IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, TNF-\( \alpha \) and IFN-\( \gamma \) were measured and, IL-6, IL-10 and IFN-\( \gamma \) were most elevated. Transient elevation of cytokines was observed in the first two days following start of blinatumomab infusion. The elevated cytokine levels returned to baseline within 24 to 48 hours during the infusion. In subsequent treatment cycles, cytokine elevation occurred in fewer patients with lesser intensity compared to the initial 48 hours of the first treatment cycle.

**Clinical efficacy and safety**

A total of 456 patients aged \( \geq 18 \) years of age with relapsed or refractory B-precursor ALL were exposed to BLINCYTO during the phase II and phase III clinical studies described below.

The safety and efficacy of BLINCYTO compared to standard of care (SOC) chemotherapy were evaluated in a randomised, open-label, multicentre, phase III study. Eligible patients were \( \geq 18 \) years of age and ECOG status \( \leq 2 \) with relapsed or refractory B-cell precursor ALL (had \( > 5\% \) blasts in the bone marrow and either relapse at any time after allogeneic HSCT, untreated first relapse with first remission duration \( < 12 \) months, or refractory to last therapy).

Patients were randomised 2:1 to receive BLINCYTO or 1 of 4 prespecified, investigator-selected, SOC backbone chemotherapy regimens. Randomisation was stratified by age (\( < 35 \) years versus \( \geq 35 \) years of age), prior salvage therapy (yes versus no), and prior allogeneic HSCT (yes versus no) as assessed at the time of consent. The demographics and baseline characteristics were well-balanced between the two arms (see table 1).
Table 1. Demographics and baseline characteristics in phase III study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BLINCYTO (N = 271)</th>
<th>SOC chemotherapy (N = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median, years (min, max)</td>
<td>37 (18, 80)</td>
</tr>
<tr>
<td></td>
<td>Mean, years (SD)</td>
<td>40.8 (17.1)</td>
</tr>
<tr>
<td></td>
<td>≥ 65 Years, n (%)</td>
<td>33 (12.2)</td>
</tr>
<tr>
<td>Prior salvage therapy</td>
<td></td>
<td>164 (60.5)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>114 (42.1)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>91 (33.6)</td>
</tr>
<tr>
<td></td>
<td>≥ 2</td>
<td>66 (24.3)</td>
</tr>
<tr>
<td>Prior alloHSCT</td>
<td></td>
<td>94 (34.7)</td>
</tr>
<tr>
<td>ECOG status - n (%)</td>
<td>0</td>
<td>96 (35.4)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>134 (49.4)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>41 (15.1)</td>
</tr>
<tr>
<td>Refractory status- n (%)</td>
<td>Primary refractory</td>
<td>46 (17.0)</td>
</tr>
<tr>
<td></td>
<td>Refractory to salvage therapy</td>
<td>87 (32.1)</td>
</tr>
<tr>
<td>Maximum of central/local bone marrow blasts - n (%)</td>
<td>≥ 50%</td>
<td>201 (74.2)</td>
</tr>
</tbody>
</table>

AlloHSCT = allogeneic haematopoietic stem cell transplantation
SOC = standard of care

BLINCYTO was administered as a continuous intravenous infusion. In the first cycle, the initial dose was 9 mcg/day for week 1, then 28 mcg/day for the remaining 3 weeks. The target dose of 28 mcg/day was administered in cycle 2 and subsequent cycles starting on day 1 of each cycle. Dose adjustment was possible in case of adverse events. Of the 267 patients who received BLINCYTO, the mean number of completed treatment cycles was 2.0; of the 109 patients who received SOC chemotherapy, the mean number of treatment cycles was 1.3.

The primary endpoint was overall survival (OS). The median OS was 4.0 months (95% CI: 2.9, 5.3) in the SOC chemotherapy arm compared with 7.7 months (95% CI: 5.6, 9.6) in the BLINCYTO arm. The hazard ratio (95% CI) was 0.71 (0.55, 0.93) between treatment arms favouring BLINCYTO, indicated a 29% reduction in hazard rate in the BLINCYTO arm (p-value = 0.012 (stratified log-rank test)), see figure 1. Consistency in OS results was shown in subgroups by stratification factors.

Consistent results were observed after censoring at the time of HSCT; median OS, censored at the time of HSCT, was 6.9 months (95% CI: 5.3, 8.8) in the BLINCYTO group and 3.9 months (95% CI: 2.8, 4.9) in the SOC group (HR, 0.66; 95% CI: 0.50, 0.88; p value = 0.004). The mortality rate following alloHSCT among all responders who did not receive anti-leukemic therapy was 10/38 (26.3%; 95% CI: 13.4, 43.1) in the BLINCYTO group and 3/12 (25%; 95% CI: 5.5, 57.2) in the SOC group; such mortality rate at 100 days post alloHSCT was 4/38 (12.4%; 95% CI: 4.8%, 29.9%) in the BLINCYTO group and 0/12 (0%; 95% CI: not estimable) in the SOC group. Efficacy results from other key endpoints in the study are summarised in table 2.
Figure 1. Kaplan-Meier curve of overall survival

Number of Subjects at Risk

<table>
<thead>
<tr>
<th></th>
<th>Blinicyto</th>
<th>SOC Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>271</td>
<td>176</td>
<td>124</td>
</tr>
<tr>
<td>79</td>
<td>45</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

A censored subject is indicated by a vertical bar |.

Median OS, mo

Blinicyto (N=271) 7.7 (5.6, 9.6)
SOC Chemo (N=134) 4.0 (2.3, 5.3)

HR (Blinicyto/SOC Chemo) (95% CI) 0.71 (0.55, 0.93)

p-value (2-sided) 0.012
Table 2. Efficacy results in patients ≥ 18 years of age with Philadelphia chromosome negative relapsed or refractory B-cell precursor ALL

<table>
<thead>
<tr>
<th></th>
<th>BLINCYTO (N = 271)</th>
<th>SOC chemotherapy (N = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete remission (CR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/CRh*/CRi*, n (%) [95% CI]</td>
<td>119 (43.9) (37.9, 50.0)</td>
<td>33 (24.6) (17.6, 32.8)</td>
</tr>
<tr>
<td>Treatment difference [95% CI]</td>
<td>19.3 (9.9, 28.7)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>CR, n (%) [95% CI]</td>
<td>91 (33.6) (28.0, 39.5)</td>
<td>21 (15.7) (10.0, 23.0)</td>
</tr>
<tr>
<td>Treatment difference [95% CI]</td>
<td>17.9 (9.6 – 26.2)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Event-free survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-month estimate % [95% CI]</td>
<td>30.7 (25.0, 36.5)</td>
<td>12.5 (7.2, 19.2)</td>
</tr>
<tr>
<td>18-months estimate % [95% CI]</td>
<td>9.5 (5.1, 15.6)</td>
<td>7.9 (3.7, 14.2)</td>
</tr>
<tr>
<td>HR [95% CI]</td>
<td>0.55 (0.43, 0.71)</td>
<td></td>
</tr>
</tbody>
</table>

**Duration of haematological response**

- Median time to event [95% CI]
  - CR: 8.3 (5.7, 10.7) vs 7.8 (2.2, 19.0)
  - CR/CRh*/CRi: 7.3 (5.8, 9.9) vs 4.6 (1.8, 19.0)

**MRD* response for CR/CRh*/CRi**

- MRD evaluable patients (% [95% CI]): 74/97 (76.3) (66.6, 84.3) vs 16/33 (48.5) (30.8, 66.5)

**Duration of MRD response**

- Median time to event [95% CI]: 4.5 months (3.6, 9.0) vs 3.8 months (1.9, 19.0)

**Postbaseline alloHSCT - n (%)**

- Overall subjects: 65 (24) vs 32 (23.9)
- Hematological responders (CR/CRh*/CRi): 50 (42.0) vs 18 (54.5)

**Time to alloHSCT among all transplanted patients**

- Median time to event (Interquartile range): 3.7 months (3.0, 5.3) (N = 65) vs 3.1 months (2.6, 4.3) (N = 32)

**Time to alloHSCT among CR/CRh*/CRi responders**

- Median time to event [95% CI] (KM estimate): 11.3 months (5.2, NE) (N = 119) vs 3.6 months (2.3, 7.2) (N = 33)

**100 day mortality after alloHSCT**

- n/N (%), [95% CI]: 4/38, 12.4% (4.8, 29.9) vs 0/12, 0.0% (0.0, NE)

---

*a.* CR was defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/microlitre and absolute neutrophil counts [ANC] > 1,000/microlitre).

*b.* CRh* (complete remission with partial haematologic recovery) was defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/microlitre and ANC > 500/microlitre).

*c.* CRi (complete remission with incomplete haematologic recovery) was defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and incomplete recovery of peripheral blood counts (platelets > 100,000/microlitre or ANC > 1,000/microlitre).

*d.* EFS time was calculated from the time of randomisation until the date of disease assessment indicating a relapse after achieving a CR/CRh*/CRi or death, whichever is earlier. Subjects who fail to achieve a CR/CRh*/CRi within 12 weeks of treatment initiation are considered treatment failures and assigned an EFS duration of 1 day.

*e.* MRD (minimum residual disease) response was defined as MRD by PCR or flow cytometry < 1 x 10^-4.

*f.* Patients who achieved CR/CRh*/CRi and had an evaluable post baseline MRD assessment.
Health related quality of life

In this open-label study, Health related quality of life (HRQoL) reported by patients were measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30). In a post-hoc sensitivity analysis, compared to SOC, BLINCYTO consistently delayed the time to clinically meaningful deterioration of HRQoL (≥ 10 point worsening from baseline) for global health status [median BLINCYTO versus SOC: 8.1 months versus 1.0 month; HR = 0.60 (95% CI = 0.42, 0.85)], functional scales, symptom scales and individual items. Because the health related quality of life results are based on a post-hoc sensitivity analysis, the results should be interpreted with caution.

BLINCYTO was also evaluated in an open-label, multicentre, single-arm phase II study of 189 patients. Eligible patients were ≥ 18 years of age with Philadelphia chromosome negative relapsed or refractory B-precursor ALL (relapsed with first remission duration of ≤ 12 months in first salvage, or relapsed or refractory after first salvage therapy, or relapsed within 12 months of allogeneic HSCT, and had ≥ 10% blasts in bone marrow).

Premedication, BLINCYTO dose per treatment cycle and route of administration were identical to those in the phase III study. Patients were premedicated with a mandatory cerebrospinal fluid prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines within 1 week prior to start of BLINCYTO treatment. BLINCYTO was administered as a continuous intravenous infusion. In the first cycle, the initial dose was 9 mcg/day for week 1, then 28 mcg/day for the remaining 3 weeks. The target dose of 28 mcg/day was administered in cycle 2 and subsequent cycles starting on day 1 of each cycle. Dose adjustment was possible in the case of adverse events. The treated population included 189 patients who received at least 1 infusion of BLINCYTO; the mean number of cycles per patient was 1.6. Patients who responded to BLINCYTO but later relapsed had the option to be retreated with BLINCYTO. Among treated patients, the median age was 39 years (range: 18 to 79 years, including 25 patients ≥ 65 years of age), 64 of 189 (33.9%) had undergone HSCT prior to receiving BLINCYTO and 32 of 189 (16.9%) had received more than 2 prior salvage therapies.

The primary endpoint was the complete remission/complete remission with partial haematological recovery (CR/CRh*) rate within 2 cycles of treatment with BLINCYTO. Eighty-one of 189 (42.9%) patients achieved CR/CRh* within the first 2 treatment cycles with the majority of responses (64 of 81) occurring within 1 cycle of treatment. In the elderly population (≥ 65 years of age) 11 of 25 patients (44.0%) achieved CR/CRh* within the first 2 treatment cycles (see section 4.8 for safety in elderly). Four patients achieved CR during consolidation cycles, resulting in a cumulative CR rate of 35.4% (67/189; 95% CI: 28.6% - 42.7%). Thirty-two of 189 (17%) patients underwent allogeneic HSCT in CR/CRh* induced with BLINCYTO (see table 3).
Table 3. Efficacy results in patients ≥ 18 years of age with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL)

<table>
<thead>
<tr>
<th>n (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 189</td>
<td></td>
</tr>
<tr>
<td>Complete remission (CR)/Complete remission with partial haematological recovery (CRh*)</td>
<td>81 (42.9%)</td>
</tr>
<tr>
<td>CR</td>
<td>63 (33.3%)</td>
</tr>
<tr>
<td>CRh*</td>
<td>18 (9.5%)</td>
</tr>
<tr>
<td>Blast free hypoplastic or aplastic bone marrow</td>
<td>17 (9%)</td>
</tr>
<tr>
<td>Partial remission</td>
<td>5 (2.6%)</td>
</tr>
<tr>
<td>Relapse-free survival (RFS) for CR/CRh*</td>
<td>5.9 months</td>
</tr>
<tr>
<td>Overall survival</td>
<td>6.1 months</td>
</tr>
</tbody>
</table>

1. CR was defined as ≤5% of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/microlitre and absolute neutrophil counts [ANC] > 1,000/microlitre).
2. CRh* was defined as ≤5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/microlitre and ANC > 500/microlitre).
3. Blast free hypoplastic or aplastic bone marrow was defined as bone marrow blasts ≤5%, no evidence of disease, insufficient recovery of peripheral blood counts: platelets ≤50,000/microlitre and/or ANC ≤500/microlitre.
4. Partial remission was defined as bone marrow blasts 6% to 25% with at least a 50% reduction from baseline.
5. Relapse was defined as haematological relapse (blasts in bone marrow greater than 5% following CR) or an extramedullary relapse.

In a prespecified exploratory analysis, 60 of 73 MRD evaluable patients with CR/CRh* (82.2%) also had a MRD response (defined as MRD by PCR < 1 x 10^4).

Patients with prior allogeneic HSCT had similar response rates to those without prior HSCT, older patients had similar response rates to younger patients, and no substantial difference was observed in remission rates based on the number of lines of prior salvage treatment.

In patients with non-CNS/non-testes extramedullary disease (defined as at least 1 lesion ≥ 1.5 cm) at screening (N = 8/189) clinical response rates (25% [95% CI: 3.2-65.1] were lower compared with patients with no evidence of extramedullary disease (N = 181, 43.6% [95% CI: 36.3 - 51.2]) (see figure 2).

Patients with the highest tumour burden as measured by the percentage of bone marrow blast cells at baseline (≥ 90%) still had a clinically meaningful response with a CR/CRh* rate of 21.6% (CI 12.9 – 32.7) (see figure 2). Patients with low tumour burden (< 50%) responded best to BLINCYTO treatment with CR/CRh* rate of 72.9% (CI 59.7 – 83.6).
Figure 2. Forest plot of CR/CRh* rate during the first two cycles for study MT103-211 (primary analysis set)

n = number of patients who achieved CR or CRh* in the first two cycles of treatment in the specified subgroup.
N = total number of patients in the specified subgroup.

There is limited data in patients with late first relapse of B-precursor ALL defined as a relapse occurring more than 12 months after first remission or more than 12 months after HSCT in the first remission. In clinical studies, 88.9% (8/9) of patients with late first relapse as defined in the individual studies achieved CR/CRh* within the first 2 treatment cycles with 62.5% (6/9) achieving MRD response and 37.5% (3/9) undergoing allogeneic HSCT after treatment with BLINCYTO. The median overall survival (OS) was 17.7 months (CI 3.1 – not estimable).

Paediatric population

There is limited experience in paediatric patients, see section 4.8.

The European Medicines Agency has deferred the obligation to submit the results of studies with BLINCYTO in children from 1 month to less than 18 years of age with acute lymphoblastic leukaemia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to 90 mcg/m²/day (approximately equivalent to 9-162 mcg/day) in adult patients. Following continuous intravenous infusion, the steady state serum concentration (Css) was achieved within a day and remained stable over time. The increase in mean Css values was approximately proportional to the dose in the range tested. At the clinical doses of 9 mcg/day and 28 mcg/day for the treatment of relapsed/refractory ALL, the mean (SD)Css was 230 (359) pg/mL and 612 (532) pg/mL, respectively.

Distribution

The estimated mean (SD) volume of distribution based on terminal phase (Vz) was 4.52 (2.89) L with the continuous intravenous infusion of blinatumomab.
**Biotransformation**

The metabolic pathway of blinatumomab has not been characterised. Like other protein therapeutics, blinatumomab is expected to be degraded into small peptides and amino acids via catabolic pathways.

**Elimination**

The estimated mean (SD) systemic clearance with continuous intravenous infusion in patients receiving blinatumomab in clinical studies was 2.92 (2.83) L/hour. The mean (SD) half-life was 2.11 (1.42) hours. Negligible amounts of blinatumomab were excreted in the urine at the tested clinical doses.

**Body weight, body surface area, gender and age**

A population pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics on blinatumomab pharmacokinetics. Results suggest that age (18 to 80 years), gender, body weight (44 to 134 kg), and body surface area (1.39 to 2.57) do not influence the pharmacokinetics of blinatumomab. There is very limited experience with blinatumomab in adults weighing less than 45 kg.

**Renal impairment**

No formal pharmacokinetic studies of blinatumomab have been conducted in patients with renal impairment.

Pharmacokinetic analyses showed an approximately 2-fold difference in mean blinatumomab clearance values between patients with moderate renal dysfunction and normal renal function. However high inter-patient variability was discerned (CV% up to 95.6%), and clearance values in renal impaired patients were essentially within the range observed in patients with normal renal function, no clinically meaningful impact of renal function on clinical outcomes is expected.

**Hepatic impairment**

No formal pharmacokinetic studies of blinatumomab have been conducted in patients with hepatic impairment. Baseline ALT and AST levels were used to assess the effect of hepatic impairment on the clearance of blinatumomab. Population pharmacokinetic analysis suggested that there was no association between ALT or AST levels and the clearance of blinatumomab.

**Paediatric population**

There is limited experience in paediatric patients.

5.3 **Preclinical safety data**

Repeat-dose toxicity studies conducted with blinatumomab and the murine surrogate revealed the expected pharmacologic effects (including release of cytokines, decreases in leukocyte counts, depletion of B-cells, decreases in T-cells, decreased cellularity in lymphoid tissues). These changes reversed after cessation of treatment.

Reproductive toxicity studies have not been conducted with blinatumomab. In an embryo-foetal developmental toxicity study performed in mice, the murine surrogate crossed the placenta to a limited extent (foetal-to-maternal serum concentration ratio < 1%) and did not induce embryo-foetal toxicity or teratogenicity. The expected depletions of B- and T-cells were observed in the pregnant mice but haematological effects were not assessed in foetuses. No studies have been conducted to evaluate treatment-related effects on fertility. There were no effects on male or female reproductive organs in toxicity studies with the murine surrogate.
6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

**Powder**

- Citric acid monohydrate (E330)
- Trehalose dihydrate
- Lysine hydrochloride
- Polysorbate 80
- Sodium hydroxide (for pH-adjustment)

**Solution (stabiliser)**

- Citric acid monohydrate (E330)
- Lysine hydrochloride
- Polysorbate 80
- Sodium hydroxide (for pH-adjustment)
- Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

**Unopened vials**

- 5 years

**Reconstituted solution**

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C – 8°C or 4 hours at or below 27°C.

From a microbiological point of view, unless the method of reconstituting precludes the risks of microbial contamination, the reconstituted solution should be diluted immediately. If not diluted immediately, in-use storage times and conditions are the responsibility of the user.

**Diluted solution (prepared infusion bag)**

Chemical and physical in-use stability has been demonstrated for 10 days at 2°C – 8°C or 96 hours at or below 27°C.

From a microbiological point of view, the prepared infusion bags 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 the vials in the original package 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

Each BLINCYTO pack contains 1 vial of powder for concentrate for solution for infusion and 1 vial of solution (stabiliser):

- 38.5 micrograms blinatumomab powder in a vial (type I glass) with a stopper (elastomeric rubber), seal (aluminium) and a flip off cap and
- 10 mL solution in a vial (type I glass) with a stopper (elastomeric rubber), seal (aluminium) and a flip off cap.

6.6 Special precautions for disposal and other handling

Aseptic preparation

Aseptic handling must be ensured when preparing the infusion. Preparation of BLINCYTO should be:
- performed under aseptic conditions by trained personnel in accordance with good practice rules especially with respect to the aseptic preparation of parenteral products.
- prepared in a laminar flow hood or biological safety cabinet using standard precautions for the safe handling of intravenous agents.

It is very important that the instructions for preparation and administration provided in this section are strictly followed to minimise medication errors (including underdose and overdose).

Special instructions to support accurate preparation

- A solution (stabiliser) is provided inside the BLINCYTO package and is used to coat the pre-filled infusion bag prior to addition of reconstituted BLINCYTO. Do not use this solution (stabiliser) for reconstitution of BLINCYTO powder for concentrate.
- The entire volume of the reconstituted and diluted BLINCYTO will be more than the volume to be administered to the patient (240 mL). This is to account for intravenous infusion line loss and to assure that the patient will receive the full dose of BLINCYTO.
- When preparing an infusion bag, remove all air from infusion bag. This is particularly important when using an ambulatory infusion pump.
- Use the specific volumes described in the reconstitution and dilution instructions below to minimise errors in calculation.

Other instructions

- BLINCYTO is compatible with polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes.
- Pump specifications: The infusion pump to administer BLINCYTO solution for infusion should be programmable, lockable and have an alarm. Elastomeric pumps should not be used.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Preparation of the solution for infusion

Specific reconstitution and dilution instructions are provided for each dose and infusion time. Verify the prescribed dose and infusion time of BLINCYTO and identify the appropriate dosing preparation...
in the relevant table below, following the steps for reconstituting BLINCYTO and preparing the infusion bag.

Before preparation, ensure you have the correct number of BLINCYTO packages available as required by the dosing table below:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Infusion duration (hours)</th>
<th>Infusion rate (mL/hour)</th>
<th>Number of BLINCYTO packages</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 mcg/day</td>
<td>24</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>3.3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>2.5</td>
<td>2</td>
</tr>
<tr>
<td>28 mcg/day</td>
<td>24</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>3.3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>2.5</td>
<td>4</td>
</tr>
</tbody>
</table>

These supplies are also required, but not included in the package
- Sterile single-use disposable syringes
- 21-23 gauge needle(s) (recommended)
- Water for injections
- Infusion bag with 250 mL sodium chloride 9 mg/mL (0.9%) solution for injection;
  - To minimise the number of aseptic transfers, use a 250 mL pre-filled infusion bag.
  - **BLINCYTO dose calculations are based on a usual overfill volume of 265 to 275 mL sodium chloride 9 mg/mL (0.9%) solution for injection.**
  - Use only polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes.
- Polyolefin, PVC non-DEHP, or EVA intravenous tubing with a sterile, non-pyrogenic, low protein-binding 0.2 micron in-line filter.
  - Ensure that the tubing is compatible with the infusion pump.

Reconstitution and preparation of BLINCYTO solution for infusion using an infusion bag pre-filled with 250 mL sodium chloride 9 mg/mL (0.9%) solution for injection

1. Use an infusion bag pre-filled with 250 mL sodium chloride 9 mg/mL (0.9%) solution for injection that usually contains a total volume of 265 to 275 mL.
2. To coat the infusion bag, using a syringe, aseptically transfer 5.5 mL of the solution (stabiliser) to the infusion bag. Gently mix the contents of the bag to avoid foaming. Discard the remaining solution (stabiliser) vial.
3. Using a syringe, reconstitute each vial of BLINCYTO powder for concentrate using 3 mL of water for injections. Direct the water for injections toward the side of the vial during reconstitution. Gently swirl contents to avoid excess foaming. **Do not shake.**
   - **Do not reconstitute BLINCYTO powder for concentrate with the solution (stabiliser).**
   - The addition of water for injections to the powder for concentrate results in a total volume of 3.08 mL for a final BLINCYTO concentration of 12.5 mcg/mL.
4. Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to infusion. The resulting solution should be clear to slightly opalescent, colourless-to-slightly yellow. **Do not use if the solution is cloudy or has precipitated.**
5. Using a syringe, aseptically transfer the required volume of reconstituted BLINCYTO into the infusion bag (see table 4). Gently mix the contents of the bag to avoid foaming. Discard any remaining BLINCYTO reconstituted solution.
6. Under aseptic conditions, attach the intravenous tubing to the infusion bag with the sterile 0.2 micron in-line filter.
7. Remove air from the infusion bag and prime the intravenous infusion line only with the prepared solution for infusion. Do not prime with sodium chloride 9 mg/mL (0.9%) solution for injection.

8. Store at 2°C – 8°C if not used immediately.

Table 4. For patients weighing greater than or equal to 45 kg: volumes of sodium chloride 9 mg/mL (0.9%) solution for injection, solution (stabiliser), and reconstituted BLINCYTO to add to infusion bag

| Pre-filled bag containing sodium chloride 9 mg/mL (0.9%) solution for injection | 250 mL (usual overfill volume of 265 to 275 mL) |
| Solution (stabiliser) | 5.5 mL |

<table>
<thead>
<tr>
<th></th>
<th>Infusion duration (hours)</th>
<th>Infusion rate (mL/hour)</th>
<th>Reconstituted BLINCYTO (number of packages)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 mcg/day</td>
<td>24</td>
<td>10</td>
<td>0.83 mL (1)</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>5</td>
<td>1.7 mL (1)</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>3.3</td>
<td>2.5 mL (1)</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>2.5</td>
<td>3.3 mL (2)</td>
</tr>
<tr>
<td>28 mcg/day</td>
<td>24</td>
<td>10</td>
<td>2.6 mL (1)</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>5</td>
<td>5.2 mL (2)</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>3.3</td>
<td>8 mL (3)</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>2.5</td>
<td>10.7 mL (4)</td>
</tr>
</tbody>
</table>

For instructions on administration, see section 4.2.

7. MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1047/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 November 2015
Date of last renewal: 22 September 2016

10. DATE OF REVISION OF THE TEXT

ANNEX II

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

Name and address of the manufacturer of the biological active substance

Lonza Biologics plc
228 Bath Road
Slough
Berkshire, SL1 4DX
UK

Name and address of the manufacturers responsible for batch release

Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

Amgen NV
Arianelaan 5
1200 Brussel
Belgium

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

The requirements for submission of periodic safety update reports 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 shall submit the first periodic safety update report 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 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.

**Additional risk minimisation measures**

Prior to launch of BLINCYTO in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where BLINCYTO is marketed, all healthcare professionals (HCP) and patients / caregivers who are expected to prescribe, dispense and use BLINCYTO are provided with the following educational packages:
- Physician educational material
- Pharmacist educational material
- Nurse educational material
- Patient / caregivers educational material
- Patient alert card

**The physician educational material** should contain:
1. The *Summary of Product Characteristics* (*SmPC*)
2. The *guide for physicians* shall contain the following key elements:
   - Remarks on the importance of reporting ADRs
   - Information on treatment with BLINCYTO, administration and posology, duration of hospitalisation, interruption and / or permanent discontinuation of the treatment

**Medication errors (ME)**
- Data from clinical trials, causes of ME, frequency, severity and outcomes.
- Reminder to counsel the patients on how to reduce the risk of ME while using the infusion pump.

**Neurologic events**
- Data from clinical trials, frequency and severity (grade 3 and 4 neurological toxicities were observed)
- Recommendation to monitor patients for signs and symptoms of neurotoxicity
- Management of neurotoxicity (including dose adjustment and dose interruption)
- Recommendation for patients not to drive while receiving BLINCYTO and to contact immediately the treating physician if they experience neurological symptoms

**The pharmacist educational material** should contain:
1. The *Summary of Product Characteristics* (*SmPC*)
2. The *guide for pharmacists*, containing the following key elements:
   - Remarks on the importance of reporting ADRs
   - Detailed description of the reconstitution and preparation procedures of BLINCYTO infusion solution for intravenous administration under aseptic conditions, using aseptic techniques.

**The nurse educational material** should contain:
1. The *Summary of Product Characteristics* (*SmPC*)
2. The *nurse educational guide*, including the following key elements:
   - Remarks on the importance of reporting ADRs
   - Description of the administration procedures of BLINCYTO
   - Description on patient’s monitoring and management of early signs and symptoms of neurological events
- Recommendation for patients not to drive while receiving BLINCYTO and to contact immediately the treating physician/nurse if they experience neurological symptoms

**The patient (including caregivers) educational material** should contain:

1. The **patient information guide**, including the following key elements:
   - Remarks on the importance of reporting ADRs
   - Description of the administration procedures of BLINCYTO and how to reduce the risk of ME while using the infusion pump.
   - Description of the main signs and/or symptoms of neurologic events and the importance of notifying the treating physician or nurse immediately if symptoms occur
   - Recommendation for patients not to drive while receiving BLINCYTO

2. The **package leaflet**

**The patient alert** card should contain:

- A warning message for HCPs treating the patient at any time, including emergency conditions, that the patient is using BLINCYTO
- Contact details of the BLINCYTO prescriber
- BLINCYTO treatment start date
- Remarks on the importance of reporting ADRs

**Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

<table>
<thead>
<tr>
<th>Description</th>
<th>Due date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-interventional post-authorisation safety study (PASS): Study 20150136:</td>
<td>Q42021</td>
</tr>
<tr>
<td>an observational study of blinatumomab safety and effectiveness, utilisation, and treatment practices*</td>
<td></td>
</tr>
</tbody>
</table>

* The study protocol needs to be developed and presented for PRAC review within 2 months after the EU Commission Decision.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

#### 1. NAME OF THE MEDICINAL PRODUCT

BLINCYTO 38.5 micrograms powder for concentrate and solution for solution for infusion blinatumomab

#### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 38.5 micrograms of blinatumomab. After reconstitution with water for injections each vial contains 12.5 micrograms/mL of blinatumomab.

#### 3. LIST OF EXCIPIENTS

Powder: citric acid monohydrate (E330), trehalose dihydrate, lysine hydrochloride, polysorbate 80 and sodium hydroxide.
Solution (stabiliser): citric acid monohydrate (E330), lysine hydrochloride, polysorbate 80, sodium hydroxide and water for injections.
See leaflet for further information.

#### 4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate and solution for solution for infusion
1 vial of powder.
1 vial of solution (stabiliser). Add to the sodium chloride bag only.

#### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

#### 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

Do not shake the reconstituted solution.

#### 8. EXPIRY DATE
9. **SPECIAL STORAGE CONDITIONS**

Store and transport refrigerated.
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**

Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/15/1047/001

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Justification for not including Braille accepted.
| **MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS** |
| **POWDER VIAL** |

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

BLINCYTO 38.5 mcg powder for concentrate
blinatumomab
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**
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).
BLINCYTO

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

Add to the sodium chloride bag only.
B. PACKAGE LEAFLET
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 using 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.
- 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 BLINCYTO is and what it is used for**

   The active ingredient in BLINCYTO is blinatumomab. This belongs to a group of medicines called antineoplastic agents which target cancer cells.

   BLINCYTO is used to treat adults with acute lymphoblastic leukaemia. Acute lymphoblastic leukaemia is a cancer of the blood in which a particular kind of white blood cell called “B-lymphocyte” is growing out of control. This medicine works by enabling your immune system to attack and destroy these abnormal white blood cancer cells.

2. **What you need to know before you use BLINCYTO**

   **Do not use BLINCYTO:**
   - if you are allergic to blinatumomab or any of the other ingredients of this medicine (listed in section 6).
   - if you are breast-feeding.

   **Warnings and precautions**

   **Talk to your doctor, pharmacist or nurse before using BLINCYTO** if any of these apply to you. BLINCYTO may not be suitable for you:
   - if you have ever had neurological problems, for example, shaking (or tremor), abnormal sensations, seizures, memory loss, confusion, disorientation, loss of balance, or difficulty in speaking. If you are still suffering from active neurological problems or conditions, tell your doctor. If your leukaemia has spread to your brain and/or spinal cord, your doctor may have to treat this first before you can start treatment with BLINCYTO. Your doctor will assess your nervous system and conduct tests before deciding if you should receive BLINCYTO. Your doctor may need to take special care of you during your treatment with BLINCYTO.
   - if you have an active infection.
• if you have ever had an infusion reaction after previously using BLINCYTO. Symptoms may include wheezing, flushing, face swelling, difficulty breathing, low or high blood pressure.
• if you think you may need any vaccinations in the near future, including those needed to travel to other countries. Some vaccines must not be given within two weeks before, at the same time as or in the months after you receive treatment with BLINCYTO. Your doctor will check if you should have the vaccination.

Tell your doctor, pharmacist or nurse immediately if you experience any of the following reactions whilst receiving BLINCYTO as these may need to be treated and your dose adjusted:
• if you experience seizures, difficulty in speaking or slurred speech, confusion and disorientation, or loss of balance.
• if you develop chills or shivering, or feel warm; you should take your temperature as you may have a fever – these may be symptoms of an infection.
• if you develop a reaction at any time during your infusion, which may include dizziness, feeling faint, nauseated, face swelling, difficulty breathing, wheezing, or rash.
• if you have severe and persistent stomach pain, with or without nausea and vomiting, as these may be symptoms of a serious and potentially fatal condition known as pancreatitis (inflammation of the pancreas).

Tell your doctor, pharmacist or nurse immediately if you became pregnant whilst receiving BLINCYTO. Your doctor will talk to you about precautions in using vaccinations for your baby.

Before each infusion cycle of BLINCYTO, you will be given medicines which help reduce a potentially life-threatening complication known as tumour lysis syndrome, which is caused by chemical disturbances in the blood due to the breakdown of dying cancer cells. You may also be given medicines to reduce fever.

During treatment, especially in the first few days after treatment start, you may experience a severe low white blood cell count (neutropenia), severe low white blood cell count with a fever (febrile neutropenia), elevated liver enzymes, or elevated uric acid. Your doctor will take regular blood tests to monitor your blood counts during treatment with BLINCYTO.

Children and adolescents

BLINCYTO should not be used in children and adolescents below 18 years of age.

Other medicines and BLINCYTO

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

Pregnancy and breast-feeding

If you are pregnant, are breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or nurse for advice before taking this medicine.

Contraception

Women who are able to become pregnant have to use effective contraception during treatment and for at least 48 hours after your last treatment. Talk to your doctor or nurse about suitable methods of contraception.
Pregnancy

The effects of BLINCYTO in pregnant women are not known but based on its mechanism of action, BLINCYTO may harm your unborn baby. You should not use BLINCYTO during pregnancy, unless your doctor thinks that it is the best medicine for you.

If you become pregnant during BLINCYTO treatment, please inform your doctor or nurse. Your doctor will talk to you about precautions in using vaccinations for your baby.

Breast-feeding

You must not breast-feed during and for at least 48 hours after your last treatment. It is not known whether BLINCYTO is excreted in breast milk but a risk for suckling baby cannot be excluded.

Driving and using machines

Do not drive, use heavy machines, or engage in hazardous activities while you are being given BLINCYTO. BLINCYTO can cause neurological problems such as dizziness, seizures, confusion, coordination and balance disorders.

BLINCYTO contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially ‘sodium-free’.

3. How to use BLINCYTO

Always use this medicine exactly as your doctor, pharmacist or nurse have told you. Check with your doctor, pharmacist or nurse if you are not sure.

How BLINCYTO is given

BLINCYTO will be given to you through a vein (intravenous) continuously for 4 weeks using an infusion pump (this is 1 treatment cycle). You will then have a 2-week break where you will not be given the infusion. Your infusion catheter will be attached to you at all times during each cycle of your treatment.

BLINCYTO is usually given for 2 treatment cycles. If you respond to BLINCYTO treatment after the first 2 cycles, your doctor may decide to give you up to 3 additional cycles of treatment. The number of treatment cycles and the dose which you will be given will depend on how you tolerate and respond to BLINCYTO. Your doctor will discuss with you how long your treatment will last. Your treatment may also be interrupted depending on how you tolerate BLINCYTO.

It is recommended that the first 9 days of treatment will be given to you in a hospital or clinic under the supervision of a doctor or nurse experienced in the use of anti-cancer medicines. If you have or had neurological problems, it is recommended that the first 14 days of treatment will be given to you in a hospital or clinic. Your doctor will discuss with you if you can continue treatment at home after your initial hospital stay. Treatment may include a bag change by a nurse.

Your doctor will determine when your BLINCYTO infusion bag will be changed, which may range from every day to every 4 days. The infusion rate may be faster or slower depending on how often the bag is changed.
Your first cycle

The recommended initial dose in your first cycle is 9 micrograms per day for 1 week. Your doctor may decide to then increase your dose to 28 micrograms per day for weeks 2, 3, and 4 of your treatment.

Your next cycles

If your doctor determines that you should be given more cycles of BLINCYTO, your pump will be set to infuse a dose of 28 micrograms per day.

Medicines given before each cycle of BLINCYTO

Before your treatment with BLINCYTO, you will be given other medicines (pre-medication) to help reduce infusion reactions and other possible side effects. These may include corticosteroids (e.g. dexamethasone).

Infusion catheter

If you have a catheter for infusion, it is very important to keep the area around the catheter clean; otherwise you could get an infection. Your doctor or nurse will show you how to care for your catheter site.

Infusion pump and intravenous tubing

Do not adjust the settings on the pump, even if there is a problem or the pump alarm sounds. Any changes to the pump settings may result in a dose that is too high or too low.

Contact your doctor or nurse immediately if:

- there is a problem with the pump or the pump alarm sounds
- the infusion bag empties before the scheduled bag change
- if the infusion pump stops unexpectedly. Do not try to restart your pump.

Your doctor or nurse will advise you on how to manage your daily activities around your infusion pump. Contact your doctor or nurse if you have questions.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some of these side effects may be serious.

Tell your doctor immediately if you get any of the following or combination of the following side effects:

- chills, shivering, fever, rapid heart rate, decreased blood pressure, aching muscles, feeling tired, coughing, difficulty breathing, confusion, redness, swelling or discharge in the affected area or at the site of the infusion line – these may be signs of an infection.
- neurologic events: shaking (or tremor), confusion, disturbances of brain function (encephalopathy), difficulty in communicating (aphasia), seizure (convulsion).
- fever, swelling, chills, decreased or increased blood pressure and fluid in the lungs, which may become severe – these may be signs of a so-called cytokine release syndrome.
- if you have severe and persistent stomach pain, with or without nausea and vomiting, as these may be symptoms of a serious and potentially fatal condition known as pancreatitis (inflammation of the pancreas).

Treatment with BLINCYTO can cause a decrease in the levels of certain white blood cells with or without fever (febrile neutropenia or neutropenia) or can lead to increased blood levels of potassium,
uric acid, and phosphate and decreased blood levels of calcium (tumour lysis syndrome). Your doctor will take regular blood tests during treatment with BLINCYTO.

Other side effects include:

**Very common side effects** (may affect more than 1 in 10 people):
- infections in the blood including bacteria, fungi, viruses, or other types of infection
- decreased levels of certain white blood cells with or without fever ((febrile) neutropenia, leukopenia), decreased levels of red blood cells, decreased levels of platelets
- fever, swelling, chills, decreased or increased blood pressure and fluid in the lungs, which may become severe (cytokine release syndrome)
- low levels of antibodies called “immunoglobulins” which help the immune system fight infection (decreased immunoglobulins)
- not being able to sleep
- headache, shaking (or tremor)
- rapid heart rate (tachycardia)
- low blood pressure
- cough
- rash
- back pain, pain in extremity, bone pain
- fever (pyrexia), swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (oedema), chills
- increased levels of liver enzymes (ALT, AST, GGT)
- reactions related to infusion may include, wheezing, flushing, face swelling, difficulty breathing, low blood pressure, high blood pressure.

**Common side effects** (may affect up to 1 in 10 people):
- serious infection which can result in organ failure, shock or can be fatal (sepsis)
- lung infection (pneumonia)
- increased levels of white blood cell count (leucocytosis), decreased levels of certain white blood cells (lymphopenia), swollen lymph nodes (lymphadenopathy)
- allergic reaction
- complications occurring after cancer treatment leading to increased blood levels of potassium, uric acid, and phosphate and decreased blood levels of calcium (tumour lysis syndrome)
- confusion, disorientation
- disturbances of brain function (encephalopathy) such as difficulty in communicating (aphasia), tingling of skin (paraesthesia), seizure, difficulty thinking or processing thoughts, difficulty remembering, difficulty in controlling movement (ataxia)
- feeling sleepy (somnolence), numbness, dizziness
- wheezing or difficulty in breathing (dyspnoea), breathlessness (respiratory failure)
- high blood pressure (hypertension)
- flushing
- coughing with phlegm
- increased bilirubin in the blood
- chest pain or other pain
- high levels of some enzymes including blood and liver enzymes
- increase in your weight

**Uncommon side effects** (may affect up to 1 in 100 people):
- fever, swelling, chills, decreased or increased blood pressure and fluid in the lungs, which may be severe and can be fatal (cytokine storm)
- excessive activation of white blood cells associated with inflammation
- difficulty in speaking
- a condition which causes fluid to leak from the small blood vessels into your body (capillary leak syndrome)
nerve problems affecting the head and neck such as visual disturbances, drooping eyelid and/or sagging muscles on one side of the face, difficulty hearing or trouble swallowing (cranial nerve disorders)

**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 VI. By reporting side effects you can help provide more information on the safety of this medicine.

5. **How to store BLINCYTO**

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 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).
- Do not freeze.
- Store in the original carton in order to protect from light.

**Reconstituted solution (BLINCYTO solution):**
- When refrigerated, the reconstituted solution must be used within 24 hours. Alternatively the vials can be stored at room temperature (up to 27°C) for up to 4 hours.

**Diluted solution (prepared infusion bag):**
If your infusion bag is changed at home:
- Infusion bags containing BLINCYTO solution for infusion will arrive in special packaging containing cooling packs.
  - Do not open the package.
  - Store the package at room temperature (up to 27°C).
  - Do not refrigerate or freeze the package.
- The package will be opened by your nurse and the infusion bags will be stored in a refrigerator until infusion.
- When refrigerated, the infusion bags must be used within 10 days of preparation.
- Once at room temperature (up to 27°C) the solution will be infused within 96 hours.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. **Contents of the pack and other information**

**What BLINCYTO contains**
- The active substance is blinatumomab. Each vial of powder contains 38.5 micrograms of blinatumomab. Reconstitution with water for injections results in a final blinatumomab concentration of 12.5 micrograms/mL.
- The other ingredients in the powder are citric acid monohydrate (E330), trehalose dihydrate, lysine hydrochloride, polysorbate 80, and sodium hydroxide.
- The solution (stabiliser) contains citric acid monohydrate (E330), lysine hydrochloride, polysorbate 80, sodium hydroxide and water for injections.
What BLINCYTO looks like and contents of the pack

BLINCYTO is a powder for concentrate and solution for solution for infusion. Each pack of BLINCYTO contains:

- 1 glass vial containing a white to off-white powder.
- 1 glass vial containing a colourless-to-slightly yellow, clear solution.

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Minervum 7061
4817 ZK Breda
The Netherlands

Marketing Authorisation Holder
Amgen Europe B.V.
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Manufacturer
Amgen NV
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### This leaflet was last revised in

This leaflet was last revised in **2023**.

### Other sources of information


### The following information is intended for healthcare professionals only:

**BLINCYTO** solution for infusion 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.

The recommended initial dose of **BLINCYTO** in the first cycle is 9 mcg/day for week 1 (first 7 days) of treatment.

The dose should be increased to 28 mcg/day starting at week 2 through week 4 of the first cycle. All subsequent cycles should be dosed at 28 mcg/day throughout the entire 4-week treatment period.
The therapeutic dose of 9 mcg/day or 28 mcg/day should be administered to the patient by infusing a total of 240 mL BLINCYTO solution for infusion at one of 4 constant infusion rate and associated infusion durations:

- Infusion rate of 10 mL/h for a duration of 24 hours
- Infusion rate of 5 mL/h for a duration of 48 hours
- Infusion rate of 3.3 mL/h for a duration of 72 hours
- Infusion rate of 2.5 mL/h for a duration of 96 hours

The choice of the infusion duration should be made by the treating physician considering the frequency of the infusion bag changes. The target therapeutic dose of BLINCYTO delivered does not change.

**Aseptic preparation**

Aseptic handling must be ensured when preparing the infusion. Preparation of BLINCYTO should be:

- performed under aseptic conditions by trained personnel in accordance with good practice rules especially with respect to the aseptic preparation of parenteral products.
- prepared in a laminar flow hood or biological safety cabinet using standard precautions for the safe handling of intravenous agents.

It is very important that the instructions for preparation and administration provided in this section are strictly followed to minimise medication errors (including underdose and overdose).

**Special instructions to support accurate preparation**

- A solution (stabiliser) is provided inside the BLINCYTO package and is used to coat the pre-filled infusion bag prior to addition of reconstituted BLINCYTO. **Do not use this solution (stabiliser) for reconstitution of BLINCYTO powder for concentrate.**
- The entire volume of the reconstituted and diluted BLINCYTO will be more than the volume to be administered to the patient (240 mL). This is to account for intravenous infusion line loss and to assure that the patient will receive the full dose of BLINCYTO.
- When preparing an infusion bag, remove all air from infusion bag. This is particularly important when using an ambulatory infusion pump.
- Use the specific volumes described in the reconstitution and dilution instructions below to minimise errors in calculation.

**Other instructions**

- BLINCYTO is compatible with polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes.
- Pump specifications: The infusion pump to administer BLINCYTO solution for infusion should be programmable, lockable and have an alarm. Elastomeric pumps should not be used.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**Preparation of the solution for infusion**

Specific reconstitution and dilution instructions are provided for each dose and infusion time. Verify the prescribed dose and infusion time of BLINCYTO and identify the appropriate dosing preparation in the relevant table below, following the steps for reconstituting BLINCYTO and preparing the infusion bag.
Before preparation, ensure you have the correct number of BLINCYTO packages available as required by the dosing table below:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Infusion duration (hours)</th>
<th>Infusion rate (mL/hour)</th>
<th>Number of BLINCYTO packages</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 mcg/day</td>
<td>24</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>3.3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>2.5</td>
<td>2</td>
</tr>
<tr>
<td>28 mcg/day</td>
<td>24</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>3.3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>2.5</td>
<td>4</td>
</tr>
</tbody>
</table>

These supplies are also required, but not included in the package:
- Sterile single-use disposable syringes
- 21-23 gauge needle(s) (recommended)
- Water for injections
- Infusion bag with 250 mL sodium chloride 9 mg/mL (0.9%) solution for injection;
  - To minimise the number of aseptic transfers, use a 250 mL pre-filled infusion bag. **BLINCYTO dose calculations are based on a usual overfill volume of 265 to 275 mL sodium chloride 9 mg/mL (0.9%) solution for injection.**
  - Use only polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes.
- Polyolefin, PVC non-DEHP, or EVA intravenous tubing with a sterile, non-pyrogenic, low protein-binding 0.2 micrometre in-line filter.
  - Ensure that the tubing is compatible with the infusion pump.

Reconstitution and preparation of BLINCYTO solution for infusion using an infusion bag pre-filled with 250 mL sodium chloride 9 mg/mL (0.9%) solution for injection

1. Use an infusion bag pre-filled with 250 mL sodium chloride 9 mg/mL (0.9%) solution for injection that usually contains a total volume of 265 to 275 mL.
2. To coat the infusion bag, using a syringe, aseptically transfer 5.5 mL of the solution (stabiliser) to the infusion bag. Gently mix the contents of the bag to avoid foaming. Discard the remaining solution (stabiliser) vial.
3. Using a syringe, reconstitute each vial of BLINCYTO powder for concentrate using 3 mL of water for injections. Direct the water for injections toward the side of the vial during reconstitution. Gently swirl contents to avoid excess foaming. **Do not shake.**
   - **Do not reconstitute BLINCYTO powder for concentrate with the solution (stabiliser).**
   - The addition of water for injections to the powder for concentrate results in a total volume of 3.08 mL for a final BLINCYTO concentration of 12.5 mcg/mL.
4. Visually inspect the reconstituted solution for particulate matter and discolouration during reconstitution and prior to infusion. The resulting solution should be clear to slightly opalescent, colourless-to-slightly yellow. **Do not use if the solution is cloudy or has precipitated.**
5. Using a syringe, aseptically transfer the required volume of reconstituted BLINCYTO into the infusion bag (see table 1). Gently mix the contents of the bag to avoid foaming. Discard any remaining BLINCYTO reconstituted solution.
6. Under aseptic conditions, attach the intravenous tubing to the infusion bag with the sterile 0.2 micron in-line filter.
7. Remove air from the infusion bag and prime the intravenous infusion line **only** with the prepared solution for infusion. **Do not prime with sodium chloride 9 mg/mL (0.9%) solution for injection.**
8. Store at 2°C – 8°C if not used immediately.
Table 1. For patients weighing greater than or equal to 45 kg: volumes of sodium chloride 9 mg/mL (0.9%) solution for injection, solution (stabiliser), and reconstituted BLINCYTO to add to infusion bag

<table>
<thead>
<tr>
<th>Dose</th>
<th>Infusion duration (hours)</th>
<th>Infusion rate (mL/hour)</th>
<th>Reconstituted BLINCYTO (number of packages)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 mcg/day</td>
<td>24</td>
<td>10</td>
<td>0.83 mL (1)</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>5</td>
<td>1.7 mL (1)</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>3.3</td>
<td>2.5 mL (1)</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>2.5</td>
<td>3.3 mL (2)</td>
</tr>
<tr>
<td>28 mcg/day</td>
<td>24</td>
<td>10</td>
<td>2.6 mL (1)</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>5</td>
<td>5.2 mL (2)</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>3.3</td>
<td>8 mL (3)</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>2.5</td>
<td>10.7 mL (4)</td>
</tr>
</tbody>
</table>

For instructions on administration, see Summary of Product Characteristics section 4.2.

Method of administration

Important Note: Do not flush infusion lines into the patient, as it will cause an inadvertent bolus of BLINCYTO to be administered. BLINCYTO should be infused through a dedicated lumen.

BLINCYTO solution for infusion 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.

The BLINCYTO solution for infusion must be administered using intravenous tubing that contains a sterile, non-pyrogenic, low protein-binding 0.2 micrometre in-line filter.

The infusion bag must be changed at least every 96 hours by a health care professional for sterility reasons.

Storage conditions and shelf life

Unopened vials:
5 years (2°C – 8°C)

Reconstituted solution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C – 8°C or 4 hours at or below 27°C.

From a microbiological point of view, unless the method of reconstituting precludes the risks of microbial contamination, the reconstituted solution should be diluted immediately. If not diluted immediately, in-use storage times and conditions are the responsibility of the user.
Diluted solution (prepared infusion bag)

Chemical and physical in-use stability has been demonstrated for 10 days at 2°C – 8°C or 96 hours at or below 27°C.

From a microbiological point of view, the prepared infusion bags 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.