▼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):

Cycle 1		2 week-treatment free interval (Days 29 – 42)	Cycle 2 and subsequent cycles (Days 1 - 28)
Starting dose Days 1 - 7	Subsequent dose Days 8 - 28		
9 mcg/day via continuous infusion	28 mcg/day via continuous infusion		28 mcg/day via continuous infusion

Premedication and additional medication recommendations

Dexamethasone 20 mg intravenous 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.

Toxicity	Grade*	Action
Cytokine release syndrome, tumour lysis syndrome	Grade 3	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.
	Grade 4	Discontinue BLINCYTO permanently.
Neurological toxicity	Convulsion	Discontinue BLINCYTO permanently if more than one convulsion occurs.
	Grade 3	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.
	Grade 4	Discontinue BLINCYTO permanently.
Elevated liver enzymes	Grade 3	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.
	Grade 4	Consider discontinuing BLINCYTO permanently.
Other clinically relevant (as determined by treating physician) adverse reactions	Grade 3	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.
	Grade 4	Consider discontinuing BLINCYTO permanently.

*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. The median time from initiation of blinatumomab to onset of a neurologic event was 9 days. The majority of events resolved after treatment interruption.

Elderly patients experienced a higher rate of neurological toxicities, including cognitive disorder, encephalopathy, and confusion. Patients with a medical history of neurologic signs and symptoms (such as dizziness, hypoaesthesia, hyporeflexia, tremor, dysaesthesia, paraesthesia, memory impairment) demonstrated a higher rate of neurologic events (such as tremor, dizziness, confusional state, encephalopathy and ataxia). The median time to onset of a neurologic event in these patients was 12 days.

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 lymphohistiocytosis/macrophage activation syndrome (HLH/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 pivotal clinical study (N = 189).

The most serious adverse reactions that may occur during blinatumomab treatment include: infections (31.7%), neurologic events (16.4%), neutropenia/febrile neutropenia (15.3%), cytokine release syndrome (0.5%), and tumour lysis syndrome (0.5%).

The most common adverse reactions were: infusion-related reactions (67.2%), infections (63.0%), pyrexia (59.8%), headache (34.4%), febrile neutropenia (28%), peripheral oedema (25.9%), nausea (24.3%), hypokalaemia (23.8%), constipation (20.6%), anaemia (20.1%), cough (18.5%), diarrhoea (18.0%), tremor (17.5%), neutropenia (17.5%), abdominal pain (16.9%), insomnia (15.3%), fatigue (15.3%) and chills (15.3%).

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 pivotal clinical study (N = 189). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**
Infections and infestations	Bacterial infections[a, b] Fungal infections[a, b] Viral infections[a, b] Other pathogen infections[b]	Sepsis Pneumonia	

MedDRA system organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**
Blood and lymphatic system disorders	Febrile neutropenia Anaemia Neutropenia Thrombocytopenia Leukopenia	Leukocytosis Lymphopenia	
Immune system disorders	Cytokine release syndrome[a]	Cytokine storm Hypersensitivity	
Metabolism and nutrition disorders	Hypokalaemia Hypomagnesaemia Hyperglycaemia Decreased appetite	Hypophosphatemia Hypoalbuminemia Tumour lysis syndrome	
Psychiatric disorders	Insomnia	Confusional state[a] Disorientation	
Nervous system disorders	Headache Tremor[a] Dizziness	Encephalopathy[a] Aphasia Paraesthesia Convulsion Cognitive disorder Memory impairment	Cranial nerve disorder [b]
Cardiac disorders		Tachycardia	
Vascular disorders	Hypotension		Capillary leak syndrome
Respiratory, thoracic and mediastinal disorders	Cough		
Gastrointestinal disorders	Nausea Constipation Diarrhoea Abdominal pain Vomiting		Pancreatitis[a]
Skin and subcutaneous tissue disorders	Rash		
Musculoskeletal and connective tissue disorders	Back pain Pain in extremity Arthralgia Bone pain		
General disorders and administration site conditions	Pyrexia Peripheral oedema Chills Fatigue Chest pain	Oedema	
Investigations	Increased alanine aminotransferase[a] Increased aspartate aminotransferase[a]	Decreased immunoglobulins Increased blood bilirubin Increased liver enzymes (gamma-glutamyl transferase)	

MedDRA system organ class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)
Injury, poisoning and procedural complications	Infusion-related reactions (and associated symptoms including wheezing, flushing, face swelling, dyspnoea, hypotension, and hypertension)		

[a] Additional information is provided in "Description of selected adverse reactions".
[b] MedDRA high level group terms (MedDRA version 16.1).

Description of selected adverse reactions

Neurologic events

In the pivotal clinical study (N = 189), 51.9% 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 16.4% and 12.7% of patients respectively, of which the most common were encephalopathy, tremor, and confusional state. Fatal encephalopathy has been reported, however, the majority of neurologic events (74.5 %) were clinically reversible and resolved following interruption of BLINCYTO. The median time to onset of neurologic event was 9 days. 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. 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 the pivotal clinical study (N = 189), serious CRS reactions were reported in 0.5% of patients with a median time to onset of 2 days. For clinical management of CRS, see section 4.4.

Elevated liver enzymes

In the pivotal clinical study (N = 189), 27.5% of patients reported elevated liver enzymes. Serious and grade ≥ 3 adverse reactions (such as ALT increased, AST increased, and blood bilirubin increased) were observed in 2.1% and 15.3% of patients respectively. The median time to onset to the first event was 3 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 case of PML has been reported in the pivotal 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 the pivotal clinical study (N = 189), less than 1.4% of patients treated with blinatumomab tested positive for binding and neutralising anti-blinatumomab antibodies. All patients who tested positive for binding antibodies also tested positive for neutralising anti-blinatumomab antibodies. Anti-blinatumomab antibody formation might affect pharmacokinetics of blinatumomab.

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.

Belgium
Federal agency of medicines and health products
Vigilance Division
EUROSTATION II
Victor Hortaplein, 40/ 40
B-1060 Brussels
Website: www.famhp.be
e-mail: adversedrugreactions@fagg-afmps.be

Luxembourg
Direction de la Santé – Division de la Pharmacie et des Médicaments
Villa Louvigny – Allée Marconi
L-2120 Luxembourg
Website: http://www.ms.public.lu/fr/activites/pharmacie-medicament/index.html

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 mcg/m^2/day or $\geq$ 9 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-α and IFN-γ were measured and, IL-6, IL-10 and IFN-γ 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 225 patients aged ≥ 18 years of age with relapsed or refractory B-precursor ALL were exposed to BLINCYTO during clinical trials.

BLINCYTO was 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).

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 1).

Table 1. Efficacy results in patients ≥ 18 years of age with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL)

	n (%) **n = 189**	**95% CI**
Complete remission (CR)[1]/Complete remission with partial haematological recovery (CRh*)[2]	81 (42.9%)	[35.7% – 50.2%]
CR	63 (33.3%)	[26.7% – 40.5%]
CRh*	18 (9.5%)	[5.7% – 14.6%]
Blast free hypoplastic or aplastic bone marrow[3]	17 (9%)	[5.3% – 14.0%]
Partial remission[4]	5 (2.6%)	[0.9% – 6.1%]
Relapse[5]-free survival (RFS) for CR/CRh*	5.9 months	[4.8 to 8.3 months]
Overall survival	6.1 months	[4.2 to 7.5 months]

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.

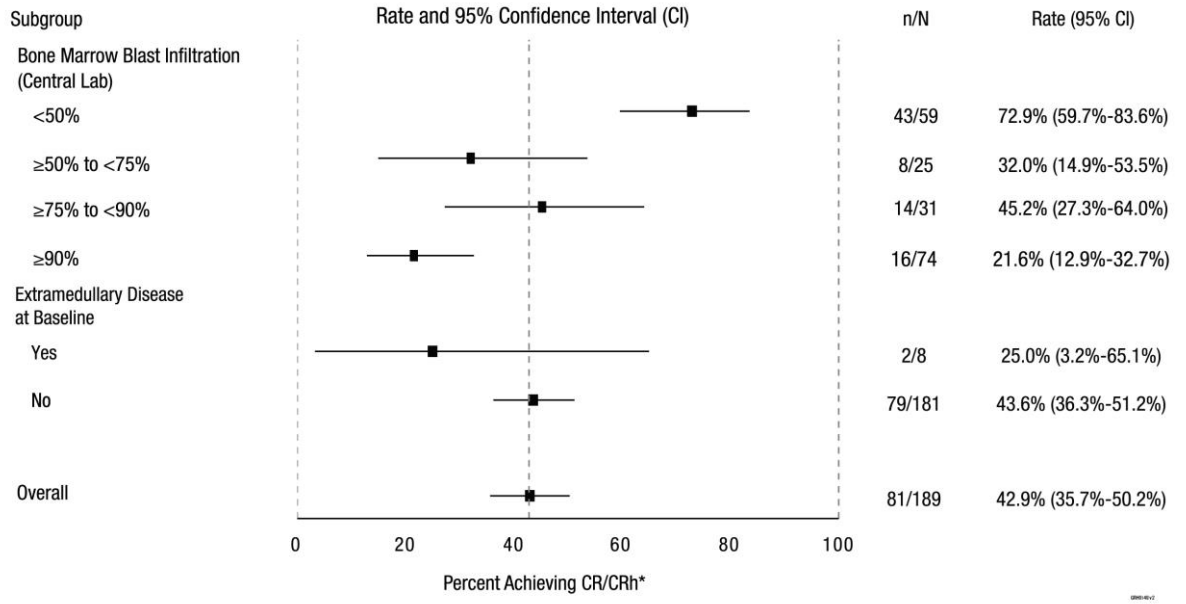
In a prespecified exploratory analysis, 60 of 73 MRD evaluable patients with CR/CRh* (82.2%) also had a MRD response (defined as MRD by PCR < 1 x 10^{-4}).

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 1).

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 1). Patients with low tumour burden (< 50%) responded best to BLINCYTO treatment with CR/CRh* rate of 72.9% (CI 59.7 – 83.6).

Figure 1. 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.

In an open-label, multicentre, dose-escalation phase II study of 36 patients (≥ 18 years of age with B-precursor ALL relapsed after at least induction and consolidation or having refractory disease with > 5% blasts in bone marrow, ECOG performance status ≤ 2, life expectancy of ≥ 12 weeks, who did not have autologous haematopoietic stem cell transplantation (HSCT) within 6 weeks prior to start of BLINCYTO treatment, allogeneic HSCT within 3 months prior to start of BLINCYTO treatment, or previous treatment with BLINCYTO), the safety and efficacy of BLINCYTO were evaluated. Fifteen of 36 (41.7%) patients had undergone allogeneic HSCT prior to receiving BLINCYTO. The CR/CRh* rate was 69.4% (25 out of 36 patients: 15 [41.7%; 95% CI: 25.5% - 59.2%] CR; 10 [27.8%; 95% CI: 14.2% - 45.2%] CRh*). In the elderly population (≥ 65 years of age) 4 of 5 patients (80.0%) achieved CR/CRh* within 2 treatment cycles (see section 4.8 for safety in elderly). Twenty-two of 25 (88%) patients with haematologic complete remission also had minimal residual disease (MRD) responses (defined as MRD by PCR < 1 x 10^{-4}). The median duration of remission was 8.9 months, and the median relapse-free survival (RFS) was 7.6 months. The median overall survival (OS) was 9.8 months.

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).

This medicinal product has been authorised under a so called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency

will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to 90 mcg/m^2/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 211 (258) pg/mL and 621 (502) 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 section listed below. Follow the steps for reconstituting BLINCYTO and preparing the infusion bag.

a) for 9 mcg/day infused over 24 hours at a rate of 10 mL/h
b) for 9 mcg/day infused over 48 hours at a rate of 5 mL/h
c) for 9 mcg/day infused over 72 hours at a rate of 3.3 mL/h
d) for 9 mcg/day infused over 96 hours at a rate of 2.5 mL/h
e) for 28 mcg/day infused over 24 hours at a rate of 10 mL/h
f) for 28 mcg/day infused over 48 hours at a rate of 5 mL/h
g) for 28 mcg/day infused over 72 hours at a rate of 3.3 mL/h
h) for 28 mcg/day infused over 96 hours at a rate of 2.5 mL/h

Before preparation, ensure you have the following supplies ready:

Dose	Infusion duration (h)	Infusion rate (mL/h)	Number of BLINCYTO packages
9 mcg/day	24	10	1
	48	5	1
	72	3.3	1
	96	2.5	2
28 mcg/day	24	10	1
	48	5	2
	72	3.3	3
	96	2.5	4

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.

a) Preparation of BLINCYTO 9 mcg/day infused over 24 hours at a rate of 10 mL/h

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 one 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 <u>not</u> shake.**
   - **Do <u>not</u> 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 <u>not</u> use if the solution is cloudy or has precipitated.**
5. Using a syringe, aseptically transfer 0.83 mL of reconstituted BLINCYTO into the infusion bag. 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.

b) Preparation of BLINCYTO 9 mcg/day infused over 48 hours at a rate of 5 mL/h

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 one 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 <u>not</u> shake.**
   - **Do <u>not</u> 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 <u>not</u> use if the solution is cloudy or has precipitated.**
5. Using a syringe, aseptically transfer 1.7 mL of reconstituted BLINCYTO into the infusion bag. 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.

c) Preparation of BLINCYTO 9 mcg/day infused over 72 hours at a rate of 3.3 mL/h

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 one 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 <u>not</u> 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 <u>not</u> use if the solution is cloudy or has precipitated.**
5. Using a syringe, aseptically transfer 2.5 mL of reconstituted BLINCYTO into the infusion bag. 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.

d) Preparation of BLINCYTO 9 mcg/day infused over 96 hours at a rate of 2.5 mL/h

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. Use two vials of BLINCYTO powder for concentrate. 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 <u>not</u> shake.**
   - **Do <u>not</u> 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 <u>not</u> use if the solution is cloudy or has precipitated.**
5. Using a syringe, aseptically transfer 3.3 mL of reconstituted BLINCYTO into the infusion bag (2.0 mL from one vial and the remaining 1.3 mL from the second vial). 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.

e) Preparation of BLINCYTO 28 mcg/day infused over 24 hours at a rate of 10 mL/h

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 one 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 <u>not</u> shake.**
   - **Do <u>not</u> 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 <u>not</u> use if the solution is cloudy or has precipitated.**
5. Using a syringe, aseptically transfer 2.6 mL of reconstituted BLINCYTO into the infusion bag. 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.

f) Preparation of BLINCYTO 28 mcg/day infused over 48 hours at a rate of 5 mL/h

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. Use two vials of BLINCYTO powder for concentrate. 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 <u>not</u> shake.**
   - **Do <u>not</u> 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 <u>not</u> use if the solution is cloudy or has precipitated.**
5. Using a syringe, aseptically transfer 5.2 mL of reconstituted BLINCYTO into the infusion bag (2.7 mL from one vial and the remaining 2.5 mL from the second vial). 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.

g) Preparation of BLINCYTO 28 mcg/day infused over 72 hours at a rate of 3.3 mL/h

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. Use three vials of BLINCYTO powder for concentrate. 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 <u>not</u> 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 <u>not</u> use if the solution is cloudy or has precipitated.**
5. Using a syringe, aseptically transfer 8 mL of reconstituted BLINCYTO into the infusion bag (2.8 mL from each of the first two vials and the remaining 2.4 mL from the third vial). 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.

h) Preparation of BLINCYTO 28 mcg/day infused over 96 hours at a rate of 2.5 mL/h

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. Use four vials of BLINCYTO powder for concentrate. 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 <u>not</u> shake.**
   - **Do <u>not</u> 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 <u>not</u> use if the solution is cloudy or has precipitated.**
5. Using a syringe, aseptically transfer 10.7 mL of reconstituted BLINCYTO into the infusion bag (2.8 mL from each of the first three vials and the remaining 2.3 mL from the fourth vial). 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.

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

September 2017

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.