AWMSG Secretariat Assessment Report – Limited submission

Blinatumomab (Blincyto®▼) 38.5 micrograms powder for concentrate and solution for solution for infusion

Company: Amgen Ltd.

Licensed indication under consideration: Monotherapy for the treatment of paediatric patients aged 1 year or older with Philadelphia chromosome negative CD19 positive B-cell precursor acute lymphoblastic leukaemia (ALL) which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation.

▼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.

Date of licence extension: 23 August 2018

Comparator(s)

- Comparators suggested by the company are two different regimens consisting of sequential phases of high-dose chemotherapies: R3 (see appendix) and fludarabine, cytarabine and granulocyte stimulating factor with idarubicin (FLAG-Ida). Clinical experts in Wales advise that blinatumomab won't displace any current treatment.

Limited submission details

- A minor licence extension for use in children aged one year or older.

Clinical effectiveness

- Blinatumomab (Blincyto®) was recommended by the National Institute for Health and Care Excellence (NICE) in June 2017 for treating previously-treated Philadelphia chromosome-negative ALL in adults (TA450).
- Relapsed or refractory ALL is a rare aggressive bone marrow cancer. First-line treatment with chemotherapy has a high cure rate but the prognosis for patients who relapse or have refractory disease is very poor. Relapsed or refractory ALL is a life-threatening condition with a high unmet need. Treatment aims to achieve complete response (CR) so that patients are eligible for allogeneic haematopoietic stem cell transplantation (HSCT), which is the only chance of a cure.
- The company's submission includes a single-arm, open-label phase I/II study (MT103-205) of blinatumomab to treat relapsed or refractory ALL in 70 children. Supportive data are included from an ongoing, single-arm, open-label study (RIALTO) in patients from Europe and North America.
- In study MT103-205, 70 patients (aged < 1–17 years; 39 with refractory disease and 40 having undergone a previous allogeneic HSCT) received the licensed

dose of blinatumomab as a four-week continuous intravenous infusion, followed by a two-week treatment-free interval, for up to five treatment cycles. Twenty-seven patients (39%) achieved the study's primary endpoint of CR within the first two treatment cycles. Among all patients, the median overall survival was 7.5 months. Twenty-four patients (34%) received allogeneic HSCT after blinatumomab treatment. These outcomes are broadly in line with the efficacy of blinatumomab in adults with relapsing/refractory ALL.

- Comparative efficacy data are included from two retrospective historical comparator studies (20120299 and 20140228) in which paediatric patients with relapsing/refractory ALL received standard of care chemotherapy. The EMA stated that no clear conclusions could be drawn from comparing these studies with study MT103-205 because of the heterogeneity and small size of the study populations.
- Supportive data from the RIALTO safety study for patients who have received two cycles of blinatumomab show that 25 out of 40 patients (63%) achieved CR.
- The most common adverse events (≥ Grade 3) were cytopenias and blood chemistry changes. No new safety signals were reported in the pivotal study in children when compared to adverse reactions to blinatumomab in adults.

Budget impact

- The company estimates that up to [commercial in confidence figure removed] children will be diagnosed with relapsed or refractory B-cell ALL every year in Wales and that [commercial in confidence figure removed] of these would receive blinatumomab.
- The estimated net acquisition cost of treating these [commercial in confidence figure removed] patients with blinatumomab versus the R3 regimen is [commercial in confidence figure removed] per year in each of Years 1 to 5, based on the patient access scheme (PAS) price. Sensitivity analysis of blinatumomab costs versus the FLAG-Ida treatment regimen gave a similar net acquisition cost ([commercial in confidence figure removed] per year).
- Using blinatumomab instead of the current standard-of-care chemotherapy regimens was estimated to significantly reduce inpatient care costs resulting in a potential resource saving of [commercial in confidence figure removed] each year (versus R3).
- AWTTC-sought clinical expert's opinion was that blinatumomab would not displace chemotherapy and therefore savings from inpatient care and from displaced chemotherapy would not be realised. AWTTC estimated the budget impact would be [commercial in confidence figure removed] per year (based on PAS price) with a resource cost of [commercial in confidence figure removed] per year based on [commercial in confidence figure removed] patients receiving blinatumomab.

Consideration of AWMSG's policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases

- AWTTC considers blinatumomab eligible to be appraised as an ultra-orphan medicine because it has European Medicines Agency designated orphan status and the full population of the licensed indication eligible for treatment would be seven patients in Wales which is ≤ 1 in 50,000 people.
- The New Medicines Group (NMG) and AWMSG will consider additional criteria (see Table 1) if they consider blinatumomab meets the criteria to be appraised in line with the policy for orphan, ultra-orphan and medicines developed specifically for rare diseases.

Table 1. Evidence considered by NMG/AWMSG

NMG/AWMSG considerations	AWTTC comments
The degree of severity of the disease as presently managed, in terms of survival and quality of life impacts on patients and their carers	People with relapsed or refractory ALL have a poor prognosis with continued chemotherapy. Children with a first relapse of ALL that doesn't respond to treatment have a reported median survival of 2.5 to 5.9 months. In children, ALL causes fatigue and lethargy, weakness, shortness of breath, pain, frequent infections, fever and bruising or bleeding easily. Patients are usually extremely ill at the time the disease relapses. Relapsed ALL is also associated with a higher incidence of psychiatric morbidity compared to those not in relapse. Patients with relapsed ALL have lower health-related quality-of-life (HRQoL) scores than those in remission or consolidation. The HRQoL of parents and carers of a child with ALL is also affected, with family life disrupted by the burden of continued and regular treatments for patients. ALL in children is associated with psychiatric morbidity among their caregivers.
Whether the medicine addresses an unmet need (e.g. no other licensed medicines)	There is an unmet need for treatment because current treatments for relapsed or refractory ALL in children are limited to chemotherapy regimens. Outcomes are poor: only 9% of patients have a CR and median survival is < 6 months. Standard of care is associated with reduction in HRQoL, a high incidence of toxicity and demand on hospital resources.
Whether the medicine can reverse or cure, rather than stabilise the condition	Blinatumomab does not reverse or cure the condition but patients who achieve a remission can proceed to a HSCT which is the only form of cure. In study MT103-205, 39% of patients had a CR after two treatment cycles.
Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy) and that this "definitive" therapy is currently in development	Blinatumomab treatment may act as a bridge to HSCT, which is the treatment goal of ALL. In study MT103-205 48% of patients with a CR after two treatment cycles received allogeneic HSCT in remission, and eight of them received HSCT without any other subsequent anti-leukaemia treatments. The overall allogeneic HSCT rate in the study was 34%: 24 of 70 patients.
The innovative nature of the medicine	Blinatumomab is a monoclonal antibody with a new mechanism of action targeting precursor B-cell ALL.
Added value to the patient (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity)	Blinatumomab may be administered in outpatient departments, thus reducing the length of time patients spend in hospital compared with current salvage chemotherapy regimens. This is a particular benefit to patients: their quality of life may improve with more time spent at home with their families. Blinatumomab is likely to bring benefits to wider society by giving a young patient population a treatment that may lead to more patients achieving long-term remission and survival.
Added value to the patient's family (e.g. impact on a carer or family life)	If patients are able to spend more time at home rather than in hospital receiving lengthy chemotherapy treatments, this may also improve the quality of life of their parents, families and carers.

ALL: acute lymphoblastic leukaemia; AWMSG: All Wales Medicines Strategy Group; AWTTC: All Wales Therapeutics & Toxicology Centre; CR: complete response; EMA: European Medicines Agency; HSCT: haematopoietic stem cell transplantation; NMG: New Medicines Group.

End of life

- NICE concluded that blinatumomab met end-of-life criteria in the adult population.
- Blinatumomab is indicated for patients with a short life expectancy, analysis of the historical control studies in paediatric relapsed or refractory ALL showed that

current chemotherapy is associated with a median overall survival of 2.5 to 5.9 months.
- In study MT103-205, the median overall survival was 7.5 months in children treated with the licensed dose of blinatumomab. A naive comparison to historical data is complicated by the difference in baseline characteristics of patients, but analyses submitted to the EMA support an extension of an additional 3 months to life compared with current treatments.

Additional information

- AWTTC is of the opinion that, if recommended, blinatumomab (Blincyto®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.
- The company does not anticipate that blinatumomab (Blincyto®) will be supplied by a home healthcare provider.

Evidence search

Date of evidence search: 3 December 2018.
Date of range of evidence search: No date limits were applied to database searches.

Further information

This assessment report will be considered for review every three years.

References are available on request. Please email AWTTC at AWTTC@Wales.nhs.uk for further information.

This report should be cited as: All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Blinatumomab (Blincyto®) 38.5 micrograms powder for concentrate and solution for solution for infusion. Reference number: 3769. March 2019.

Appendix: R3 regimen used by company

Phase	Treatment
Phase 1: Induction (weeks 1–4)	**Methotrexate** intrathecal, 2 days (1,8)
	Dexamethasone oral, 10 days
	Mitoxantrone (intravenous) IV, 2 days
	Vincristine IV, 4 days
	PEG-asparaginase intra-muscular (IM), 2 days
Phase 2: Consolidation (weeks 5–8)	**Dexamethasone** oral, 5 days
	Vincristine IV, 1 day
	Methotrexate intrathecal, 1 day
	Methotrexate IV, 1 day
	Cyclophosphamide IV 5 days
	Etoposide IV, 5 days
Phase 3: Consolidation/ Intensification (weeks 9–12)	**Methotrexate intrathecal**, 2 days
	Dexamethasone oral, 5 days
	Vincristine IV, 1 day
	Cytarabine IV, 4 days
	Erwinase IM, 5 days
	Methotrexate IV, 1 day