Blinatumomab

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.3. Immunomodulators

EMLc | ATC codes: L01FX07

Indication	B lymphoblastic leukaemia or lymphoma, not elsewhere classified ICD11 code: 2A70.0
INN	Blinatumomab
Medicine type	Biological agent
List type	Complementary
Additional notes	*including quality assured biosimilars
Formulations	**Parenteral > General injections > IV:** 35 µg in vial ; 38.5 µg in vial
EML status history	First added in 2025 (TRS 1064)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Blinatumomab
DrugBank	Blinatumomab

Expert Committee recommendation

The Expert Committee considered the disproportionate burden of B-lineage acute lymphoblastic leukaemia in low- and middle-income countries compared to high-income countries, as the number of years of life lost is substantial and cure rates are much lower. The Committee noted data from randomized clinical trials shows superiority of blinatumomab over chemotherapy in meaningfully improving: • survival in children, adolescents and adults with relapsed B-lineage acute lymphoblastic leukaemia; • survival in adults with B-lineage acute lymphoblastic leukaemia in the frontline setting; • disease-free survival in children with standard risk and higher risk B-lineage acute lymphoblastic leukaemia treated in the frontline setting. The evidence in adults is more mature, and the effect size in children is similar to that seen in adult patients. The Committee recognized that blinatumomab is a major advance in therapy for patients with B-lineage acute lymphoblastic leukaemia across all age ranges, and that it should have a considerable impact in low- and middle-income countries by increasing the number of lives saved through treatment. The Committee noted that the application projected that with universal access to blinatumomab in low- and middle-income countries, deaths would fall by 50%. In response to questions about the maturity of currently available data, the Committee believed that the likelihood of more evidence changing the confidence in the estimates of effect in the relapsed and refractory settings, which are substantial and compelling, was unlikely. The Committee noted that frontline data in adults and children are more recent, with data on adults more mature than the available data on children. However, the Committee was confident that emerging evidence

was likely to confirm the benefit of blinatumomab in this setting. In terms of safety, blinatumomab was shown to be associated with fewer grade ≥ 3 adverse events when compared with chemotherapy; the latter was associated with substantial risks of myelosuppression, infection and secondary malignancies. The Committee highlighted that adverse events specific to blinatumomab, such as cytokine release syndrome and neurotoxicity, and the potential for heightened risk of infections related to induced hypogammaglobulinaemia (which can be prolonged) are important. They therefore require specialist management and may represent a barrier to implementation. The Committee noted the potential need for immunoglobulin treatment to counteract hypogammaglobulinaemia due to B-cell depletion, and that immunoglobulin is already included on the Model Lists for other indications. The Committee highlighted that training programmes to administer blinatumomab and manage toxicities have been successfully implemented in some in low- and middle-income countries. Overall, the Committee considered that the balance of benefits to risks of blinatumomab was strongly favourable. However, the compelling efficacy data notwithstanding, the Committee recognized that a number of barriers existed to implementation including: • the requirement for intravenous infusion over 4 weeks, necessitating use of central lines and specialized pumps, which are associated with infection risk, additional costs, potential loss of school time in children and the need for supervision by trained staff; • the currently high acquisition costs for the medicine; • the cost of supportive care (administration hardware and immunoglobulin). In considering the feasibility of implementing blinatumomab, the Committee recognized that countries considering including blinatumomab on national EMLs would need to consider their capacity to accommodate requirements for safe administration and management of adverse events. The Committee also noted the requirement of a companion diagnostic test to identify patients with B-lineage acute lymphoblastic leukaemia eligible for treatment. The Expert Committee noted that toxicity and management of adverse events associated with the existing standard of care for patients with B-ALL also poses feasibility challenges. Treatment has historically relied on intensive multi-agent chemotherapy regimens as salvage therapy, often serving as a bridge to haematopoietic stem cell transplantation or newer immunotherapies. The total duration of treatment is long and varies by phase: induction typically lasts 4 to 6 weeks, followed by consolidation and intensification phases lasting several months. In paediatric protocols, maintenance therapy can extend up to 2-3 years, whereas adults generally receive shorter, more intensive cycles, often prior to transplant or immunotherapy. Adverse effects are frequent and severe, reflecting the intensity of treatment and can include myelosuppression and risk of infection, mucositis, neurotoxicity, cardiotoxicity and hepatotoxicity, depending on the chemotherapeutic regimen used. In children, long-term endocrine or growth effects are also concerns. Adults generally tolerate intensive regimens less well, leading to higher cumulative toxicity and treatment-related mortality. The Committee noted the current high cost of blinatumomab, and that while it has been determined to be cost-effective in some high-income settings, cost–effectiveness studies in other settings have been variable, depending on patient population and line of therapy. The Committee appreciated the ongoing efforts of WHO's Global Initiative for Childhood Cancer. The Committee noted that the inclusion of medicines in the Global Platform for Access to Childhood Cancer medicines, which provides cancer medicines for children at no cost to selected countries, is contingent upon their EMLc listing. Based on these considerations, the Expert Committee recommended the inclusion of blinatumomab on the complementary list of the EML and EMLc for the treatment of children, adolescents and adults with CD19-positive B-lineage acute lymphoblastic leukaemia in frontline and relapsed/refractory settings based on a favourable benefit to risk profile in which clinical cure is a realistic goal. The Committee considered that national prioritization for use in children and adolescents could be implemented in countries where financial constraints preclude providing blinatumomab for all age groups and where societal values place more weight on life-saving therapies for young people over otherwise equivalent health gains for older people. The Committee noted that a subcutaneous formulation of blinatumomab is currently being evaluated in clinical trials, with encouraging interim results. The Committee considered that future availability of a subcutaneously administered formulation may significantly reduce the current implementation barriers of central lines and risk of infection. Once available, the Committee advised that it would welcome an application for the subcutaneous formulation for consideration for inclusion on the Model Lists.

Background

Blinatumomab has not previously been evaluated for inclusion on the EMLc. The EMLc currently includes the

tyrosine kinase inhibitor imatinib for paediatric patients with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia, and multiple cytotoxic and supportive medicines for unspecified acute lymphoblastic leukaemia.

Public health relevance

According to data from the 2021 Global Burden of Disease study, acute lymphoid leukaemia had a global prevalence of almost 400 000 cases, and an annual incidence of almost 104 000 cases (all ages). In 2021, in people younger than 20 years, the global prevalence and incidence was 387 000 cases and 53 500 cases, respectively (1). The number of reported deaths globally due to acute lymphoid leukaemia in 2021 was almost 24 000. Acute lymphoblastic leukaemia is the most common childhood cancer and is one of the six index cancers of the WHO Global Initiative for Childhood Cancer (2). Cure rates are much lower in low- and middle-income countries than in high-income countries, where lack of access to essential medications, barriers to diagnosis and risk stratification, suboptimal supportive care, and inadequate logistical support can lead to excess relapse, death due to toxicity and abandonment of therapy (3–10). The number of years of life lost due to the disease is substantial. Estimates of the number of potential years of life lost due to acute lymphoblastic leukaemia range from 66 to 77 in people aged 1–19 years and from 24 to 39 in people older than 20 years (11). Before the availability of blinatumomab, conventional frontline treatment for paediatric patients diagnosed with acute lymphoblastic leukaemia involved systemic, multidrug cytotoxic chemotherapy regimens over multiple years, given in distinct phases: (i) induction (commonly used agents include vincristine, corticosteroids, and asparaginase, with most regimens adding an anthracycline, usually doxorubicin or daunorubicin); (ii) consolidation/intensification (commonly used agents include mercaptopurine, thioguanine, methotrexate, cyclophosphamide, etoposide and cytarabine); and (iii) maintenance (typically low intensity therapy with methotrexate and mercaptopurine) (12).

Benefits

Frontline B-lineage acute lymphoblastic leukaemia The Children's Oncology Group (COG) AALL1731 study is a phase III trial in which 1440 children (median age 4.3 years, interquartile range (IQR) 2.8 to 6.4 years) with standard-risk B-lineage acute lymphoblastic leukaemia and an average or higher risk of relapse were randomized to receive two cycles of blinatumomab plus chemotherapy (n = 718) or chemotherapy alone (n = 722) (13). At a median follow-up of 2.5 years, the estimated 3-year disease-free survival significantly favoured the blinatumomab plus chemotherapy group (96.0% versus 87.9%; difference in restricted mean survival time, 72 days 95% confidence interval (CI) 36 days to 108 days; $P < 0.001$). Estimated 3-year overall survival was 98.4% and 97.1% in the blinatumomab plus chemotherapy and chemotherapy alone groups, respectively. The study was terminated early following results from the first interim efficacy analysis. A prospective, single-arm phase II study evaluated the efficacy and safety of one post-induction course of blinatumomab added to chemotherapy in 30 infants younger than 1 year with newly diagnosed KMT2A-rearranged acute lymphoblastic leukaemia (14). Median follow-up was 26.3 months. Two-year disease-free survival with blinatumomab was 81.6% (95% CI 60.8% to 92.0%), compared with that of historical controls with chemotherapy from the Interfant-06 trial (49.4%, 95% CI 42.5% to 56.0%). Corresponding results for overall survival were 93.3% (95% CI 75.9% to 98.3%) with blinatumomab and 65.8% (95% CI 58.9 to 71.8) with chemotherapy. Relapsed/refractory B-lineage acute lymphoblastic leukaemia The COG ALL1311 study is a phase III study that compared survival of 255 children, adolescents and young adults aged 1–30 years with low-risk first relapse of B-lineage acute lymphoblastic leukaemia treated with chemotherapy alone or chemotherapy plus blinatumomab (15). The primary endpoint was disease-free survival (time from randomization to relapse, second malignancy or death). The secondary endpoint was overall survival (time from randomization to death from any cause). Median follow-up among living patients was 3.5 years. A total of 97 disease-free survival events were reported, 42 in the blinatumomab group and 55 in the chemotherapy group. Among low-risk patients with bone marrow ± extramedullary relapse, the 4-year disease-free survival rates were 53.7% for blinatumomab and 72.7% for chemotherapy (hazard ratio (HR) 0.53, 95% CI 0.30 to 0.95). Four-year overall survival rates were 97.1% for blinatumomab and 84.8% for chemotherapy (HR 0.28, 95% CI 0.08 to 1.02). Among all low-risk patients, the 4-year disease-free survival rates were 49.5% for blinatumomab and 61.2% for

chemotherapy (HR 0.76, 95% CI 0.51 to 1.14) and 4-year overall survival rates were 90.4% for blinatumomab and 79.6% for chemotherapy (HR 0.65, 95% CI 0.32 to 1.30). A 2023 systematic review and meta-analysis of 12 studies (two randomized controlled trials versus chemotherapy and 10 single-arm studies) with 652 participants evaluated the efficacy and safety of blinatumomab in children and adolescents with relapsed/refractory B-lineage acute lymphoblastic leukaemia (16). The primary outcomes were complete response, overall survival, event-free survival, minimal residual disease response and allogeneic haematopoietic stem cell transplantation. Results for the randomized controlled trials and single-arm studies were reported separately. Only the single-arm studies reported complete response data. Pooled results showed that 183/336 patients achieved a complete response with a pooled complete response rate of 56% (95% CI 54% to 68%). Overall survival data were reported in the randomized controlled trials and nine single-arm studies. Pooled data from the trials showed no significant difference between blinatumomab and chemotherapy for 1-year overall survival (odds ratio (OR) 1.51, 95% CI 0.95 to 2.42) but a significant difference favouring blinatumomab for 2-year overall survival (OR 1.97, 95% CI 1.23 to 3.15). All-time overall survival also significantly favoured blinatumomab (OR 1.73, 95% CI 1.24 to 2.41). The pooled overall survival rate from the experimental arm of the randomized controlled trials and the single-arm studies was 43% (95% CI 32% to 54%). Event-free survival data were reported in the randomized controlled trials and five single-arm studies. Pooled data from the trials showed significant differences favouring blinatumomab for 1-year (OR 1.84, 95% CI 1.16 to 2.90), 2-year (OR 2.63, 95% CI 1.58 to 4.39) and all-time event-free survival (OR 2.16, 95% CI 1.54 to 3.03). The pooled event-free survival rate from the experimental arm of the randomized controlled trials and the single-arm studies was 31% (95% CI 21% to 41%). Minimal residual disease response data were reported in all included studies. Pooled data from the randomized controlled trials showed a significant difference favouring blinatumomab (OR 4.71, 95% CI 2.84 to 7.81). The pooled minimal residual disease response rate for blinatumomab from all studies was 51% (95% CI 34% to 68%). Data from the randomized controlled trials reported 82 and 122 patients in the chemotherapy and blinatumomab groups, respectively, received allogeneic haematopoietic stem cell transplantation any time after the first blinatumomab infusion. Pooled data showed a significant difference between treatment groups for allogeneic haematopoietic stem cell transplantation (OR 3.24, 95% CI 1.96 to 5.35) (16). Another 2023 systematic review and meta-analysis of 18 studies (one randomized controlled trial, seven single-arm trials, 10 retrospective studies; 1373 participants) assessed the efficacy and safety of blinatumomab in patients with relapsed/refractory acute lymphoblastic leukaemia, without age restrictions (17). The mean age of patients in these studies ranged from 6 months to 58 years. Efficacy outcome measures reported were complete response, minimal residual disease response, overall survival and relapse-free survival. The pooled complete response rate of blinatumomab was 54% (95% CI 44% to 64%; 16 studies, 1249 participants), the pooled minimal residual disease response rate of blinatumomab was 43% (95% CI 34% to 51%; 14 studies, 942 participants), and pooled median overall survival and relapse-free survival of blinatumomab were 8.16 months (95% CI 6.64 to 9.69) and 6.02 months (95% CI 4.63 to 7.41), respectively. Frontline B-lineage acute lymphoblastic leukaemia – adults A randomized, phase III trial compared blinatumomab plus chemotherapy versus chemotherapy alone in 224 adults aged 30–70 years with minimal residual disease-negative acute lymphoblastic leukaemia after induction and intensification chemotherapy (18). The primary endpoint was overall survival from the time of randomization; relapse-free survival was a secondary endpoint. At a median follow-up of 42 months, 17 and 40 deaths were reported in the blinatumomab plus chemotherapy and chemotherapy alone groups, respectively. The 3-year overall survival was 85% versus 68% in the blinatumomab plus chemotherapy and chemotherapy alone groups, respectively (HR for death 0.41, 95% CI 0.23 to 0.73). The 3-year relapse-free survival was 80% versus 64% in the blinatumomab plus chemotherapy and chemotherapy alone groups, respectively (HR for relapse or death 0.53, 95% CI 0.32 to 0.87).

Harms

In the 2023 systematic review of blinatumomab in relapsed/refractory B-lineage acute lymphoblastic leukaemia in children and adolescents, results of combined data of the randomized controlled trials showed the odds of grade 3 or higher adverse events was significantly reduced in patients randomized to blinatumomab compared with those randomized to chemotherapy (OR 0.31, 95% CI 0.16 to 0.60). The pooled adverse event rate in the experimental arms of the randomized controlled trials and seven single-arm studies was 65% (95% CI 54% to 76%). The most

commonly reported adverse events were cytokine release syndrome, neutropenia, death and neurological events. The frequency of cytokine release syndrome, grade 3 or higher neutropenia and death during blinatumomab therapy was 16%, 34% and 24%, respectively (16). In the 2023 systematic review of blinatumomab in relapsed/refractory acute lymphoblastic leukaemia in patients of all ages, analysis of seven prospective studies (743 participants) reported a pooled incidence of grade ≥ 3 adverse events of 80% (95% CI 72% to 88%). The pooled incidence of neurological toxicity grade ≥ 3 was 7% (95% CI 4% to 11%; 12 studies, 885 participants) and the pooled incidence of grade ≥ 3 cytokine release syndrome was 3% (95% CI 2% to 5%; nine studies, 776 participants) (17). Four studies reported haematological toxicity and the pooled incidence was 31% (95% CI 14% to 47%). The most frequently reported haematological toxicities associated with blinatumomab were neutropenia (31%) and anaemia (28%). A 2022 systematic review and meta-analysis of two phase I/II (97 participants) and two phase III trials (208 participants) evaluated the safety profile of blinatumomab compared with chemotherapy in paediatric patients with B-lineage acute lymphoblastic leukaemia (19). Compared to chemotherapy, blinatumomab was associated with a lower risk of febrile neutropenia (risk ratio (RR) 0.13, 95% CI 0.6 to 0.26), infection (RR 0.40, 95% CI 0.29 to 0.56), serious adverse events (RR 0.56, 95% CI 0.32 to 0.99), and adverse events ≥ grade 3 (RR 0.79, 95% CI 0.67 to 0.93). No difference was found between treatment groups in the risk of cytokine release syndrome (RR 8.37, 95% CI 0.27 to 260.97) or seizures (RR 6.43, 95% CI 0.79 to 53.08). Blinatumomab was associated with a higher risk for encephalopathy (RR 8.90, 95% CI 1.08 to 73.29).

Cost / cost effectiveness

Available list prices per vial for blinatumomab reported in the application range from 1389 United States dollars (US$) in Mexico to US$ 10 654 in Argentina. Excluding Argentina and the United States (where the reported list price is US$ 5145 per vial), the median price per vial is about US$ 2244. Although blinatumomab is relatively expensive, it has proven cost-effective in both frontline and relapsed settings because it induces durable remissions and reduces the need for more expensive interventions, such as repeated hospitalizations, intensive chemotherapy, haematopoietic stem cell transplantation and chimeric antigen receptor-T cell therapy (22–27). A 2024 study evaluated the cost–effectiveness of blinatumomab versus standard consolidation chemotherapy for treatment of paediatric patients with high-risk, first-relapsed, Philadelphia chromosome-negative B-lineage acute lymphoblastic leukaemia from a Mexican health-care payer perspective (22). The study used a decision analytic model to estimate life years and costs over a lifetime horizon and a discount rate of 5%. Analyses were conducted using the medicine acquisition costs for blinatumomab in Mexico in 2023. In the base-case analysis, the incremental cost–effectiveness ratio for blinatumomab versus consolidation chemotherapy was 121 526 Mexican pesos (US$ 6829) per life-year gained. In sensitivity analyses, the incremental cost–effectiveness ratio was most sensitive to the discount rate for costs and outcomes, the percentage of patients undergoing allo-haematopoietic stem cell transplantation, blinatumomab dose and vial sharing. In a probabilistic sensitivity analysis, there was a 99.5% and 87.1% probability of blinatumomab being considered cost-effective at willingness-to-pay thresholds of 600 000 and 200 000 Mexican pesos per life-year gained, respectively. A similar study, with a lifetime horizon and 5% discount rate was conducted from the Brazilian health-system perspective in 2022 (27). The base-case incremental cost–effectiveness ratio was 78 873 Brazilian reals per quality-adjusted life year (US$ 1 = 5.165 reals at the time of the study). Sensitivity analyses found the incremental cost–effectiveness ratio was sensitive to the discount rate, exclusion of blinatumomab waste by vial sharing and change in infusion time. Probabilistic analysis found a 65.7% probability of blinatumomab being cost-effective at a willingness-to-pay threshold of 95 501 Brazilian reals.

WHO guidelines

WHO guidelines for the treatment of B-lineage acute lymphoblastic leukaemia are not currently available. Guidelines from the European Society of Medical Oncology, and the National Comprehensive Cancer Network were updated in 2024. Both include recommendations for the use of blinatumomab for people with B-lineage acute lymphoblastic leukaemia regardless of age in the frontline and relapsed/refractory settings (20, 21).

Availability

As of October 2024, blinatumomab has regulatory approval in 69 countries. Biosimilars are not currently available. Blinatumomab has been provided in low- and middle-income countries through access programmes in collaboration with St Jude Children's Research Hospital and major academic centres in India, Pakistan and Viet Nam (28). The application asserts that access to blinatumomab in low- and middle-income countries is anticipated to improve with support from the WHO Global Platform for Access to Childhood Cancer Medicines.

Other considerations

After developing and validating the European Society for Medical Oncology's Magnitude of Clinical Benefit Scale (ESMO-MCBS) for solid tumours, the ESMO-MCBS Working Group has collaborated with the European Hematology Association to develop a version of the scale for haematological malignancies to apply the system in evaluating the magnitude of clinical benefit derived from clinical studies of haematological malignancies (29). The application reported that blinatumomab had been evaluated in relapsed/refractory acute lymphoblastic leukaemia in adults based on data from the TOWER study (30) and received a score of 5 on the MCBS for haematological malignancies (the highest score for life-extending therapies). As currently supplied as a lyophilized powder in a single-dose vial for reconstitution, blinatumomab is administered as a continuous intravenous infusion at a constant flow rate using an infusion pump. Administration requires basic infrastructure commonly available in tertiary oncology centres, including infusion pumps, trained medical personnel and central venous access. Special tubing and filters (non-di(2-ethylhexyl) phthalate) are needed for the infusions. These resources are available in most tertiary care centres in low- and middle-income countries (28). A phase I/II open-label study investigating the safety, efficacy and pharmacokinetics of subcutaneous blinatumomab for the treatment of acute lymphoblastic leukaemia is ongoing (31). The EML cancer experts group reviewed the application and provided its advice for the Expert Committee. The group supported the inclusion of blinatumomab on the EMLc for the treatment of paediatric patients with B-lineage acute lymphoblastic leukaemia in frontline and relapsed/refractory settings based on a positive benefit–risk profile. The group also suggested an application be sought for the inclusion of blinatumomab on the EML for treatment of adults with B-lineage acute lymphoblastic leukaemia. The cancer team within the Department of Noncommunicable Diseases, Rehabilitation and Disability reviewed and provided comments on the application. The technical team supported the inclusion of blinatumomab on the EMLc. The team highlighted that inclusion of blinatumomab would provide a valuable opportunity to enhance sustainable and equitable access through initiatives such as the Global Platform for Access to Childhood Cancer Medicines.

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