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SMC2808

blinatumomab powder for concentrate and solution for solution for infusion (Blincyto®)

Amgen Ltd

08 August 2025

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

blinatumomab (Blincyto®) is accepted for restricted use within NHSScotland.

Indication under review: for the treatment of adult patients with Philadelphia chromosome negative CD19-positive B-cell precursor acute lymphoblastic leukaemia (ALL) in the consolidation phase.

SMC restriction: in the frontline consolidation phase.

In a phase III study of patients with minimal residual disease negative, Philadelphia chromosome negative, B-cell precursor ALL, the addition of blinatumomab to standard of care consolidation chemotherapy significantly improved overall survival.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Blinatumomab is a bi-specific T-cell engager antibody which binds to both CD3 expressed on the surface of patient's own T-cells and to CD19 expressed on the surface of malignant and benign cells of B-lineage origin. Blinatumomab activates the T-cell, resulting in the formation of a synapse between the T-cell and malignant B-cell. With this formation, proteolytic enzymes kill proliferating and resting target cells.[1]

For this indication, the recommended dose of blinatumomab in adults is 28 micrograms/day for patients ≥45 kg and 15 micrograms/m^2/day body surface area (maximum of 28 micrograms/day) for patients <45 kg by continuous intravenous infusion for 28 days followed by a 14-day treatment-free period. Patients may receive up to four cycles of blinatumomab consolidation treatment (one cycle is defined as 28 days of treatment followed by a 14-day treatment-free interval). See Summary of Product Characteristics (SPC) for more details.[1]

Previously, blinatumomab was licensed as monotherapy for the treatment of adults with Philadelphia chromosome negative, CD19 positive, B-precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%, which SMC accepted for restricted use (to patients who are in first complete remission with MRD ≥0.1% [SMC2234]).

1.2. Disease background

Acute lymphoblastic leukaemia (ALL) is an aggressive form of cancer that specifically affects immature lymphocytes that are derived from T- or B- lymphocyte stem cells. It is a rare condition, with 40% of cases occurring in adults. The predisposing risk factors for adult ALL are not well understood, however incidence increases with age. Diagnosis includes a comprehensive study of cell morphology, immunophenotype, genetics/cytogenetics, and genomics, with the majority of patients being diagnosed with B-lineage, Philadelphia (Ph) chromosome negative ALL. At present prognosis for patients with ALL remains poor, with 5-year overall survival rates estimated to be 30% to 40%.[2-4] After the induction phase of treatment, patients are tested for MRD. Patients with MRD positive ALL are more likely to relapse and die than those with MRD negative ALL. However, studies have shown that around 36% of MRD negative patients will relapse, and 40% of MRD negative patients will die within 10 years.[5]

1.3. Company proposed position

The submitting company initially requested that blinatumomab was restricted for use in patients with MRD negative disease (defined as MRD <0.01%) in the frontline consolidation phase. Due to increased precision of testing and the evolving definition of MRD positive, this would have led to an unaddressed gap for patients with MRD 0.01 to 0.09%. Following further discussion with the company and consultation with clinical experts, SMC committee voted on the use of blinatumomab in the frontline consolidation phase, irrespective of MRD status.

1.4. Treatment pathway and relevant comparators

Treatment is administered to patients with the aim of inducing complete haematological remission by following treatment protocols comprised of several phases (pre-phase, induction, intensification, consolidation and maintenance). Following induction and intensification treatment

phases to induce complete remission, patients with MRD negative ALL and a complete response receive standard of care consolidation (SoC) chemotherapy to remove residual disease and reduce relapse risk. Allogenic haematopoietic stem cell transplantation (alloSCT) may be offered to small numbers of patients at high risk of relapse. In Scotland, the majority of adult patients follow the UKALL14 treatment protocol. The UKALL14 SoC consolidation chemotherapy protocol consists of four cycles of chemotherapy including etoposide, cytarabine, pegaspargase, methotrexate, daunorubicin, vincristine, dexamethasone, cyclophosphamide and mercaptopurine. Younger adults and adults aged >55 years typically follow the UKALL11 and UKALL60+ protocols respectively which differ in treatment intensity to UKALL14.The UKALL11 protocol is highly intensive and the UKALL60+ protocol may be less intensive.[6] Current SoC consolidation chemotherapy treatments are highly cytotoxic and poorly tolerated.[2]

1.5. Category for decision-making process

Eligibility for interim acceptance decision option

Blinatumomab received an Innovation Passport allowing entry into the Innovative Licensing and Access Pathway from the Medicines and Healthcare Products Regulatory Agency.

Eligibility for a PACE meeting

Blinatumomab meets SMC orphan criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of blinatumomab for the MRD negative population comes from step 3 of the E1910 study. Details are presented in Table 2.1.

Table 2.1. Overview of relevant study

Criteria	E1910 [2, 7, 8]
Study design	International, randomised, open-label, phase III study.
Eligible patients	• Patients aged ≥30 years and ≤70 years of age with newly diagnosed Ph-negative B-cell precursor ALL (centrally confirmed with bone marrow or peripheral blood samples using flow cytometry or PCR assay). • Patients with an ECOG performance status of 0 to 2. • Maintained peripheral blood evidence of remission and a complete response or complete response with incomplete blood count recovery.
Treatments	After induction (step 1) and intensification (step 2), patients in morphologic remission with MRD ≤0.01% were randomised to receive SoC consolidation chemotherapy, with or without blinatumomab (step 3). SoC consolidation chemotherapy included cytarabine, etoposide, methotrexate, pegaspargase, rituximab (if CD20 positive), daunorubicin, vincristine, dexamethasone, cyclophosphamide and mercaptopurine following the E1910 study protocol for dosing and administration (based on the UKALL12 protocol). Blinatumomab was administered by continuous intravenous infusion at a dose of 28 micrograms/day for 28 days followed by a 14-day treatment-free period each cycle. In the blinatumomab plus chemotherapy group, treatment consisted of two cycles of blinatumomab followed by either alloSCT or four cycles of consolidation chemotherapy and two additional cycles of blinatumomab. Patients in the chemotherapy group received four cycles of consolidation chemotherapy and

	were allowed to receive an alloSCT at any time after the commencement of consolidation chemotherapy. After receipt of consolidation chemotherapy, patients proceeded to maintenance therapy (step 4), which continued for 2.5 years from the start of the intensification phase.
Randomisation	Patients were randomised equally. Randomisation was stratified according to MRD status (positive versus negative), age (30 to 54 years versus ≥55 years), CD20+ status (positive versus negative), rituximab use (yes versus no), and whether subjects intended to receive haematopoietic stem cell transplantation (yes versus no).
Primary outcome	OS, defined as the time between date of randomisation and death due to any cause.
Secondary outcomes	RFS, defined as the time between date of randomisation until relapse or death due to any cause (whichever occurred first).
Statistical analysis	Efficacy analyses were performed in the full analysis set, defined as all step 3 patients who underwent randomisation and were assessed as MRD negative after induction and intensification chemotherapy. A hierarchical statistical testing strategy was not applied in the study, therefore the results reported for secondary outcomes are descriptive only and not inferential (no p-values reported).

Abbreviations: ALL = acute lymphoblastic leukaemia; alloSCT = allogenic haematopoietic stem cell transplant; ECOG = Eastern Cooperative Oncology Group; MRD = minimal residual disease; OS = overall survival; PCR = polymerase-chain reaction; Ph-negative = Philadelphia negative; RFS = relapse-free survival; SoC = standard of care.

At the interim analysis (data cut-off 23 June 2023), after a median follow-up of 4.5 years, the addition of blinatumomab to standard of care consolidation chemotherapy resulted in a statistically significant improvement in overall survival (OS).[7] See Table 2.2 for details.

Table 2.2: Primary and selected secondary outcomes from E1910 (data cut-off 23 June 2023, FAS).[2, 7]

	Blinatumomab plus chemotherapy (n=112)	**Chemotherapy (n=112)**
Primary outcome: OS		
Median follow-up	4.5 years	4.5 years
Deaths, n	19	40
Median OS, years	NE	NE
Stratified HR (95% CI), p-value	0.44 (0.25 to 0.76), p=0.003	
KM-estimated OS at 1 year	96%	90%
KM-estimated OS at 2 years	90%	82%
Secondary outcome: RFS		
Median follow-up	4.5 years	4.5 years
RFS events, n	25	43
Median RFS, years	NE	NE
Stratified HR (95% CI)	0.53 (0.32 to 0.88)	
KM-estimated RFS at 1 year	90%	82%
KM-estimated RFS at 2 years	82%	72%

Abbreviations: FAS = full analysis set; HR = hazard ratio; KM = Kaplan-Meier; NE = not estimable; OS = overall survival; RFS = relapse-free survival.

Sensitivity analyses were performed for OS and relapse-free survival (RFS) in which patients who received alloSCT were censored at the time of alloSCT. Results were consistent with the primary analysis of OS and secondary analysis of RFS and favoured chemotherapy plus blinatumomab compared with chemotherapy.[2, 7]

3. Summary of Safety Evidence

Evidence from E1910 supports the relative safety of blinatumomab plus chemotherapy compared with SoC consolidation chemotherapy, which is the most relevant comparator in this submission.

In the E1910 study at data cut-off 23 June 2023, patients reporting a grade 3 or higher adverse event (AE) were 98% in both groups (109/111 in the blinatumomab plus chemotherapy group and 110/112 in the chemotherapy group). The most frequently reported treatment-emergent AEs of grade 3 or higher in the blinatumomab plus chemotherapy group versus the chemotherapy group respectively were: neutrophil count decreased (87% versus 95%), platelet count decreased (70% versus 78%) and white blood cell count decreased (54% versus 66%).[2]

Cytokine release syndrome, medication errors (specifically device malfunctions) and neurological events were treatment-emergent AEs of special interest. In the blinatumomab plus chemotherapy group versus the chemotherapy group respectively, cytokine release syndrome was reported in 17% versus zero, medication errors in 0.9% versus zero and neurological events were reported in 65% versus 38%. The most frequently reported neurologic event was headache in both groups (41% versus 32%).[2]

Overall, the safety profile of blinatumomab was consistent with the established safety profile of blinatumomab and toxicities were considered to be manageable. Hospitalisation is recommended for the first 3 days of the first cycle and the first 2 days of the second cycle. For patients with history or presence of central nervous system pathology, prolonged hospitalisation is required at the start of the first cycle. See the SPC for further information including advice on administration, monitoring, dose modifications, treatment interruption and withdrawal.[1, 2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Study E1910 was a randomised phase III study that compared blinatumomab plus consolidation chemotherapy with consolidation chemotherapy alone. Consolidation chemotherapy is the most relevant comparator, and the study protocol for consolidation chemotherapy can be considered representative of Scottish clinical practice.
- At the interim analysis with a median follow-up of 4.5 years, blinatumomab in combination with chemotherapy was associated with a statistically significant and clinically relevant improvement in OS compared with chemotherapy. RFS also favoured blinatumomab in combination with chemotherapy, suggesting that the effect of blinatumomab is durable.[2, 7]

4.2. Key uncertainties

- Study E1910 recruited adult patients aged 30 to 70 years old, and therefore there is some uncertainty regarding the treatment effect in excluded age groups. Additionally, the

chemotherapy regimen used in the study was different from the protocols typically followed in Scotland for patients <25 years and >55 years. However, clinical experts considered that blinatumomab is expected to also benefit younger patients. The ongoing Golden Gate study may address uncertainties relating to older patients.[9]

- OS results are not sufficiently mature to fully evaluate the effect of blinatumomab on survival. At the 23 June 2023 data cut-off, estimated median OS and median RFS was not reached in either treatment group. [7]
- Most patients had an ECOG score of 0 or 1 (96%), safety and effectiveness of blinatumomab in patients with a poorer performance status is uncertain.[2]
- Subgroup analyses were generally consistent with the primary findings, however lower mortality rates were observed in patients aged <55 years versus patients >55 years and in CD20-negative patients versus CD20-positive patients. Patients ≥65 years in the blinatumomab plus chemotherapy group had worse OS and RFS than the chemotherapy group, however there were small patient numbers and subgroups were not powered to detect a difference therefore it is difficult to draw conclusions.[2, 7]
- Health-related quality of life outcomes were not assessed as part of E1910. BLAST and TOWER were used to inform the economic case for health-related quality of life outcomes. However, these studies had limitations and the populations of E1910, BLAST and TOWER were not fully aligned. There were small patient numbers in both studies, the BLAST study used a lower dose of blinatumomab (15 micrograms/m^2/day) and the TOWER study evaluated blinatumomab monotherapy compared with chemotherapy.[10, 11]
- E1910 had an open-label design due to differences in administration regimens and safety profiles of treatments. This could introduce potential bias for subjective safety outcomes and these should be interpreted with caution.

4.3. Innovative Licensing and Access Pathway (ILAP)

The final analysis of E1910 is expected in 2030, this may provide further survival data but is unlikely to address the other key uncertainties in the clinical evidence presented.[2]

4.4. Clinical expert input

Clinical experts consulted by SMC considered that blinatumomab fills an unmet need and is a therapeutic advancement when used in addition to standard of care chemotherapy, due to the notable improvements in clinical outcomes reported in clinical studies. They stated that blinatumomab will be used in addition to current standard of care consolidation chemotherapy.

4.5. Service implications

Clinical experts consulted by SMC considered that the introduction of this medicine may impact on service delivery as hospitalisation is recommended for the first 3 days of the first cycle and first 2 days of the second cycle. Infusions are required to be changed twice a week, requiring resource from chemotherapy day units and pharmacy aseptic services. However, patient numbers are small.

Diagnostic test required to identify patients eligible for treatment: contact local laboratory for information.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of blinatumomab, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- ALL is a rare, rapidly progressing, life-threatening form of leukaemia with a high rate of relapse. Philadelphia chromosome negative (Ph-) precursor B-cell ALL, accounts for about 75% of ALL cases. Patients in complete remission following treatment can still have residual cancer cells present (termed MRD). MRD positive is associated with a higher risk of relapse and poorer outcomes, however relapses can also occur in patients without evidence of MRD (termed MRD negativity). In patients who relapse or who have refractory disease, the 5-year survival rate is 10%.
- Blinatumomab is accepted for use in NHSScotland in patients with MRD positive Ph-negative precursor B-cell ALL. Patients with MRD positive disease are at higher risk of relapse, however relapses can also occur in patients with MRD negative disease. The morbidity and mortality of patients who relapse is very poor. Therefore, PACE participants consider that there is an urgent unmet need for blinatumomab, an effective frontline treatment that reduces the risk of relapse and improves survival for patients with MRD negative.
- PACE participants consider that blinatumomab has significant and substantial health-related benefits. They consider that blinatumomab is a major therapeutic advancement, as it is an effective targeted treatment that will help patients stay in remission for longer, reduce rates of relapse and improve survival in patients with MRD negativity. It is expected that fewer patients will relapse and this will reduce the need for subsequent, more aggressive and burdensome salvage treatments including allogeneic stem cell transplantation.
- Blinatumomab is well tolerated compared with chemotherapy only, and cytokine release syndrome and neurotoxicity side effects are low in patients with MRD negativity. Blinatumomab may be given in an outpatient setting from established ALL treatment centres, this is advantageous to patients and may help to improve quality of life, emotional wellbeing and reduce the burden associated with inpatient treatment.
- PACE participants consider that the introduction of blinatumomab will have a wider impact on families and carers, as improved outcomes and reduced risk of relapse will thereby reduce caring responsibilities and the emotional, practical and financial impacts associated with this.
- Blinatumomab should be given as per the licensed indication. PACE participants note that there was an unaddressed gap in the company submission for patients with MRD 0.01% to 0.09% and support the use of blinatumomab for these patients.

Additional Patient and Carer Involvement

We received a patient group submission from Leukaemia Care which is a registered charity. Leukaemia Care has received 9.48% pharmaceutical company funding in the past two years,

including from the submitting company. A representative from Leukaemia Care participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

An economic case was presented and is summarised in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	A lifetime time horizon of 50 years.
Population	Adult patients with Ph-negative B-cell precursor ALL that are MRD negative in the frontline consolidation phase.
Comparators	Standard of care (SoC) consolidation chemotherapy regimen (UKALL12 as used in the E1910 study). SoC consolidation chemotherapy was also used in the blinatumomab arm.
Model description	A three-state partitioned survival model was used with health states of relapse-free survival (RFS), post-relapse survival (PRS) and death. All patients enter the model in the RFS health state. Within this health state patients have disease that is stable or not actively progressing. Patients could thereafter transition to the PRS or death health states. Patients remaining relapse-free for 5 years were assumed to be cured. Patients in PRS health state were assumed to have relapsed and could receive second-line treatment. Patients in the PRS state could either stay within the PRS state, or transition to the death state.
Clinical data	Data on RFS, OS, all grade 3 and above adverse events in greater than 5% of patients (as well as cytokine release syndrome) for blinatumomab plus SoC consolidation chemotherapy and SoC consolidation chemotherapy alone were from the E1910 study.[2, 7] A standardised mortality ratio (SMR) applied to general population mortality of 1.09 was sourced from literature in diffuse large B-cell lymphoma.[12]
Extrapolation	In the base case, mixture cure models were used to extrapolate survival outcomes for both model arms. Mixture cure models account for a proportion of the treated population that can be considered "cured" by estimating an implicit cure fraction. Survival for the cured group was assumed to follow general population mortality, adjusted using the SMR, while the uncured group followed a standard parametric survival trajectory. RFS in both model arms were extrapolated using separately fitted log-normal mixture cure models. OS in both model arms were extrapolated using separately fitted Gamma mixture cure models. Patients who remained relapse-free for 5 years were considered cured in the model. Post-cure patients' utility values reverted to those of the general population, ALL-related costs (subsequent therapy and terminal care costs) were no longer incurred, and mortality followed the general population with the SMR of 1.09 applied to account for any residual ALL complications.
Quality of life	Utility values were sourced from EQ-5D data in the BLAST and TOWER studies. Utility values for MRD-responders (i.e. patients converting from MRD positive to MRD negative status) from the BLAST study were used to estimate pre-relapse utilities for both treatment arms. Utility values of patients who were receiving SoC salvage chemotherapy (no prior salvage subgroup only) in the TOWER study were used to estimate post-relapsed utilities for both arms. The utility values applied in the model were 0.840 for blinatumomab plus SoC consolidation

	chemotherapy (on treatment), 0.850 for blinatumomab plus SoC consolidation chemotherapy (off-treatment) and SoC consolidation chemotherapy, and 0.692 for post-relapse. For patients who remained relapse-free for 5 years and were considered cured, general population utilities were used. Disutilities of death within 6 months of 0.129 and alloSCT of 0.57 were included. Adverse event disutilities were also included.
Costs and resource use	Medicine acquisition, maintenance treatment, subsequent treatment, alloSCT, administration costs (including pump acquisition), adverse events, and healthcare resource use costs were included. A proportion starting each treatment cycle was applied to each treatment cycle's acquisition costs for blinatumomab plus SoC consolidation chemotherapy and SoC consolidation chemotherapy alone. This was derived from the discontinuation rate for all reasons, including relapse, from the E1910 study.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

6.2. Results

In the base case analysis, the company estimated an incremental cost-effectiveness ratio (ICER) of £30,165 per quality-adjusted life-year (QALY).

6.3. Sensitivity analyses

Scenario analyses are presented in Table 6.2. The ICER was most sensitive to the SMR applied to general population mortality.

Table 6.2: Scenario analysis results (including blinatumomab PAS)

	Parameter	**Base case**	**Scenario**	**ICER (£/QALY)**
-	Base case	-	-	30,165
1	RFS and OS extrapolation	MCM	Standard parametric modelling, RFS (Log-normal), OS (Log-normal)	25,206
2a	RFS extrapolation	Log-normal MCM	Exponential MCM	31,278
2b			Log-logistic MCM	30,652
3a	OS extrapolation	Gamma MCM	Weibull MCM	30,843
3b			Gompertz MCM	31,226
4	Blinatumomab dose adjustment in E1910	Excluded	Included	26,272
5	Cure timepoint	5 years	3 years	30,067
6a	SMR	1.09	2.00	34,923
6b			3.00	39,626
6c			4.00	44,110
7	RFS cap	RFS risk per cycle never lower than OS risk per cycle	% relapse-free never higher than % alive	32,853
8	Treatment costs per cycle	Apply proportion of patients starting treatment cycle from E1910	Assume all RFS patients incur 100% of treatment costs per cycle	40,601
9	Progressed disease utility value	0.692	0.35 (SMC 1145/16)	29,910

Abbreviations: ICER = incremental cost-effectiveness ratio; Incr. = incremental; LY = life years; MCM = mixture cure model; OS = overall survival; RFS = relapse-free survival; SMR = standardised mortality ratio; QALYs: quality-adjusted life years.

6.4. Key strengths

- A partitioned survival model was an appropriate choice for the economic model.
- Clinical efficacy data for blinatumomab with SoC consolidation chemotherapy and SoC consolidation chemotherapy alone were sourced from a randomised phase III study.
- The sources used to value medicine and healthcare resource use costs were appropriate.
- A comprehensive selection of parameters was considered in one-way deterministic scenario analysis.

6.5. Key uncertainties

- The SMR of 1.09 applied to general population mortality was subject to uncertainty. Scenario analysis using SMRs of 3.00 and 4.00, sourced from previous B-cell precursor ALL UK health technology assessments showed an upward impact on the ICER (Scenarios 6b and 6c). The submitting company considered the SMR of 3.00 to be inappropriate, as the clinical study used in the assessment (TA893) focussed on relapsed or refractory patients. Similarly, the SMR of 4.00 was deemed unsuitable, as it was sourced from a study evaluating survival post-transplant.[13] While these justifications could be reasonable, the variation in SMRs generated uncertainty in the economic case. SMC clinical experts were asked to comment on the appropriateness of the base case SMR. One expert expressed uncertainty in accurately estimating the SMR and stated 1.09 as appearing low. Given this, an additional SMR of 2.00 was considered (Scenario 6a). However, other experts supported the base case SMR, noting that fewer patients in the MRD negative population require intensive chemotherapy or alloSCT.
- There were uncertainties associated with the utility values used in the economic model. Since health-related quality of life outcomes were not assessed as part of E1910, utility values were instead sourced from clinical studies used in prior UK health technology assessments, BLAST and TOWER. The submitting company considered the populations of these studies to be similar to that of the decision problem. However, some uncertainty remains, as the populations in the E1910, BLAST and TOWER studies were not fully aligned. SMC clinical experts were asked to comment on the appropriateness of using the BLAST and TOWER studies to derive utility values and generally viewed the approach as reasonable. In addition, the utility value for progressed disease appeared high when compared to the value of 0.35 in SMC 1145/16. A scenario analysis using this lower utility value showed a limited impact on the ICER (Scenario 9). Utility values were also not identified as sensitive parameters in one-way deterministic sensitivity analysis.
- There were uncertainties in the extrapolation of RFS and OS outcomes, as median RFS and OS were not reached. Several plausible alternative mixture cure models were available in scenario analysis, although their impact on the ICER was limited (Scenarios 2 and 3). Additionally, a scenario that removed the mixture cure models and instead applied standard parametric survival analysis using log-normal distributions for both RFS and OS in each arm decreased the ICER (Scenario 1). The model also included a cap to ensure that the RFS risk per cycle could not fall below the OS risk per cycle. A scenario using an

alternative method, of capping the proportion of RFS patients to ensure it did not exceed the proportion alive, showed a small ICER increase (Scenario 7).

- The 5-year timepoint to apply the cure assumption for patients who remained relapse-free was subject to uncertainty. A timepoint of 3 to 5 years was raised by the company clinical experts, and published clinician's perspectives, with a 3-year time point previously used in SMC2548.[14] Applying a 3-year time point led to a minor decrease in the ICER (Scenario 5).
- The economic evaluation is based on E1910 study data in which patients received the UKALL12 chemotherapy regimen, while current NHSScotland practice generally uses the UKALL14 regimen. As chemotherapy was included in both model arms and both company and SMC clinical experts consider the UKALL12 and UKALL14 broadly comparable, any impact on relative costs or outcomes is likely minimal. However, SMC clinical experts highlighted that, in practice, patients aged over 55 would typically be treated with the UKALL60+ regimen. Since this differs substantially from the UKALL12 regimen, the economic results may be less generalisable to older patients.
- The model did not explicitly account for the impact of alloSCT on RFS and OS outcomes, although the costs and disutility associated with alloSCT were included. The model may therefore not fully capture the clinical benefits or risk associated with transplant. Incorporating these relationships by using additional health states could improve the accuracy of the modelled clinical outcomes and economic results, albeit with increased modelling complexity. However, as the proportions receiving alloSCT were balanced between treatment arms, the overall impact on economic results may be minor.
- The medicine acquisition costs for blinatumomab with SoC consolidation chemotherapy and SoC consolidation chemotherapy in each treatment cycle were adjusted based on the proportion staring treatment data from E1910, derived from the discontinuation for all reasons, including relapse. A scenario analysis removed this adjustment, with all RFS patients incurring 100% of the treatment costs per cycle, until the maximum treatment duration for blinatumomab with SoC consolidation chemotherapy (42 weeks) or SoC consolidation chemotherapy alone (18 weeks) (Scenario 8). This is a conservative cost scenario which increased the ICER.

*Other data were also assessed but remain confidential.**

7. Conclusion

The Committee considered the benefits of blinatumomab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as blinatumomab is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted blinatumomab for restricted use in NHSScotland.

8. Guidelines and Protocols

The European Leukaemia Net (ELN) working group published recommendations for the management of ALL in adults in May 2024.[15]

The European Society for Medical Oncology (ESMO) published the clinical practice guideline interim update on the use of targeted therapy in ALL in January 2024.[3]

ESMO published the clinical practice guideline for ALL in adult patients in April 2016.[4]

9. Additional Information

9.1. Product availability date

16 December 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per cycle (£)
blinatumomab	**28 micrograms/day via continuous intravenous infusion for 28 days per cycle for up to four cycles (adult patients ≥45 kg) (14-day treatment-free period between cycles)**	**56,476**

Costs from BNF online on 23 April 2025. Costs calculated using the full cost of vials assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 10 patients eligible for treatment with blinatumomab in each year. The estimated uptake rate was 50% in year 1 and 90% in year 3 with a discontinuation rate of 0% applied each year. This resulted in 5 patients estimated to receive treatment in year 1 rising to 9 patients in year 3.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 12 June 2025.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.