



Cost-effectiveness of blinatumomab (Blincyto®) for the treatment of relapsed or refractory B precursor Philadelphia chromosome negative acute lymphoblastic leukaemia in adults.

The NCPE assessment of blinatumomab has demonstrated evidence of benefit in overall survival (OS), although the size of the long-term OS gain is highly uncertain. There is a very low probability of cost effectiveness and a high probability that the ICER far exceeds the cost effectiveness threshold for existing treatments. The NCPE recommends that blinatumomab not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Amgen) economic dossier on the cost effectiveness of blinatumomab (Blincyto®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In August 2017, Amgen submitted a dossier of clinical, safety and economic evidence in support of blinatumomab for the treatment of adult patients with relapsed or refractory B precursor Philadelphia chromosome negative acute lymphoblastic leukaemia. Final data submitted by the applicant was received on 9th February 2018.

Blinatumomab is a bi-specific monoclonal antibody designed to bind specifically to CD19 on B-cells and CD3 on T-cells. By connecting CD3 and CD19 on benign and malignant B cells, it activates an endogenous T-cell response against the B-cells. Blinatumomab is administered by continuous intravenous infusion (CIVI); the dosage details are provided in Table 1 below. The licensed treatment duration is for two cycles induction therapy and up to three cycles of consolidation therapy, based on the single arm MT103-211 study considered during the marketing authorisation process. The treatment duration in the Phase III randomised controlled trial (RCT) considered by the NCPE as part of the review process, the TOWER study, was longer than in the current marketing authorisation, allowing for up to four additional cycles to be administered (nine cycles in total).

Table 1 Blinatumomab administration, as per European marketing authorisation

Method of administration	Blinatumomab is administered via continuous intravenous infusion (CIVI) at a constant flow rate delivered by an infusion pump.
Dose	Cycle 1: 9 microgram over 24 hours, Days 1-7 via CIVI 28 microgram over 24 hours, Days 8-28 via CIVI, followed by a two week break
	Cycle 2 to Cycle 5: 28 microgram over 24 hours, Days 1-28 via CIVI. There should be a two week break between each cycle.
Note	In the TOWER study, patients could receive maintenance therapy (i.e. >5 cycles) for up to 12 months after the 5 th cycle was completed, with an interval of 8 weeks between each cycle after the 5 th cycle.

1. Comparative effectiveness of blinatumomab

In the submission, the chemotherapy regimen FLAG-IDA (fludarabine, idarubicin, cytarabine and filgrastim) was the comparator investigated. This was considered appropriate by the NCPE.

Relative efficacy outcomes for the comparison with FLAG-IDA were derived from the TOWER study. This study was an open-label, multi-national, Phase III RCT of 405 patients with relapsed or refractory Philadelphia chromosome negative B precursor acute lymphoblastic leukaemia. Patients were assigned to one of two arms on a 2:1 basis, blinatumomab as per the dosage scheduled outlined in Table 1, or the Investigators choice of one of four treatment options outlined in Table 2. Efficacy analyses were performed in the intent-to-treat population.

Table 2 Investigator choice of chemotherapy in the TOWER study

FLAG with/without anthracycline
HiDAC-based regimen with/without anthracycline and/or other agents including asparaginase
High-dose methotrexate (500mg-3g/m ²) regimen with E-coli asparaginase
Clofarabine 20mg/m ² /day for up to 5 days, with/without other agents

The trial met its primary endpoint of an increase in overall survival (OS), HR 0.71 (95% CI 0.55, 0.93). The median OS with blinatumomab was 7.7 months (95% CI 5.6, 9.6) compared to 4 months (95% CI 2.9, 5.3) with SOC. Blinatumomab was associated with an increase in complete remission (CR) rate compared to the chemotherapy arm, 33.6% versus 15.7%. There was a statistically significant difference in event-free survival (EFS), defined as time since randomisation until date of relapse after achieving a CR/Complete remission with partial haematological recovery (CRh*)/Complete remission with incomplete haematological recovery (CRi) or death, in favour of blinatumomab, HR 0.55 (95% CI 0.43, 0.71). The rate of allogeneic stem cell transplant (allo-SCT) was similar across treatment arms, at 24%. The company provided additional confidential information and analyses on the results of the TOWER study at the request of the NCPE.

2. Safety of blinatumomab

Safety and tolerability was a secondary endpoint of the TOWER study. Treatment emergent adverse events (TEAEs) occurred in all patients in the TOWER study. Grade ≥ 3 adverse events (AEs) occurred in 86.5% blinatumomab patients compared to 91.7% in SOC arm. The most common Grade ≥ 3 adverse events of interest with blinatumomab were neutropenia (37.8%), infection (34.1%), elevated liver enzymes (12.7%) and neurological events (9.4%).

Serious AEs were more frequent with blinatumomab (62% versus 45%). AEs leading to interruption or discontinuation of treatment were far more common with blinatumomab

(32.2% and 12.4% respectively) compared to SOC (5.5% and 8.3%). Fatal TEAEs occurred at similar incidence in both arms, 19.1% with blinatumomab and 17.4% with SOC. Three deaths from multi-organ failure occurred with blinatumomab. Additional information was provided in confidence to the NCPE. The EMA requested specific risk minimisation measures to address the safety concerns regarding medication errors and neurologic events, including the agreement of an educational program with the competent authority in each country, requiring physician, pharmacist and nurse educational material, patient/caregivers educational material and a patient alert card.

In conclusion, blinatumomab has a different AE profile to SOC, but is still associated with significant toxicity as demonstrated by the high level of Grade \geq 3 AEs and SAEs. Neurological AEs are of concern, and the risk of medication error (by prescribers, during compounding and administration) is high.

3. Cost effectiveness of blinatumomab

For the cost-effectiveness analysis, the key effectiveness inputs in the model were OS, EFS and rate of CR/CRh*/CRi within 12 weeks of treatment initiation, all derived from the TOWER study. Cost-effectiveness was investigated using a five health state model, with a 50 year time horizon. The model simulates patients through five health states: 'Initial (pre-response) for 12 weeks from treatment initiation, 'Response' and 'Relapsed/Refractory' based on CR/CRh*/CRi from TOWER, while time spent within these states or progressing to the 'Cured' and 'Death' states is driven by the EFS and OS curves. All health states are mutually exclusive and 'Death' is the absorbing state. Patient characteristics, dose intensity, and utility measurements used in the model are derived from TOWER.

Survival outcomes from TOWER were extrapolated to the full time horizon of the model using a variety of extrapolation methods. Resource use in the model captured costs for drug acquisition and administration, costs of allo-SCT, salvage therapy and terminal care.

The incremental cost per QALY (incremental cost-effectiveness ratio (ICER)) for the applicant's base case was €69,400/QALY (incremental costs €86,807, incremental QALYs 1.25). The probability of cost-effectiveness at a willingness to pay (WTP) threshold of €45,000/QALY was 12.5%. The NCPE did not consider that the applicant's submitted model and resulting ICER are a complete reflection of the cost effectiveness of blinatumomab, and

explored the impact of alternative utility values, treatment durations and treatment efficacy estimates on cost effectiveness results. The NCPE implemented a number of changes to the model based on plausible alternative assumptions, resulting in increases in the ICER up to €472,215/QALY (incremental costs €104,693, incremental QALYs 0.22). At this ICER the probability of cost-effectiveness at a willingness to pay (WTP) threshold of €45,000/QALY was 0%.

4. Budget impact of blinatumomab

Blinatumomab is submitted for reimbursement under the hospital oncology drug management system. The proposed ex-manufacturer price per vial is €2,826. The reimbursement cost for a treatment course of two cycles for a patient is €139,237.02 ex VAT and €173,035.98 including VAT. Based on the applicant estimate of the current eligible population and assuming 100% market share, the projected gross budget impact of the drug acquisition over the first five years is €6.92 million including VAT. The net budget impact is €6.79 million. These estimates are highly sensitive to treatment duration and are based on the assumption of only two cycles per eligible patient. The use of blinatumomab will be associated with cost offsets through reduced hospitalisation; the NCPE estimate the net cost offsets at approximately €1.37 million over 5 years.

5. Patient Organisation Submissions

No patient organisation submissions were received as part of this submission.

6. Conclusion

The NCPE assessment of blinatumomab has demonstrated additional benefit in OS, but the magnitude of this benefit in the long-term is uncertain. There is a very low probability of cost effectiveness and a high probability that the ICER far exceeds the cost effectiveness threshold for existing treatments. The NCPE recommends that blinatumomab not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.