NICE National Institute for Health and Care Excellence

NICE guidance

Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia

Technology appraisal guidance
Published: 28 June 2017

www.nice.org.uk/guidance/ta450

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Blinatumomab is recommended within its marketing authorisation as an option for treating Philadelphia-chromosome-negative relapsed or refractory precursor B-cell acute lymphoblastic leukaemia in adults, only if the company provides it with the discount agreed in the patient access scheme.

2 The technology

Table 1 Summary of blinatumomab

Description of the technology	Blinatumomab (Blincyto, Amgen) is a T-cell engager antibody targeting CD19 and the CD3/T-cell receptor.
Marketing authorisation	Blinatumomab is indicated for the treatment of adults with Philadelphia-chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia.
Adverse reactions	The most common frequently reported adverse reactions are infusion-related reactions, infections, pyrexia, headache and febrile neutropenia. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	Patients may have 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 experience complete remission after 2 treatment cycles may have up to 3 additional cycles of consolidation treatment, based on an individual benefits-risks assessment. Blinatumomab is administered at a dose of 9 micrograms per day for the first 7 days of the first cycle. All doses after that are 28 micrograms per day.
Price	Blinatumomab costs £2,017 per 38.5-microgram vial (excluding VAT, BNF online March 2017). The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of blinatumomab, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee considered evidence submitted by Amgen and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of blinatumomab, having considered evidence on the nature of acute lymphoblastic leukaemia and the value placed on the benefits of blinatumomab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical management

4.1 The committee heard from a patient expert that living with precursor B-cell acute lymphoblastic leukaemia, particularly when the condition has failed to respond to first line chemotherapy, can have a profound effect on a person's physical and psychological wellbeing. The committee acknowledged that acute lymphoblastic leukaemia does not affect the patient in isolation, but also places emotional strain on their families and friends. The committee heard from the patient expert that patients whose disease responds to blinatumomab can live a relatively normal life during treatment, with minimal side effects. The clinical experts emphasised that the side effects of blinatumomab are much less severe than currently available therapies such as fludarabine, cytarabine and granulocyte stimulating factor (FLAG) based regimens.

4.2 The committee noted that the aim of treatment is to induce remission so that people who are fit enough can have allogeneic stem cell transplantation, which could cure the disease. Clinical experts advised that although the summary of product characteristics stipulates minimum inpatient treatment for 9 days in the first cycle and 2 days in subsequent cycles, in clinical practice blinatumomab is so well tolerated that most patients are treated as inpatients for only 4 days in cycle 1 and 2 days in cycle 2. This means that they can have treatment mostly in the outpatient setting, apart from attending hospital for the intravenous infusion bag to be changed every 4 days. The committee concluded that the availability of an effective treatment that could be delivered primarily in the outpatient setting was hugely beneficial to patients and would have a major impact on their quality of life.

4.3 The committee considered the most appropriate comparators for blinatumomab for treating relapsed or refractory acute lymphoblastic leukaemia and the likely position of blinatumomab in the treatment pathway. It heard from the patient expert and clinical experts that people with relapsed or refractory acute lymphoblastic leukaemia will have combination chemotherapy. In most cases this would be FLAG with idarubicin (FLAG-IDA), which involves prolonged hospitalisation for treatment and is associated with debilitating side effects. It heard that clofarabine is sometimes used instead, but noted that its marketing authorisation is only for children. The clinical experts stated that in clinical practice blinatumomab would be most useful at first relapse, before other salvage therapies that are poorly tolerated. The committee concluded that blinatumomab would be used before other salvage therapies and that FLAG-IDA was the most appropriate comparator for this appraisal.

Clinical effectiveness of blinatumomab

4.4 The clinical evidence for blinatumomab in people with relapsed or refractory precursor B-cell acute lymphoblastic leukaemia is from 2 clinical trials, TOWER and Study MT103-211:

- TOWER (n=405) was a phase III randomised controlled trial, comparing blinatumomab with one of 4 different standard of care chemotherapy regimens.
- Study MT103-211 was a phase II single-arm trial, assessing the safety and effectiveness of blinatumomab. The company used an historical cohort (Study 21020310) to allow comparison with 4 different standard of care chemotherapy regimens, which were similar to those in the control arm of TOWER.

Generalisability of the trial results to the NHS

4.5 The committee noted that TOWER included patients with refractory precursor B-cell acute lymphoblastic leukaemia that was refractory to primary induction therapy or relapsed within 12 months of first line chemotherapy, or after

subsequent therapy, or after allogenic stem cell transplantation. The committee heard from the clinical experts that the trial specifically recruited people with a poor prognosis. People who relapsed 12 months or more after primary induction therapy were excluded from the trial, but would have a better prognosis than those who relapsed earlier. The committee also noted that TOWER compared blinatumomab with standard of care (FLAG with or without an anthracycline such as idarubicin, a high-dose methotrexate based regimen or high-dose cytarabine with or without anthracycline). Most people in the trial had FLAG-IDA, which is consistent with clinical practice in England. The committee noted that the marketing authorisation specifies a maximum of 5 cycles of blinatumomab, but some patients in TOWER had more than 5 cycles. The committee also considered the generalisability of Study MT103-211. Similarly to TOWER, patients were excluded if they had relapsed following a remission that lasted over 12 months. The committee concluded that the trial populations broadly correspond with those in clinical practice but reflect people with a relatively poor prognosis.

Clinical effectiveness results – TOWER

4.6 In the trial, blinatumomab increased overall survival compared with standard of care chemotherapy (hazard ratio [HR] 0.71; 95% confidence interval [CI] 0.55 to 0.93). The committee noted that although blinatumomab was associated with improved overall survival up to 15 months, the Kaplan–Meier curves of the 2 treatment arms came together at this point. However it also noted that the data were immature and that there were very small numbers of patients alive at 15 months. The committee concluded that blinatumomab is clinically effective in improving overall survival compared with standard care in the short term, but there is uncertainty about the long-term overall survival benefit.

4.7 Results of a pre-specified subgroup analysis suggested that blinatumomab is more effective in people who have had no, or only 1 salvage therapy. The committee noted that the study was not powered to detect differences in efficacy between these subgroups but it appeared that blinatumomab was more effective if given earlier, and it recalled the clinical experts' view that blinatumomab would be used as the first salvage therapy (see section 4.3).

4.8 The committee noted that the rates of allogeneic stem cell transplants were

similar in the blinatumomab and standard of care chemotherapy arms (24.0% compared to 23.9% respectively). The committee heard from the clinical experts that these may not be directly comparable because treatment decisions were made on an individual basis and may be affected by multiple factors. For example, some patients in the chemotherapy arm of TOWER may have had a stem cell transplantation despite not achieving a complete remission, which would not happen in the NHS. It also heard that that there may have been other confounding factors, such as a delay in offering transplantation to people who responded well to blinatumomab (time to transplant was longer in the blinatumomab than standard of care arm in the trial). The committee concluded that it was uncertain from the available evidence whether blinatumomab would enable more patients to undergo allogeneic stem cell transplantation. However given the higher rate of complete remission with blinatumomab than standard of care (33.6% compared with 15.7%) this would be expected.

4.9 Blinatumomab was associated with fewer serious (grade 3 and above) adverse events than standard of care chemotherapy. The committee recalled hearing from the patient experts that the side effects of blinatumomab are minimal (see section 4.1) and it concluded that blinatumomab would be well-tolerated compared with standard of care chemotherapy.

Clinical effectiveness results – Study MT103-211

4.10 The committee noted that the ERG only regarded the comparison with the historical cohort as relevant and therefore it did not consider further the results of Study MT103-211 alone. To account for the different populations in the trial and the historical comparator, the company used 2 different methods to match patients based on their characteristics: a reweighted analysis and an inverse probability of treatment weighting analysis. The committee noted that the arms were not significantly different once matched, except for by region. The committee concluded that the matched analysis was appropriate for comparing blinatumomab with standard of care based on a historical cohort.

Cost effectiveness

4.11 The company used a 4-state partitioned-survival economic model, representing an initial pre-response state, a response state, a refractory/relapsed state and death. All clinical parameters in the model were derived from TOWER. The committee agreed that the model structure was appropriate.

4.12 In the model, patients had either blinatumomab or FLAG-IDA. The company used the results of the whole standard of care chemotherapy arm of TOWER to estimate the effectiveness of FLAG-IDA. The committee noted that clinical advisers to the ERG thought it plausible for the efficacy of the whole standard of care arm to be similar to FLAG-IDA, and that the trial was not powered to assess the relative clinical effectiveness of different chemotherapy regimens. It noted that FLAG-IDA was the most common chemotherapy regimen in the trial. The committee concluded that the chemotherapy arm of TOWER offered a reasonable representation of the clinical effectiveness of FLAG-IDA.

Modelling of overall survival

4.13 The committee recalled that the data on overall survival from TOWER were immature (see section 4.6). The company fitted parametric survival curves to the observed blinatumomab data and used a Gompertz distribution, based on clinical plausibility and visual inspection. The committee noted that the company's extrapolation of overall survival was subject to uncertainty because in TOWER the overall survival curves converged at around 15 months, which suggested that the proportional hazards assumption was not met. However the committee also noted that the number of patients at this time point in the trial was very small. It heard from the ERG that they were unable to identify a more clinically plausible survival curve for use in the economic model. The committee noted that the proportional hazards assumption did appear to be met in the first 12 months but there is uncertainty about the long-term extrapolation of overall survival. It concluded that the company's extrapolation was acceptable for the purposes of decision making.

4.14 The committee discussed the time point at which it is reasonable to assume a survivor is cured, which has a substantial impact on the incremental cost-

effectiveness ratios (ICERs). It noted that the company base case assumed 48 months, while the ERG argued that 60 months would be more appropriate. It heard from the clinical experts that the time point considered to be 'cure' was debatable, but would be much less than 48 months. The committee noted that the overall survival curves in the model appeared to plateau at around 36 months and that the sooner a cure was achieved, the lower the ICER. The committee concluded that the company's assumption of patients being cured at 48 months was potentially a conservative estimate.

Utility values

4.15 The committee heard that the quality-of-life data was mapped from EORTC QLQ-C30 data collected in TOWER. It noted that the company had not adjusted for the baseline differences in utility between treatment arms. The committee concluded that although it would have preferred adjusted values, the utility estimates used in the model were acceptable.

Cost of treatment in the model

4.16 The committee discussed the resource use assumed in the company's and the ERG's models. It noted that in both models the administration costs were assumed to be the same as in TOWER, in which patients had up to 9 cycles of blinatumomab. It heard from the clinical experts that although the marketing authorisation for blinatumomab recommends a maximum of 5 cycles, most people would have 2 cycles of treatment. If the disease responded, they would proceed to transplantation. If the disease responded after 2 cycles but a suitable donor match was not immediately available, or if stem cell transplantation was not appropriate, they might have more than 2 cycles. The company assumed hospitalisation requirements for blinatumomab as per the minimum specified in the marketing authorisation, while the ERG had assumed in their preferred base case that patients would be hospitalised for the entirety of the first 2 treatment cycles. The committee noted that the hospitalisation requirements would be considerably less than either of these assumptions in clinical practice (see section 4.2). The committee also noted that the company assumed that intravenous bags were changed every 4 days, while the ERG assumed they were

changed daily. It heard from the patient expert, clinical experts and NHS England that daily bag changes would be unlikely in clinical practice. The committee concluded that it preferred the company's assumptions for healthcare utilisation, but that these would overestimate the administration costs of blinatumomab.

End-of-life considerations

4.17 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's final Cancer Drugs Fund technology appraisal process and methods. The committee concluded that the end-of-life criteria were met in the overall population based on the following discussions:

- The committee discussed whether life expectancy without blinatumomab would be less than 24 months. It noted that life expectancy was 4 months for standard of care chemotherapy in TOWER and concluded that the short life-expectancy criterion was met.
- The committee discussed whether a survival benefit of over 3 months can be expected for blinatumomab compared to its comparators. It noted that blinatumomab was associated with a median overall survival gain of 3.7 months over standard of care chemotherapy and concluded that the extension to life criterion was met.

Cost-effectiveness results

4.18 The committee considered the company's base case ICERs using the patient access scheme price for blinatumomab. It noted that the deterministic ICERs were £55,501 per quality-adjusted life year (QALY) gained for the overall population (probabilistic ICER of £57,600 per QALY gained) and £49,190 per QALY gained for people who had not had previous salvage therapy (probabilistic ICER of £58,900 per QALY gained). However, the committee considered these ICERs to have been overestimated. It was aware that the costs of blinatumomab were overestimated because up to 9 cycles of treatment had been modelled, when the marketing authorisation is for a maximum of 5 cycles. The committee also considered that the hospitalisation requirements in clinical practice (see

section 4.2) are less than those modelled, and the assumption that patients were cured at 48 months was potentially conservative (see section 4.14). The committee considered the ICER for people who had not had previous salvage therapy to be most appropriate for the purposes of decision making, because it represents the treatment position in which blinatumomab will be used in clinical practice. As blinatumomab becomes established in clinical practice the number of people who have had previous salvage chemotherapy will diminish over time. The committee also noted that there is significant unmet clinical need for people with relapsed or refractory acute lymphoblastic leukaemia, because of the shortcomings of existing regimens (see section 4.3). The committee concluded that, despite substantial uncertainty, the ICER for blinatumomab is within the range normally considered a cost-effective use of NHS resources given that the end-of-life criteria apply (see section 4.17).

Innovation

4.19 The committee considered whether blinatumomab is innovative. It heard from the patient and clinical experts that there is significant unmet need for people with relapsed or refractory acute lymphoblastic leukaemia because of the ineffective and toxic chemotherapy regimens currently available. It noted that the company considers blinatumomab to be an innovative treatment and a step-change in treatment of a very rare illness. The committee concluded that blinatumomab would be beneficial for patients, but it had not been presented with evidence of any additional benefits that were not captured in the measurement of quality-adjusted life years (QALYs).

Pharmaceutical Price Regulation Scheme (PPRS) 2014

4.20 The committee was aware of NICE's position statement on the PPRS 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for

taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has Philadelphia-chromosome-negative relapsed or refractory precursor B-cell acute lymphoblastic leukaemia and the doctor responsible for their care thinks that blinatumomab is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 The Department of Health and Amgen have agreed that blinatumomab will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to commercial-team@amgen.com.

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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ISBN: 978-1-4731-2558-2