

# Pegaspargase for treating acute lymphoblastic leukaemia

Technology appraisal guidance

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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.

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# 1 Recommendations

- 1.1 Pegaspargase, as part of antineoplastic combination therapy, is recommended as an option for treating acute lymphoblastic leukaemia in children, young people and adults only when they have untreated newly diagnosed disease.
- 1.2 This guidance is not intended to affect the position of patients whose treatment with pegaspargase was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop. For children and young people, this decision should be made jointly by the clinician and the child or young person, or the child or young person's parents or carers.

## 2 The technology

<b>Description of the technology</b>	<p>Pegaspargase (Oncaspar, Baxalta [now part of Shire Pharmaceuticals]) is a polyethylene glycol conjugate of <i>Escherichia coli</i> (<i>E. coli</i>)-derived L-asparaginase.</p> <p>L-asparaginase is a bacterial enzyme that depletes circulating asparagine, an essential amino acid on which leukaemic cells, incapable of synthesising asparagine, depend. This leads to cell death.</p>
<b>Marketing authorisation</b>	<p>Pegaspargase received its marketing authorisation in January 2016. It is indicated as 'a component of antineoplastic combination therapy in acute lymphoblastic leukaemia in paediatric patients from birth to 18 years, and adult patients'.</p>
<b>Adverse reactions</b>	<p>The most common side effects with pegaspargase (which may affect more than 1 in 10 people) are allergic reactions (including serious allergic reactions), hives, rash, high blood sugar levels, pancreatitis, diarrhoea, and abdominal pain. For full details of adverse reactions and contraindications, see the summary of product characteristics.</p>

<p><b>Recommended dose and schedule</b></p>	<p>Pegaspargase is administered as either an intramuscular or intravenous infusion.</p> <p><b>Summary of product characteristics</b></p> <p>Pegaspargase is usually used as part of combination chemotherapy protocols with other antineoplastic agents.</p> <p><b><i>Paediatric patients and adults ≤21 years</i></b></p> <p>The recommended dose of pegaspargase in patients with a body surface area <math>\geq 0.6 \text{ m}^2</math> and who are <math>\leq 21</math> years of age is 2500 IU (equivalent to 3.3 ml pegaspargase)/<math>\text{m}^2</math> body surface area every 14 days.</p> <p>Children with a body surface area <math>&lt; 0.6 \text{ m}^2</math> should have 82.5 IU (equivalent to 0.1 ml pegaspargase)/kg body weight every 14 days.</p> <p><b><i>Adults &gt;21 years</i></b></p> <p>Unless otherwise prescribed, the recommended posology in adults aged <math>&gt; 21</math> years is 2000 IU/<math>\text{m}^2</math> every 14 days.</p> <p><b><i>Clinical practice</i></b></p> <p>The protocols for the ongoing UKALL trials, on which current clinical practice is based, recommend a dosage of 1,000 IU/<math>\text{m}^2</math>.</p> <p>The UKALL trials have demonstrated that in clinical practice, dosing frequency depends on the patient's age, the phase of treatment in which pegaspargase is given (induction, consolidation, intensification, and so on), and the length of each phase.</p> <p>The average length of a course of treatment depends on the individual UKALL treatment protocols for patients in different age groups.</p>
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Price	<p>The acquisition cost of pegaspargase is £1,296.19 per vial (excluding VAT; price confirmed by company).</p> <p>For paediatric and young adult patients, a course of pegaspargase costs between £5,144 (intermediate/standard-risk patients) and £15,246 (high-risk patients), assuming that patients complete the treatment (with no hypersensitivity) as per the UKALL 2003 protocol.</p> <p>For adult patients, a course of pegaspargase costs between £6,034 (for those aged 41 years or over) and £7,544 (for those aged 40 years and under), assuming that patients complete the treatment (with no hypersensitivity) as per the UKALL14 protocol, and don't have a transplant.</p> <p>Costs are based on a dose of 1,000 IU/m<sup>2</sup> as used in clinical practice, which equates to 1 vial of pegaspargase per dose. Although the summary of product characteristics dose is higher (2,000 to 2,500 IU/m<sup>2</sup>), only 1 vial would be used per treatment administration. Costs may vary in different settings because of negotiated procurement discounts.</p>
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## 3 Evidence

The appraisal committee ([section 6](#)) considered evidence submitted by Baxalta (now part of Shire Pharmaceuticals) 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 pegaspargase, having considered evidence on the nature of acute lymphoblastic leukaemia and the value placed on the benefits of pegaspargase 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 of acute lymphoblastic leukaemia

- 4.1 The committee understood that a diagnosis of acute lymphoblastic leukaemia can have a profound effect on a person's physical and psychological wellbeing. It also acknowledged that acute lymphoblastic leukaemia does not affect the patient in isolation, but also places emotional strain on their families and friends. The committee was aware that, because of this, access to effective treatments and improving quality of life are significant benefits to patients and their families.
- 4.2 The committee heard from the clinical expert that most people with newly diagnosed acute lymphoblastic leukaemia have pegaspargase followed by *Erwinia*-derived asparaginase in cases of hypersensitivity, and that pegaspargase has been included in NHS England baseline commissioning since April 2013, even though pegaspargase did not have a marketing authorisation in the UK. The committee also heard that most patients in the UK are enrolled into the UKALL trials: UKALL 2011 for children and young adults up to the age of 25 years (previously UKALL 2003, October 2003 to June 2009), UKALL14 for adults aged 25 to 65 years, and UKALL60+ for people over the age of 60 years. Even if a patient is not enrolled in these trials directly, they will still have treatment based on the UKALL protocols because the protocols inform clinical practice in England. Both the UKALL 2011 (and previously UKALL 2003) and UKALL14 trials include pegaspargase as the preferred choice of asparaginase therapy, as a component of the multi-agent chemotherapy regimen. This is because pegaspargase has a longer half-life than the non-pegylated forms of asparaginase (*Escherichia coli* [*E. coli*]-derived

L-asparaginase and *Erwinia chrysanthemi*-derived L-asparaginase) and so can be given less frequently. This is important to patients because native *E. coli*-derived asparaginase is only available in injectable (intramuscular) forms. Intramuscular injections are painful, so less frequent injections are preferable. In addition, pegaspargase is considered preferable to native *E. coli*-derived asparaginase because pegaspargase appears to be less immunogenic. This leads to the production of anti-asparaginase antibodies in 45% to 75% of patients, which frequently cause hypersensitivity reactions that limit treatment effectiveness. The UKALL protocols also mandate switching to *Erwinia*-derived asparaginase rather than to another *E. coli*-derived asparaginase following hypersensitivity to pegaspargase, because of the risk of cross reactivity and subsequent hypersensitivity. The committee heard that adult patients with Philadelphia-positive acute lymphoblastic leukaemia may not necessarily benefit from pegaspargase. This is because evidence suggests that these patients can achieve high remission rates with tyrosine kinase inhibitor-based induction therapies without the added risks of asparaginase therapy. To this end, the UKALL14 protocol specifies that patients with Philadelphia-positive acute lymphoblastic leukaemia do not have asparaginase therapy. The committee concluded that the current treatment pathway in England for most people with newly diagnosed acute lymphoblastic leukaemia is pegaspargase followed by *Erwinia*-derived asparaginase in cases of hypersensitivity.

## Company's decision problem

- 4.3 The committee discussed the company's decision problem in relation to the marketing authorisation for pegaspargase and the final scope issued by NICE. The committee was aware that the population specified in pegaspargase's marketing authorisation was 'for acute lymphoblastic leukaemia in paediatric patients from birth to 18 years, and adult patients'. The committee was aware that the company's decision problem was narrower than both the marketing authorisation for pegaspargase and the final NICE scope, in that it focused on pegaspargase as the preferred choice of asparaginase therapy for people with untreated, newly diagnosed acute lymphoblastic leukaemia. The committee noted that the marketing authorisation does not preclude

pegaspargase's use following other asparaginase therapies or as a treatment for relapsed disease. The company considered that the current use of pegaspargase in the UK for people with untreated, newly diagnosed acute lymphoblastic leukaemia was driven by the UKALL protocols. It was also aware that the UKALL protocols do not include people with relapsed disease and that the committee was not presented with evidence on the use of pegaspargase for treating relapsed acute lymphoblastic leukaemia. The committee concluded that the company's decision problem for people with untreated, newly diagnosed acute lymphoblastic leukaemia was appropriate for its decision-making because this best reflected the use of pegaspargase in established clinical practice in England.

## Clinical effectiveness

### Untreated and newly diagnosed acute lymphoblastic leukaemia

- 4.4 For children and young people, the committee noted that the company had identified 2 studies as the focus of its submission (CCG-1962 and UKALL 2003) and 3 further studies (CCG-1961, DFCI-91-01 and DFCI ALL 05-00) as supporting evidence in children and young people. The committee was aware that all of these studies compared pegaspargase 2,500 IU/m<sup>2</sup> with native *E. coli*-derived asparaginase. The committee also noted that the evidence review group (ERG) had identified 3 further studies from the company's systematic review: DFCI ALL 05-01, which compared pegaspargase 2,500 IU/m<sup>2</sup> with native *E. coli*-derived asparaginase; and the DFCI-95-01 and EORTC-CLG 58881 studies, which compared *Erwinia*-derived asparaginase with native *E. coli*-derived asparaginase. The committee accepted the ERG's concerns about CCG-1962 being a small study and UKALL 2003 being a non-comparative study. Nevertheless, it agreed that despite the limitations of these studies, it was appropriate to consider all the available studies in its decision-making.
- 4.5 For adults, the committee noted that both the company and ERG had identified 3 non-comparative studies (Douer 2007, Douer 2014 and Wetzler 2007), all of which examined the efficacy of pegaspargase

2,000 IU/m<sup>2</sup> or 2,500 IU/m<sup>2</sup>. The committee accepted the ERG's concerns that each study was non-comparative, and so provided no evidence for the relative effectiveness of pegaspargase compared with other asparaginases as listed in the final scope issued by NICE. The committee agreed that despite the limitations of these studies, it was appropriate to consider all the available studies in its decision-making.

## Generalisability to clinical practice in England

- 4.6 The committee discussed the generalisability of the results from all the trials comparing a 2,000 IU/m<sup>2</sup> to 2,500 IU/m<sup>2</sup> dose of pegaspargase with *E. coli*-derived asparaginase or *Erwinia*-derived asparaginase to clinical practice in England (see section 4.2). The committee noted that the summary of product characteristics also recommends a pegaspargase dose of 2,000 to 2,500 IU/m<sup>2</sup>. In contrast, all the UKALL protocols used 1,000 IU/m<sup>2</sup>. The committee was aware from the company, the clinical expert and a statement received from a professional group that UKALL 2003 provided favourable long-term outcomes and safety evidence for pegaspargase 1,000 IU/m<sup>2</sup> in more than 3,200 children and young adults with acute lymphoblastic leukaemia between 2003 and 2011, accounting for more than 97% of the eligible patient population over that time. The committee was also aware that these data had reassured the clinical community in its continued use of 1,000 IU/m<sup>2</sup> as the standard of care in the UKALL 2011 paediatric protocol and to adopt it in the UKALL14 adult protocol. The committee heard from the clinical expert that there is currently no intent among clinicians to increase the dose of pegaspargase to the levels recommended in the summary of product characteristics because of the increased risk of treatment-related toxicity, which is of particular concern in children over 10 years who have higher rates of toxicity-related mortality. The committee heard that in children, clinical practice is moving towards giving lower doses more frequently, and that children will have a maximum of 8 doses of pegaspargase during their treatment for acute lymphoblastic leukaemia. The committee also heard that most clinicians choose not to increase the dosage above 1,000 IU/m<sup>2</sup> in adults and that most are offered bone or stem cell transplant if disease clearance is not achieved with 1,000 IU/m<sup>2</sup> doses of pegaspargase. The committee concluded that although there was no comparative evidence available for pegaspargase 1,000 IU/m<sup>2</sup>

compared with other asparaginases or with pegaspargase 2,500 IU/m<sup>2</sup>, it was appropriate for it to use the lower dose of pegaspargase in its decision-making, because this is reflective of the dose used in clinical practice in England.

## Clinical-effectiveness results

- 4.7 The committee was aware that 4 studies provided survival data in children for the comparison of pegaspargase 2,500 IU/m<sup>2</sup> with native *E. coli*-derived asparaginase. Of these studies, it noted that 2 showed results in favour of pegaspargase in terms of event-free survival (CCG-1961 and CCG-1962), 1 showed non-statistically significant results in favour of *E. coli*-derived asparaginase in terms of event-free survival (DFCI ALL 91-01), and 1 showed little difference between the 2 interventions in terms of overall survival and event-free survival (DFCI ALL 05-001). The committee also noted that the company's meta-analysis of 39 studies in children showed results in favour of pegaspargase in terms of 5-year event-free survival and overall survival. The committee accepted that the studies in children did not show a difference in the clinical effectiveness of pegaspargase and *E. coli*-derived asparaginase, and agreed that it was unclear as to whether this was a result of the lack of evidence or simply a lack of a difference in effect. None of the included studies was powered to assess equivalence and it was not appropriate to pool the results from the different studies because of their heterogeneity. The committee noted the lack of comparative evidence for the relative effectiveness of pegaspargase with other asparaginase therapies in adults (see section 4.6), and was aware that most of the trials in acute lymphoblastic leukaemia have been done in children and young people. The committee was also aware that as part of its regulatory submission to the European Medicines Agency, the company had included data from the UKALL 2003 and Douer 2007 trials to support its application for pegaspargase's marketing authorisation to apply to all ages. The committee heard from the clinical expert, and was aware from the statements received from professional organisations representing clinicians, that although it was difficult to establish clinical equivalence of pegaspargase and the other asparaginase therapies based on the studies alone, clinicians consider pegaspargase and *E. coli*-derived asparaginase to be equivalent in terms

of clinical effectiveness in both children and adults based on their experience in the UKALL trials. Furthermore, clinicians prefer to use pegaspargase because of the reduced risk of hypersensitivity reactions and its longer half-life (see section 4.2). The committee acknowledged that uncertainty around the clinical effectiveness of pegaspargase in people of different ages might be addressed in the ongoing UKALL 2011 and UKALL14 trials and in the post-authorisation studies required by the European Medicines Agency as a condition of its granting of the marketing authorisation. The committee accepted that although there was some uncertainty in terms of the clinical effectiveness of pegaspargase compared with *E. coli*-derived asparaginase, it was reasonable to assume on current available evidence that they were equivalent in terms of event-free survival and overall survival in people of all ages with untreated newly diagnosed acute lymphoblastic leukaemia.

## Previously treated acute lymphoblastic leukaemia

- 4.8 The committee noted that that it had not been presented with any evidence for the efficacy of pegaspargase in people with relapsed acute lymphoblastic leukaemia, because the company's decision problem was based on how pegaspargase is used in clinical practice for people with untreated, newly diagnosed acute lymphoblastic leukaemia (see section 4.6). The committee concluded that it was inappropriate to make a recommendation for pegaspargase in people with previously treated relapsed acute lymphoblastic leukaemia.

## Cost effectiveness

### Economic model

- 4.9 The company presented a combined decision tree and health state transition Markov model. The committee agreed that the structures of both parts of the model were appropriate and the combination of the 2 was well suited for the purpose of the appraisal, because it accurately reflected the treatment pathway for acute lymphoblastic leukaemia. The committee also noted that the model only included patients with untreated, newly diagnosed acute lymphoblastic leukaemia, and it heard



from the clinical expert that the model structure reflected clinical practice in England. The committee concluded that the model was in line with accepted NICE methods and therefore appropriate for its decision-making.

## Treatment sequences modelled

4.10 The company modelled 3 treatment sequences:

- Pegaspargase followed by *Erwinia*-derived asparaginase in cases of hypersensitivity, compared with *E. coli*-derived asparaginase followed by *Erwinia*-derived asparaginase in cases of hypersensitivity (comparison 1).
- Pegaspargase followed by *Erwinia*-derived asparaginase in cases of hypersensitivity, compared with *Erwinia*-derived asparaginase followed by pegaspargase in cases of hypersensitivity (comparison 2).
- Pegaspargase followed by *Erwinia*-derived asparaginase in cases of hypersensitivity, compared with *Erwinia*-derived asparaginase followed by *E. coli*-derived asparaginase in cases of hypersensitivity (comparison 3).

The committee agreed that comparisons 2 and 3 were not relevant for its decision-making, because there was no clinical scenario in which *Erwinia*-derived asparaginase would be used as the preferred choice of asparaginase, or in which pegaspargase would be used in cases of hypersensitivity (see section 4.2). For this reason it also agreed not to consider either the company's or the ERG's cost-effectiveness analyses for comparisons 2 and 3 any further. The committee considered whether comparison 1 was relevant for its decision-making. It acknowledged that although *E. coli*-derived asparaginase is no longer used as the first choice of asparaginase therapy, it was the standard of care before pegaspargase became available. The committee therefore concluded that comparison 1 was the appropriate comparison for its decision-making.

## Model inputs

4.11 The committee discussed the assumption that pegaspargase, *E. coli*-derived and *Erwinia*-derived asparaginase were equivalent in terms of overall survival and event-free survival. The committee noted

that both the company and the ERG had used this assumption in their respective base-case analyses, and that both had included a 'worst-case scenario' in which it was assumed that event-free survival was worse for pegaspargase than for *E. coli*-derived asparaginase. The committee also noted that the ERG had included a 'best-case scenario' in which it assumed that overall survival and event-free survival were better for pegaspargase than for *E. coli*-derived asparaginase. The committee recalled that it had heard from the clinical expert that clinicians consider the 3 asparaginase treatments to be equivalent in terms of clinical effectiveness in both children and adults (see section 4.6). It therefore agreed that it was appropriate to assume that pegaspargase, *E. coli*-derived and *Erwinia*-derived asparaginase were equivalent in terms of overall survival and event-free survival.

- 4.12 The committee discussed the dosage of pegaspargase used in the model. The committee noted that both the company and the ERG had presented their base-case analysis results using the 1,000 IU/m<sup>2</sup> dose of pegaspargase, and scenario analyses using the 2,500 IU/m<sup>2</sup> dose of pegaspargase. The committee agreed that it preferred to use the 1,000 IU/m<sup>2</sup> dose of pegaspargase because it reflected the dose used in clinical practice (see section 4.6).
- 4.13 The committee discussed the dosing ratio for *E. coli*- or *Erwinia*-derived asparaginase compared with pegaspargase. The committee noted that, based on expert opinion, the company had assumed a rate of 6 doses of *E. coli*-derived asparaginase or *Erwinia*-derived asparaginase for each dose of pegaspargase. The committee also noted the ERG's comments that there was no scientific evidence to prove that this was the best ratio of the different formulations and that in other countries; it is considered that 4 doses of *E. coli*- or *Erwinia*-derived asparaginase correspond with 1 dose of pegaspargase. The committee was aware of an ERG scenario analyses in which this ratio of 4:1 had been used. The committee heard from the clinical expert that the dosing ratio for *E. coli*- or *Erwinia*-derived asparaginase compared with pegaspargase would be closer to 6:1 in clinical practice, and therefore agreed that it was appropriate to use this ratio in the economic model.
- 4.14 The committee discussed the risk of hypersensitivity used in the



economic model. In its base-case analysis, the company had assumed that the risk of hypersensitivity leading to treatment switch was 2% for both first- and second-line asparaginase therapy, based on the first-line hypersensitivity observed in UKALL 2003 with the lower dose (1,000 IU/m<sup>2</sup>) of pegaspargase. The committee noted that the ERG had used a higher risk of hypersensitivity to pegaspargase in its base-case analysis, based on Nordic data for the 1,000 IU/m<sup>2</sup> dose. The committee heard from the clinical expert that the company's assumption of a 2% risk of hypersensitivity was closer to the risk seen in clinical practice for children with acute lymphoblastic leukaemia. The committee therefore concluded that for all ages it preferred to use the company's assumption of 2% risk of hypersensitivity leading to treatment switch in its decision-making.

## Cost-effectiveness estimates

- 4.15 The committee noted that in the company's base-case analysis, pegaspargase followed by *Erwinia*-derived asparaginase dominated (that is, was both less costly and more effective than) *E. coli*-derived asparaginase followed by *Erwinia*-derived asparaginase in adults, children, and the whole (combined) population. The committee also noted that pegaspargase followed by *Erwinia*-derived asparaginase continued to dominate *E. coli*-derived asparaginase followed by *Erwinia*-derived asparaginase in all but 1 of the company's scenario analyses for the whole population: the 'worst-case scenario', which produced an incremental cost-effectiveness ratio (ICER) of £20,326 saved per quality-adjusted life year (QALY) lost. The committee agreed that the company's worst-case scenario was not relevant to its decision-making (see section 4.11). The committee was aware that the ERG had provided a revised base case and scenario analyses for the whole population. The committee noted that the ERG's base-case analysis for the whole population was consistent with that presented by the company: that is, pegaspargase followed by *Erwinia*-derived asparaginase dominated *E. coli*-derived asparaginase followed by *Erwinia*-derived asparaginase. The committee also noted that pegaspargase followed by *Erwinia*-derived asparaginase continued to dominate *E. coli*-derived asparaginase followed by *Erwinia*-derived asparaginase in all but 2 of the ERG's scenario analyses: the worst-case

scenario and the scenario in which 4 doses of *E. coli*- or *Erwinia*-derived asparaginase were applied for each dose of pegaspargase (respective ICERs of £4,810 saved per QALY lost and £36,499 per QALY gained [incremental costs £739, incremental QALYs 0.02]). The committee agreed that neither of these scenarios were relevant to its decision-making (see sections 4.11 and 4.13). The committee agreed that both the company's and the ERG's scenario analyses demonstrated the robustness of the cost-effectiveness results for pegaspargase followed by *Erwinia*-derived asparaginase compared with *E. coli*-derived asparaginase followed by *Erwinia*-derived asparaginase; that is, pegaspargase followed by *Erwinia*-derived asparaginase dominated (that is, was both less costly and more effective). It therefore concluded that it could recommend pegaspargase as a cost-effective use of NHS resources for treating acute lymphoblastic leukaemia in children, young people and adults with untreated, newly diagnosed disease.

## Innovation

- 4.16 The company stated that it considered pegaspargase to be innovative, because it has become the standard of care for first-line asparaginase treatment for acute lymphoblastic leukaemia in people of all ages. The committee heard from the clinical expert that in clinical practice, pegaspargase is now considered to be an incremental change in the treatment of acute lymphoblastic leukaemia rather than a step change because it has been used in clinical practice for a number of years. The committee concluded that pegaspargase should not be considered a step change in the treatment of acute lymphoblastic leukaemia.

## Pharmaceutical Price Regulation Scheme (PPRS) 2014

- 4.17 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (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.

## Summary of appraisal committee's key conclusions

TA408	Appraisal title: Pegaspargase for treating acute lymphoblastic leukaemia	Section
Key conclusion		

<p>Pegaspargase, as part of antineoplastic combination therapy, is recommended as an option for treating acute lymphoblastic leukaemia in children, young people and adults only when they have untreated newly diagnosed disease.</p> <p>This guidance is not intended to affect the position of patients whose treatment with pegaspargase was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop. For children and young people, this decision should be made jointly by the clinician and the child or young person or the child or young person's parents or carers.</p> <p>The committee accepted that although there was some uncertainty in terms of the clinical effectiveness of pegaspargase compared with that of <i>Escherichia coli</i> (<i>E. coli</i>)-derived asparaginase, it was reasonable to assume on the current available evidence that they were equivalent in terms of event-free survival and overall survival in people of all ages with untreated, newly diagnosed acute lymphoblastic leukaemia.</p> <p>The committee agreed that both the company's and the evidence review group's (ERG's) scenario analyses demonstrated the robustness of the cost-effectiveness results for pegaspargase followed by <i>Erwinia</i>-derived asparaginase in cases of hypersensitivity compared with <i>E. coli</i>-derived asparaginase followed by <i>Erwinia</i>-derived asparaginase in cases of hypersensitivity; that is, pegaspargase followed by <i>Erwinia</i>-derived asparaginase dominated (was both less costly and more effective) than <i>E. coli</i>-derived asparaginase followed by <i>Erwinia</i>-derived asparaginase. The committee therefore concluded that it could recommend pegaspargase as a cost-effective use of NHS resources for treating acute lymphoblastic leukaemia in children, young people and adults with untreated, newly diagnosed disease.</p>	1.1, 1.2, 4.7, 4.15
<b>Current practice</b>	

Clinical need of patients, including the availability of alternative treatments	The committee understood that a diagnosis of acute lymphoblastic leukaemia can have a profound effect on a person's physical and psychological wellbeing. It also acknowledged that acute lymphoblastic leukaemia does not affect the patient in isolation, but also places emotional strain on their families and friends. The committee was aware that, because of this, access to effective treatments and improving quality of life are significant benefits to patients and their families.	4.1
<b>The technology</b>		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	<p>The committee heard that pegaspargase has a longer half-life than the non-pegylated forms of asparaginase (<i>E. coli</i>-derived asparaginase and <i>Erwinia</i>-derived asparaginase), so can be given less frequently to patients. This is important to patients because native <i>E. coli</i>-derived asparaginase is only available in an injectable form; intramuscular injections are painful, so less frequent injections are preferable. In addition, pegaspargase is considered preferable to native <i>E. coli</i>-derived asparaginase because pegaspargase appears to be less immunogenic. This leads to the production of anti-asparaginase antibodies in 45% to 75% of patients, which frequently cause hypersensitivity reactions that limit treatment effectiveness.</p> <p>The committee heard from the clinical expert that in clinical practice, pegaspargase is now considered to be an incremental change in the treatment of acute lymphoblastic leukaemia rather than a step change because it has been used in clinical practice for a number of years. The committee concluded that pegaspargase should not be considered a step change in the treatment of acute lymphoblastic leukaemia.</p>	4.2, 4.16

What is the position of the treatment in the pathway of care for the condition?	The committee heard from the clinical expert that most people with newly diagnosed acute lymphoblastic leukaemia have pegaspargase followed by <i>Erwinia</i> -derived asparaginase in cases of hypersensitivity and that pegaspargase has been included in NHS England baseline commissioning since April 2003. The committee also heard that most patients in the UK are enrolled into the UKALL trials. Even if a patient is not enrolled in these trials directly, they will still have treatment based on the UKALL protocols, which form the basis of clinical practice in England. Both the UKALL 2011 (and previously UKALL 2003) and UKALL14 trials include pegaspargase as the preferred choice of asparaginase therapy, as a component of the multi-agent chemotherapy regimen.	4.2
Adverse reactions	The most common side effects with pegaspargase (which may affect more than 1 in 10 people) are allergic reactions (including serious allergic reactions), hives, rash, high blood sugar levels, pancreatitis, diarrhoea, and abdominal pain.	2.0
<b>Evidence for clinical effectiveness</b>		

Availability, nature and quality of evidence	<p>For children and young people, the company identified 2 studies as the focus of its submission (CCG-1962 and UKALL 2003) and 3 further studies (CCG-1961, DFCI-91-01 and DFCI ALL 05-00) as supporting evidence. These studies compared pegaspargase 2,500 IU/m<sup>2</sup> with native <i>E. coli</i>-derived asparaginase. The ERG identified 3 further studies from the company's systematic review: DFCI ALL 05-01, which compared pegaspargase 2,500 IU/m<sup>2</sup> with native <i>E. coli</i>-derived asparaginase; and the DFCI-95-01 and EORTC-CLG 58881 studies, which compared <i>Erwinia</i>-derived asparaginase with native <i>E. coli</i>-derived asparaginase. In adults, both the company and ERG identified 3 non-comparative studies (Douer 2007, Douer 2014 and Wetzler 2007), all of which examined the efficacy of pegaspargase 2,000 IU/m<sup>2</sup> or 2,500 IU/m<sup>2</sup>.</p> <p>The committee accepted the ERG's concerns about the quality of the studies in both the children and young people and adult populations. Nevertheless, it agreed that despite the limitations of these studies, it was appropriate to consider all the available studies in its decision-making.</p>	4.4, 4.5,
Relevance to general clinical practice in the NHS	<p>The committee concluded that although there was no comparative evidence available for pegaspargase 1,000 IU/m<sup>2</sup> compared with other asparaginases or with pegaspargase 2,000–2,500 IU/m<sup>2</sup>, it was appropriate for it to take the lower dose of pegaspargase into consideration in its decision-making, because this was reflective of the dose used in clinical practice in England.</p>	4.6

Uncertainties generated by the evidence	<p>The committee accepted that the studies in children did not show a difference in the clinical effectiveness of pegaspargase and <i>E. coli</i>-derived asparaginase, but agreed that it was unclear as to whether this was a result of the lack of evidence or simply a lack of a difference in effect. None of the included studies were powered to assess equivalence and it was not appropriate to pool the results from the different studies because of their heterogeneity.</p> <p>The committee noted the lack of comparative evidence for the relative effectiveness of pegaspargase with other asparaginase therapies in adults, but was aware that most of the trials in acute lymphoblastic leukaemia have been done in children and young people.</p> <p>The committee also agreed that there was no comparative evidence available for pegaspargase at a dose of 1,000 IU/m<sup>2</sup> compared with other asparaginases or with pegaspargase at a dose of 2,000–2,500 IU/m<sup>2</sup>.</p>	4.6, 4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No subgroups were considered by the committee.	
<b>Evidence for cost effectiveness</b>		
Availability and nature of evidence	<p>The company provided an economic model that combined a decision tree and a health state transition Markov model. The committee agreed the structures of the decision tree and Markov models to be appropriate and the combination of the 2 models was well suited for the purpose of the appraisal because it reflected the treatment pathway for acute lymphoblastic leukaemia. The committee concluded that the model was in line with accepted NICE methods and therefore appropriate for its decision-making.</p>	4.9



Uncertainties around and plausibility of assumptions and inputs in the economic model	<ul style="list-style-type: none"> <li>Assumption that pegaspargase, <i>E. coli</i>-derived and <i>Erwinia</i>-derived asparaginase were equivalent in terms of overall survival and event-free survival.</li> <li>Dosage of pegaspargase used in the model (1,000 IU/m<sup>2</sup> or 2,000–2,500 IU/m<sup>2</sup>).</li> <li>Dosing ratio for <i>E. coli</i>- or <i>Erwinia</i>-derived asparaginase compared with pegaspargase.</li> <li>Risk of hypersensitivity leading to treatment switch.</li> </ul>	4.11, 4.12, 4.13, 4.14
Incorporation of health-related quality-of-life benefits and utility values	Not considered by committee.	
Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	None identified.	

Are there specific groups of people for whom the technology is particularly cost effective?	Not considered by committee.	
What are the key drivers of cost effectiveness?	The key drivers of the cost-effectiveness analysis were the event-free survival estimate for pegaspargase and the dosing ratio for <i>E. coli</i> - or <i>Erwinia</i> -derived asparaginase compared with pegaspargase.	4.15
Most likely cost-effectiveness estimate (given as an ICER)	Pegaspargase followed by <i>Erwinia</i> -derived asparaginase in cases of hypersensitivity dominated (that is, was both less costly and more effective than) <i>E. coli</i> -derived asparaginase followed by <i>Erwinia</i> -derived asparaginase in cases of hypersensitivity.	4.15
<b>Additional factors taken into account</b>		
Patient access schemes (PPRS)	Not applicable.	
End-of-life considerations	Not applicable.	

Equalities considerations and social value judgements	<p>Consultees and commentators highlighted the following potential equality issues:</p> <ul style="list-style-type: none"><li>• Acute lymphoblastic leukaemia is an orphan disease.</li><li>• It is unusual in that it is more common in children aged less than 14 years. As such, any decision not to recommend pegaspargase would disproportionately affect children.</li><li>• If NICE does not approve pegaspargase, children in the UK with acute lymphoblastic leukaemia will be the only children among developed countries not to have access to the drug.</li></ul> <p>The committee agreed that the increased prevalence in children and young people and the low number of people diagnosed with acute lymphoblastic leukaemia is a feature of the disease. Any recommendation resulting from this appraisal will apply to all people so age, as defined by the Equalities Act, is not a relevant equalities issue. The committee also agreed that variation in access to treatments between countries does not normally constitute an equality issue under equality legislation, because recommendations made by the technology appraisal committee do not address equality of access between countries.</p>	
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## 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 treating acute lymphoblastic leukaemia and the doctor responsible for their care thinks that pegaspargase is the right treatment, it should be available for use, in line with NICE's recommendations.

## 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 C](#).

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

#### Technical lead

Helen Tucker

#### Technical adviser

Nicola Hay

#### Project manager

Stephanie Yates

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