Review proposal of TA408; Pegaspargase for treating acute lymphoblastic leukaemia

TA408 was published in September 2016 and scheduled to be considered for review in 2019.

1. Proposal

The guidance should be transferred to the 'static guidance list'.

2. Rationale

No new cost or clinical effectiveness data which would lead to a change in the recommendations for technology appraisal 408. Therefore, it is considered appropriate to transfer the guidance to the static list.

3. Summary of new evidence and implications for review

Has there been any change to the price of the technology(ies) since the guidance was published?

No.

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

No.

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

The recommendations for pegaspargase for treating acute lymphoblastic leukaemia was optimised to reflect the population for which it would be used in clinical practice. The evidence presented by the company during the appraisal focused on the acute population. No evidence was presented for the efficacy of pegaspargase in people with relapsed lymphoblastic leukaemia. There have been no further trials of pegaspargase in a relapsed population so this optimised recommendation does not need to be reviewed.

During the appraisal process the committee noted the lack of comparative evidence for the relative effectiveness of pegaspargase with other asparaginase therapies in adults. The committee heard from clinical experts that pegaspargase and E. coli-derived asparaginase are considered equally effective in both children and adults. Clinicians also expressed a preference for using pegaspargase because of the reduced risk of hypersensitivity reactions. A review of the literature has indicated that the UKALL14 trial exploring the safety and efficacy of pegaspargase in adults is still on-going. A prospective analysis of patients enrolled between 2010 and 2012 suggested that pegaspargase achieves very effective asparagine depletion but also indicted that toxicity can be substantial in older patients. The study showed the importance around the timing of administration and the careful consideration

required when pegaspargase is administered with other induction therapies[1].

There are no new data to suggest that pegaspargase would be less clinically effective or cost-effective than estimated at the time the guidance was issued. Additional data on the safety of pegaspargase in adults is expected from the UKALL14 trial in 2022. There have been no changes to the treatment pathway for acute lymphoblastic leukaemia.

Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?

There are no related pieces of NICE guidance.

The search strategy from the original ERG report was adapted for the Cochrane Library, Medline, Medline In-Process and Embase. References from August 2015 to May 2019 were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

4. Equality issues

No equality and diversity issues were raised in the original guidance.

Proposal paper sign off

Nicole Elliott – Associate Director, Technology Appraisals and Highly Specialised Technologies: 19 June 2019

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Appendix A – Information from existing guidance

1. Original remit

To appraise the clinical and cost effectiveness of pegaspargase within its marketing authorisation for treating acute lymphoblastic leukaemia.

2. Current guidance

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.

3. Research recommendations from original guidance

The committee noted that there were several ongoing research projects:

- UKALL 2011 is investigating the efficacy and toxicity of pegaspargase in in people aged 1 to 24 years with newly diagnosed acute lymphoblastic leukaemia. UKALL 2011 opened in April 2012 and enrolment closes in April 2018.

- UKALL 14 is investigating the efficacy and toxicity of pegaspargase in adults aged 25 to 65 years with newly diagnosed acute lymphoblastic leukaemia. UKALL14 opened in December 2010 and closes in December 2016[a].

- Post-authorisation efficacy study: CAALL-F01, a prospective multicentre cohort study, is evaluating pegaspargase used in the first-line treatment acute lymphoblastic leukaemia in children and young people, along with multi-agent chemotherapy. The clinical study report is due to be submitted to the European Medicines Agency in December 2025.

- Post-authorisation efficacy study: a multicentre, open-label single-arm phase II trial is evaluating the efficacy and toxicity of treatment regimens including pegaspargase in adults (aged 18 to 60 years) with newly diagnosed Philadelphia chromosome-negative acute lymphoblastic leukaemia. The clinical study report is due to be submitted to the European Medicines Agency in December 2018.

4. Cost information from original guidance

“The acquisition cost of pegaspargase is £1,296.19 per vial (excluding VAT; price confirmed by company).

[a] Updated October 2018 UKALL14 still ongoing recruitment of participants. Please see https://clinicaltrials.gov/ct2/show/NCT01085617 for more information

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.

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.

Costs are based on a dose of 1,000 IU/m2 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/m2), only 1 vial would be used per treatment administration. Costs may vary in different settings because of negotiated procurement discounts.“

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the STA process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to a specific date or trial.	NICE will reconsider whether a review is necessary at the specified date.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No
The guidance should be updated in an on-going clinical guideline[b].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No

[b] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Options	Consequence	Selected – 'Yes/No'
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider.	**Yes**
The guidance should be withdrawn	The guidance is no longer relevant, and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	

Appendix C – Other relevant information

Relevant Institute work

Published

Haematological cancers: improving outcomes (2016) NICE guideline NG47

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (2018) NICE technology appraisal guidance 554

Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia (2018) NICE technology appraisal guidance 541

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia (2017) NICE technology appraisal guidance 451

Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia (2017) NICE technology appraisal guidance 450

In progress

Blinatumomab for acute lymphoblastic leukaemia for people with minimal residual disease activity in remission NICE technology appraisal guidance. Publication date to be confirmed.

Blinatumomab for treating Philadelphia-chromosome-positive relapsed or refractory acute lymphoblastic leukaemia NICE technology appraisal guidance. Publication expected July 2020.

KTE-C19 for previously treated B-precursor acute lymphoblastic leukaemia in people aged 2 to 21 NICE technology appraisal guidance. Publication date to be confirmed.

KTE-C19 for previously treated B-precursor acute lymphoblastic leukaemia NICE technology appraisal guidance. Publication date to be confirmed.

Erythrocyte encapsulated asparaginase for treating acute lymphoblastic leukaemia NICE technology appraisal guidance. Publication date to be confirmed. *July 2018: "… the company have now advised that they will not be pursuing a marketing authorisation application for erythrocyte encapsulated asparaginase from the European Medicines Authority for this indication at this time."*

Details of changes to the indications of the technology

Indication and price considered in original appraisal

“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'.”

“The acquisition cost of pegaspargase is £1,296.19 per vial (excluding VAT; price confirmed by company).”

Proposed indication (for this appraisal) and current price

The current indication (in the SPC) and the price (in Mims, accessed 16 May 19) are the same.

Registered and unpublished trials

Trial name and registration number	Details
Ongoing trials listed in the Final Appraisal Determination document for TA408	
United Kingdom Trial for children and young adults with Acute lymphoblastic Leukaemia and Lymphoma 2011 UKALL 2011; ISRCTN64515327; EudraCT number 2010-020924-22	Phase III Status: ongoing not recruiting Design: Randomised interventional treatment trial Target number of participants: 2640, age 1 to 24, newly diagnosed ALL Purpose: Primary outcomes are (Dexamethasone randomisation) Induction steroid-induced morbidity and mortality; (Methotrexate randomisation) Central nervous system (CNS) relapse; (Pulses randomisation) Bone marrow relapse. Added 08/03/2018: Any event defined as relapse, secondary tumour or death from any cause is also a primary outcome measure for each randomised comparison and the trial overall. Start date: January 2012 Estimated primary completion date: December 2027.

Trial name and registration number	Details
A Randomized Trial for Adults With Newly Diagnosed Acute Lymphoblastic Leukemia UKALL 2014; NCT01085617; CDR0000667211; UCL-08-0167; EU-21009; 2009-012717-22; UCL-UKALL14; NCRI-UCL-08-0167	Phase III Status: recruiting Design: randomised Participants: 811; age 25 to 65, newly diagnosed untreated ALL Purpose: "This randomized phase III trial is studying standard chemotherapy to see how well it works when given together with or without rituximab, and with or without nelarabine in treating patients with newly diagnosed acute lymphoblastic leukemia" (pegaspargase is one of the listed interventions). Primary outcome: event free survival Start date: December 2010 Estimated primary completion date: July 2018 Estimated study completion date: July 2023
A French Protocol for the Treatment of Acute Lymphoblastic Leukemia (ALL) in Children and Adolescents NCT02716233; AOM10205; CAALL-F01	Phase III Status: recruiting Design: part randomised, prospective multicentric cohort study Participants:1578, age 12 months to 18 years, ALL L1 or L2, B-lineage or T- lineage ALL Purpose: "What is the best way to administer pegaspargase?" (randomised); "In the High/Very High Risk groups, a non randomized intensification of the scheme of asparaginase administration is proposed during induction therapy" Start date: April 2016 Estimated primary completion date: April 2026

Trial name and registration number	Details
A Novel "Pediatric-Inspired" Regimen With Reduced Myelosuppressive Drugs for Adults (Aged 18-60) With Newly Diagnosed Ph Negative Acute Lymphoblastic Leukemia NCT01920737; 12-266	Phase II Status: recruiting Design: single group assignment Participants: 39; age 18 to 60; previously untreated Ph negative precursor B-cell or T-cell ALL Purpose: "The purpose of the study is to find out whether the combination of chemotherapy drugs that are routinely used in children with ALL, will be safe and effective in treating adult patients with ALL". Primary outcome: rate of molecular remission. Start date: August 2013 Estimated primary completion date: August 2019
Other trials	
PEG-asparaginase During Two Treatment Courses in the Treatment of Childhood Acute Lymphoblastic Leukemia NCT00192673; 2005-000658-56; 20040177; 2004-41-4276	Phase IV, non-randomised, open label trial. Status unknown. Participants: 85, age 1-14 years, newly diagnosed ALL. "The purpose of this study is • to determine the correct dose for intramuscular administration • to compare the frequency of antibody formation after intramuscular administration of native E. coli asparaginase and PEG-asparaginase during two treatment courses in the treatment of childhood lymphoblastic leukemia." Start date: June 2005 Estimated primary completion date: December 2013

Trial name and registration number	Details
Total Therapy Study XVI for Newly Diagnosed Patients With Acute Lymphoblastic Leukemia NCT00549848; TOTXVI; Aspar PK-PD-T16	Phase III Status: Active, not recruiting Design: randomised Participants: 600, less than or equal to 18 years, confirmed diagnosis of precursor B-cell or precursor T-cell acute lymphocytic leukemia (ALL), limited prior therapy Purpose: "…to compare the clinical benefit, the pharmacokinetics, and the pharmacodynamics of polyethylene glycol-conjugated (PEG) asparaginase given in higher dose (HD PEG) versus those of PEG-asparaginase given in conventional dose (CD PEG) during the continuation phase." Start date: October 2007 Estimated primary completion date: November 2020
Treatment of Newly Diagnosed Acute Lymphoblastic Leukemia in Children and Adolescents NCT03020030, 16-001	Phase III Status: recruiting Design: randomised Participants: 400, age 1 to 21 years, confirmed ALL, limited prior therapy Purpose: to examine both standard and new risk factors for deciding treatment strength; to study dosage of pegaspargase. Start date: March 2017 Estimated primary completion date: December 2026

Trial name and registration number	Details
Moscow-Berlin 2008 Multicenter Randomised Study for Treatment of Acute Lymphoblastic Leukemia in Children and Adolescents NCT01953770 ALL-MB 2008	Phase Status: active, not recruiting Design: randomised Participants: 3000, age 1-18 years Purpose: impact of early use of peg-asparaginase, effect on treatment toxicity, dosage, potential to avoid cranial irradiation, overall and event free survival. Start date: February 2008 Estimated primary completion date: June 2019 Actual primary completion date: January 2015 Estimated study completion date: June 2019
Total Therapy XVII for Newly Diagnosed Patients With Acute Lymphoblastic Leukemia and Lymphoma NCT03117751; TOT17; NCI-2017-00582	Phase II/III Status: recruiting Design: randomised Participants: 1000, age 1-18 years (inclusive), newly diagnosed with B or T- Acute Lymphoblastic Leukemia or Lymphoma, limited prior therapy. Purpose: primary outcome measures include event free survival, and rate of allergic reactions to pegaspargase in B-ALL patients Start date: March 2017 Estimated primary completion date: March 2028
International Collaborative Treatment Protocol For Children And Adolescents With Acute Lymphoblastic Leukemia NCT01117441, AIEOP-BFM ALL 2009	Phase III Status: Active, not recruiting Design: randomised Participants: 4750, 1 to 18 years, newly diagnosed ALL, limited prior therapy Purpose: “This trial is studying several different combination chemotherapy regimens to compare how well they work in treating young patients with ALL.” Start date: June 2010 Estimated primary completion date: December 2021

Trial name and registration number	Details
A Randomized Multi-Center Treatment Study (COALL 08-09) to Improve the Survival of Children With Acute Lymphoblastic Leukemia on Behalf of the German Society of Pediatric Hematology and Oncology NCT01228331 CDR0000686545; 2009-012758-18 (EudraCT Number)	Phase II/III Status: recruiting Design: randomised Participants: 660; diagnosis after the first and before the 18th birthday AND confirmed diagnosis of acute B-precursor or T-cell leukemia; limited prior therapy Purpose: "…studying the side effects of giving clofarabine compared with giving high-dose cytarabine, pegaspargase, and combination chemotherapy followed by daunorubicin hydrochloride or doxorubicin hydrochloride and to see how well it works in treating young patients with T-cell acute lymphoblastic leukemia or precursor B-cell acute lymphoblastic leukemia." One of the primary outcomes is "Disease-free survival (DFS) of high-dose methotrexate (with leucovorin rescue) vs escalating-dose methotrexate (without leucovorin rescue) and pegaspargase [Time Frame: At 4 years]" Start date: October 2010 Estimated primary completion date: March 2019

References

1. Patel B.; Kirkwood A.A.; Dey A.; Marks D.I.; McMillan A.K.; Menne T.F.; Micklewright L.; Patrick P.; Purnell S.; Rowntree C.J.; Smith P.; Fielding A.K. Pegylated-asparaginase during induction therapy for adult acute lymphoblastic leukaemia: Toxicity data from the UKALL14 trial. *Leukemia*, 31, 1, 58-64, 2017