NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Health Technology Appraisal

Erythrocyte encapsulated asparaginase for treating acute lymphoblastic leukaemia

Draft scope

Draft remit/appraisal objective

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

Background

Acute lymphoblastic leukaemia (ALL) is a cancer of lymphocyte-producing cells. Lymphocytes are white blood cells that are vital for the body's immune system. In ALL there is an excess production of immature lymphocyte-precursor cells, called lymphoblasts or blast cells, in the bone marrow. This affects the production of normal blood cells and there is a reduction in the numbers of red cells, white cells and platelets in the blood. ALL can be classified into 3 groups based on immunophenotyping: B-precursor ALL (also known as precursor-B-cell ALL), mature B-cell ALL and T-cell ALL. A specific chromosomal abnormality known as the 'Philadelphia chromosome' is present in 20–30% of adults with ALL. The disease is described as Philadelphia-chromosome-positive if the abnormality is present, and Philadelphia-chromosome-negative if it is not present.

ALL is most common in children, adolescent and young adults, with 65% of cases diagnosed in people aged under 25 years. A second increase in incidence is observed in people aged over 60 years. In England, 691 people were diagnosed with ALL in 2015 and 206 people died from ALL in 2016[1].

The aim of treatment in ALL is to achieve a cure. Treatment can take up to 3 years to complete and is generally divided into 3 phases; induction phase, consolidation and maintenance. The choice of treatment can depend on the phase and although selection of drugs, dose schedules and treatment duration may differ slightly between different subtypes of ALL, the basic treatment principles remain similar. Possible treatment options for relapsed or refractory ALL include a combination chemotherapy based regimen of fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG), followed by stem cell transplantation where a suitable donor can be found or best supportive care (including palliative care). Clofarabine is used outside its marketing authorisation in clinical practice in England through the Cancer Drugs Fund (CDF) for people with relapsed or refractory ALL 'with intent to use the treatment to bridge to bone marrow transplant' (at the time the scope

was written, CDF transition funding remains in place until a commissioning decision from NHS England).

For adults with relapsed or refractory disease, NICE technology appraisals recommend:

- blinatumomab for Philadelphia-chromosome-negative precursor B-cell ALL (technology appraisal guidance 450)

- ponatinib for Philadelphia-chromosome-positive ALL with T315I gene mutation or for whom dasatinib or imatinib cannot be used (technology appraisal guidance 451).

Other treatment options may include stem cell transplantation if a suitable donor can be found, or best supportive care (including palliative care).

There is currently no NICE guidance on treating relapsed or refractory ALL in people who are younger than 18 years old. Possible treatment options for people who are younger than 18 years old may include FLAG. The safety and efficacy of clofarabine have been assessed in studies of patients aged 21 years and younger at initial diagnosis. Clofarabine has a marketing authorisation in the UK as a treatment for ALL 'in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response'. Stem cell transplantation (SCT) may be an option for children who relapse early or who have multiple relapses.

The technology

Erythrocyte encapsulated asparaginase (GRASPA, Orphan Europe) is an encapsulated L-asparaginase. Asparaginase is an enzyme that breaks down asparagine (an amino acid) leading to cell death. Erythrocyte encapsulated asparaginase is administered by intravenous injection.

Erythrocyte encapsulated asparaginase does not currently have a marketing authorisation in the UK for treating ALL. It has been studied in a clinical trial with chemotherapy, compared with Escherichia coli (E. coli) derived L-asparagase, in people with Philadelphia chromosome-negative ALL that is refractory to or has relapsed after initial treatment.

Intervention(s)	Erythrocyte encapsulated asparaginase plus established clinical management without asparaginase
Population(s)	People with Philadelphia chromosome-negative acute lymphoblastic leukaemia that is refractory to or has relapsed after initial treatment.

Comparators	For people who are able to take chemotherapy: • E. coli asparaginase, as part of antineoplastic combination therapy • Erwinia-derived asparaginase, as part of antineoplastic combination therapy • fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG)-based combination chemotherapy • blinatumomab (for adults with B-cell ALL) • inotuzumab ozogamicin (for adults with CD22-positive B-cell precursor ALL) (subject to ongoing NICE appraisal) • tisagenlecleucel-T (for people aged 3 to 25 years with B-cell ALL) (subject to ongoing NICE appraisal) For people who are unable to take chemotherapy: • best supportive care (including palliative care).
Outcomes	The outcome measures to be considered include: • time to and duration of response • event-free survival • overall survival • rate of allergic reactions • therapeutic drug monitoring (asparaginase levels) • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related technology appraisals: Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia (2017) NICE technology appraisal 450. Review date June 2020. Appraisals in development: Blinatumomab for acute lymphoblastic leukaemia NICE technology appraisals guidance [ID1036]. Publication date to be confirmed. Inotuzumab ozogamicin for treating relapsed or refractory acute lymphoblastic leukaemia NICE technology appraisals guidance [ID893]. Publication date to be confirmed. Tisagenlecleucel-T for previously treated B-cell acute lymphoblastic leukaemia in people aged 3 to 21 at initial diagnosis NICE technology appraisals guidance [ID1167]. Publication date to be confirmed. Related guidelines:

	Haematological cancers: improving outcomes (2016) NICE guideline 47. Review date to be confirmed. Related quality standards: Haematological cancers (2017) NICE quality standard 150. Related NICE Pathways: Blood and bone marrow cancers (2017) NICE Pathway
Related National Policy	NHS England (2017) Manual for Prescribed Specialised Services 2017/18. Chapters 105 and 106. Department of Health and Social Care, NHS Outcomes Framework 2016-2017 (published 2016): Domain 1.

Questions for consultation

Have all relevant comparators for erythrocyte encapsulated asparaginase been included in the scope? Which treatments are considered to be established clinical practice in the NHS for relapsed or refractory Philadelphia chromosome-negative acute lymphoblastic leukaemia?
How should best supportive care be defined?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom erythrocyte encapsulated asparaginase is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider erythrocyte encapsulated asparaginase will fit into the existing NICE pathway, Blood and bone marrow cancers?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which erythrocyte encapsulated asparaginase will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.

Do you consider erythrocyte encapsulated asparaginase to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of erythrocyte encapsulated asparaginase can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the appraisal committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made.

- Would it be appropriate to use the cost comparison methodology for this topic?

- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?

- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?

- Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

1. Cancer Research UK (2015) Acute lymphoblastic leukaemia (ALL) statistics [online; accessed June 2018]

