National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Erythrocyte encapsulated asparaginase for treating acute lymphoblastic leukaemia

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	NCRI-RCP-ACP	Our experts are unaware of any patient in the UK receiving this product. As such it is unclear whether the topic is appropriate for NICE guidance.	Comment noted. NHS England's policy is that cancer drugs expected to receive a marketing authorisation will now be appraised by NICE.
	Orphan Europe	It may be premature in the current process to refer this to NICE for appraisal.	Comment noted. NICE aims to provide guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
	Royal College of	I do not know that this is very appropriate for NICE - to the best of my	Comment noted. NHS

Section	Consultee/ Commentator	Comments [sic]	Action
	Pathologists	knowledge no patient in the UK has ever received this product	England's policy is that cancer drugs expected to receive a marketing authorisation will now be appraised by NICE.
Wording	Orphan Europe	Yes	Comment noted. No action required.
	Leukaemia CARE	As there is currently no NICE guidance for treating ALL, we would suggest that there is an urgent need to provide guidance on the treatment options available to ALL patients. The survival rate of adults diagnosed with ALL is 35% (at five years). As such there is an urgent need for access to alternative treatment options for relapsed patients with ALL.	Comment noted. No action required.
	NCRI-RCP-ACP	Non urgent	Comment noted. NICE aims to provide guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
	Orphan Europe	A marketing authorisation is expected in [redacted]	Comment noted. No action required.
	Royal College of	non urgent	Comment noted. NICE

Section	Consultee/ Commentator	Comments [sic]	Action
	Pathologists		aims to provide guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted.
Additional comments on the draft remit	Orphan Europe	The proposed INN for erythrocyte encapsulated asparaginase is eryaspase and the trade name is Graspa®	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	NCRI-RCP-ACP	The background information mostly refers to de novo ALL whereas the population is those with 'previously treated ALL'	Comment noted. The background section of the scope has been amended to include further information about the population with previously treated ALL.
	Orphan Europe	Asparaginases are used universally in younger patients but toxicity limits their use in older and poor performance status patients and they are mostly excluded from treatment schedules in these patients.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Royal College of Pathologists	the background information mostly refers to de novo ALL whereas the population is those with "previously treated ALL"	Comment noted. The background section of the scope has been amended to include further information about the population with previously treated ALL.
The technology/ intervention	Orphan Europe	Yes	Comment noted. No action required.
	Leukaemia CARE	The technology encapsulates asparaginase into red blood cells which increases the half life of the drug and decreases the dose of enzyme required. This method extends the duration of activity of the therapy. This means that the therapy would not be required as frequently (with patients therefore receiving fewer injections) but remains an effective therapy (compared to 'native' E-coli derived asparaginase).	Comment noted. No action required.
	NCRI-RCP-ACP	Yes	Comment noted. No action required.
	Royal College of Pathologists	yes	Comment noted. No action required.
Population	Leukaemia CARE	It is necessary to identify the appropriateness of erythrocyte encapsulated asparaginase for the different age groups affected by the condition. We would consider these to be 'children', 'adults' and 'less fit adults' (who are likely to be older patients). For example, we would question whether it is an appropriate	Comment noted. During the scoping teleconference it was agreed that the population in the scope

Section	Consultee/ Commentator	Comments [sic]	Action
		therapy option for older or less fit patients.	should be 'People with acute lymphoblastic leukaemia who are intolerant or allergic to asparaginase or have disease that has relapsed on asparaginase treatment.'
	NCRI-RCP-ACP	This is unclear. 'Patients with relapsed or resistant ALL' should be stated if that is what is meant.	Comment noted. During the scoping teleconference it was agreed that the population in the scope should be 'People with acute lymphoblastic leukaemia who are intolerant or allergic to asparaginase or have disease that has relapsed on asparaginase treatment.'
	Orphan Europe	Yes	Comment noted. No action required.
	Royal College of Pathologists	not clear - should be stated 'patients with relapsed or resistant ALL if that is what is meant	Comment noted. During the scoping

Section	Consultee/ Commentator	Comments [sic]	Action
			teleconference it was agreed that the population in the scope should be 'People with acute lymphoblastic leukaemia who are intolerant or allergic to asparaginase or have disease that has relapsed on asparaginase treatment.'
Comparators	Leukaemia CARE	Treatment options currently used as a comparator to the scoped therapy: - Asparaginase derived from E-coli - Erwinia l-asparaginase - Pegasparagase Pegasparagase (in combination with chemotherapy) is currently the most commonly used treatment option for ALL. There are fewer treatment options for patients with hypersensitivity to asparaginase and erythrocyte encapsulated asparaginase has been designed to reduce morbidity due to hypersensitivity reactions.	Comment noted. It has been agreed that the comparators in the scope should be E.coli asparaginase, pegylated asparaginase and Erwinia derived asparaginase.
	NCRI-RCP-ACP	The proper comparators should be other preparations of L-asparaginase namely Pegylated asparginase, E coli asparaginase and Erwinia asparginase. These have not been listed on the scope. These comparators have extensive literatures attached to them and have	Comment noted. It has been agreed that the comparators in the scope should be E.coli asparaginase,

Section	Consultee/ Commentator	Comments [sic]	Action
		been widely studied and administered to hundreds of thousands of patients. The published literature on this agent suggests it has been administered to very few patients with ALL, certainly fewer than 100	pegylated asparaginase and Erwinia derived asparaginase.
	Orphan Europe	There are three available forms of asparaginase enzymes: Native L-asparaginase, Pegylated L-asparaginase (Oncaspar and Erwinia asparaginase (Erwinase) which have heterogeneous marketing authorisations and clinical use throughout the EU. In the UK, all three forms are licensed but the native L-asparaginase is seldom used. Our market research indicates that Oncaspar is used first line and in subsequent lines of therapy unless the patient is allergic or intolerant in which case Erwinase is used. In elderly patients (>55 years) or poor performance status patients, asparaginases may be used in the consolidation blocks of therapy.	Comment noted. It has been agreed that the comparators in the scope should be E.coli asparaginase, pegylated asparaginase and Erwinia derived asparaginase.
	Royal College of Pathologists	should be other sorts of asparaginase	Comment noted. It has been agreed that the comparators in the scope should be E.coli asparaginase, pegylated asparaginase and Erwinia derived asparaginase.
Outcomes	NCRI-RCP-ACP	Cyogenetic response is not used in this disease. Time to and duration of response is not relevant. This should be complete remission, OS and EFS	Comment noted. It was agreed at the scoping teleconference that treatment response rates (including cytogenic responses)

Section	Consultee/ Commentator	Comments [sic]	Action
			should be removed as a comparator in the scope.
	Orphan Europe	Outcome measures for this class of agent as a component of polychemotherapy and endpoints investigated in the eryaspase Phase III study comparing to native L-asparaginase included: 1). the rate of allergic reactions and 2). therapeutic drug monitoring (asparaginase levels) which are a recognised surrogate marker with this class of drug. Health related quality of life measures were not included in the Phase III study.	Comments noted. It was agreed at the scoping teleconference that the outcomes in the scope should include rate of allergic reactions and therapeutic drug monitoring. The outcome 'health-related quality of life is included in all NICE appraisals.
	Royal College of Pathologists	cyogenetic response is not used in this disease time to and duration of response not relevant should be complete remission, OS and EFS	Comment noted. It was agreed at the scoping teleconference that treatment response rates (including cytogenic responses) should be removed as a comparator in the scope.
Economic analysis	Orphan Europe	Marketing authorisation is expected at [redacted]	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Equality and Diversity	Orphan Europe	None known currently.	Comment noted. No action required.
Innovation	Orphan Europe	The technology eliminates allergic reactions to asparaginases and the erythrocyte membrane protects the enzyme from the immune system and "silent inactivation" through neutralisation of the enzyme by antibodies. The long term benefit of a patient never developing allergy to asparaginase has not been assessed in a randomised, controlled manner as yet. Publications, conference presentations. The Phase III study has not been published yet.	Comment noted. No action required.
	NCRI-RCP-ACP	The technology is innovative but the drug encapsidated within the technology is not innovative.	Comment noted. No action required.
	Royal College of Pathologists	The technology is innovative but the drug encapsidated within the technology is not innovative	Comment noted. No action required.
Other considerations	None		
Questions for consultation	NCRI-RCP-ACP	Questions for consultation How many people with ALL would be expected to be treated with erythrocyte encapsulated asparaginase in England? Possibly zero, unless part of a clinical trial. We are unaware of any patient in the UK receiving it so far. Would erythrocyte encapsulated asparaginase be expected to be used in combination with specific chemotherapy drugs or regimens? If so, which	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		chemotherapy combinations should be included in this appraisal? Yes but we have standard regimens for adult and paediatric ALL within the UK which currently included pegylated asparaginase. Without testing this particular asparaginase in combination with those regimens appropriate data are not available. A small dose finding and RCT phase 2 was carried out in patients with relapsed ALL again incorporated into a multiagent chemotherapy schedule (N=24) Reference not reported here Our experts are also aware of one published very small study of this agent in combination chemotherapy in older patients with de novo ALL Reference not reported here 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? Possibly those patients who might have allergic reactions to native asparaginase. However, a pegylated version is already used for this purpose and is standard of care in the UK 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)? It is an innovative product design in that is a product which is manufactured in real time and is given inside red blood cells. Do you consider that the use of erythrocyte encapsulated asparaginase can result in any potential significant and substantial health-related benefits that	

Section	Consultee/ Commentator	Comments [sic]	Action
		are unlikely to be included in the QALY calculation? No Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. There are some limited publications	
	Orphan Europe	Table not reported here. The above represents the expected number of patients in England with the current clinical studies and expected indication and positioning of the product. Other newer agents may be considered at comparators in the future e.g. blinatumomab, inotuzumab ozogamicin Current treatment success is determined by many factors in a complex treatment paradigm. The cure rate in younger patients is high with lower toxicity and the cure rate decreases with age, while toxicity increases. Eryaspase will be used with polychemotherapy which is possibly the most complex in cancer treatment and variable according to guidelines. The remit captures the most commonly used agents. Eryaspase is expected to be more clinically effective in older patients and those suffering allergy or intolerance with no further asparaginase treatment options remaining. The current NICE pathway does not include Acute Lymphocytic Leukaemia. Eryaspase has demonstrated a significant benefit compared to native L-asparaginase in terms of allergic reactions, duration of asparaginase activity and complete responses during induction therapy. This will confer a benefit to patients with relapsed ALL without further treatment options. Current data that are available include previous publications and peer-reviewed conference presentations and posters.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Royal College of Pathologists	How many people with ALL would be expected to be treated with erythrocyte encapsulated asparaginase in England? Possibly zero, unless part of a clinical trial. Its hard to say, in reality but I don't think any patient in the UK has received it so far. Have all relevant comparators for erythrocyte encapsulated asparaginase been included in the scope? How would established clinical management without erythrocyte encapsulated asparaginase be defined? I don't see any comparators properly listed – the proper comparators should be other preparations of L-asparaginase namely Pegylated asparginase, E coli asparaginase and Erwinia asparginase The proper comparators have massive literatures attached to them and have been widely studied and administered to hundred of thousands of patients. The published literature on this agent suggests it has been administered to very few patients with ALL, certainly fewer than 100. Would erythrocyte encapsulated asparaginase be expected to be used in combination with specific chemotherapy drugs or regimens? If so, which chemotherapy combinations should be included in this appraisal? Yes but we have standard regimens for adult and paediatric ALL within the UK which currently included pegylated asparaginase. Without testing this particular asparaginase in combination with those regimens appropriate data aren't available. A small dose finding and RCT phase 2 was carried out in patients with relapsed ALL again incorporated into a multiagent chemotherapy schedule (N=24) References not reported here I am also aware of one published very small study of this agent in	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		combination chemotherapy in older patients with de novo ALL References not reported here 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? Possibly into those patients who might have allergic reactions to native asparaginase. However, a pegylated version is already used for this purpose and is standard of care in the UK Where do you consider erythrocyte encapsulated asparaginase will fit into the existing NICE pathway, Blood and bone marrow cancers? 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)? It is an innovative product design in that is a product which is manufactured in real time and is given inside red blood cells. 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? no Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.	

Section	Consultee/ Commentator	Comments [sic]	Action
		There are some limited publications	
Additional comments on the draft scope	None		

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Medac GmBH
Royal College of Nursing