Summary form

National Institute for Health and Clinical Excellence

Rituximab for first line and relapsed chronic lymphocytic leukemia

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Chronic Lymphocytic Leukemia Support Association	Yes, this is appropriate. Rituximab therapy is well established in most advanced countries.	Comments noted. It was agreed at the scoping workshop that an appraisal of rituximab was appropriate.
	Baxter Healthcare Ltd	Yes, I feel it is appropriate for referral of this to NICE.	Comments noted. It was agreed at the scoping workshop that an appraisal of rituximab was appropriate.
	Roche	It is anticipated that rituximab combination therapy will offer a clinical advantage compared to current treatments for people with chronic lymphocytic leukaemia. Hence it is appropriate for this topic to be referred to NICE. However the differing regulatory approval timescales for the rituximab first line and relapsed licence mean that initially only first line treatment should be considered.	Comments noted. To accommodate differing timelines for first-line and relapsed disease, it was agreed at the scoping workshop that the appraisal would be split into two single technology appraisals (STAs)
	Royal College of Physicians	None	Comments noted. No action required
Wording	Chronic Lymphocytic Leukemia Support Association	Outcomes; it is likely that mortality as a endpoint will not be appropriate since CLL has a long median survival. Delete overall survival. consider; Progression free survival PLUS Complete response/partial response figures, etc.	Comments noted. It was agreed at the scoping workshop that overall survival would be included in the scope as it was measured in the trials of rituximab for CLL.

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	Baxter Healthcare Ltd	The wording is fine but may not provide enough detail. Cost-effectiveness needs is a central issue but this needs to be fully represented. Advice needs to be in line with other government organisations such as the NPSA. Rituximab was identified as an amber risk drug after implementation of NPSA alert 20 'Promoting Safer Use of Injectable Medicines'. Incidence of Chronic Lymphocytic Leukaemia is 2750 per annum and relapsing CLL will provide a large quantity on top of this meaning a possibility of several thousand extra doses being needed per year. At this point in time, some hospital trusts still prepare Rituximab at ward level or in non aseptic areas. The cost-effectiveness evaluation should involve the impact that a successful result this NICE review could have. By impact, we mean Pharmacy based compounding facilities which is where rituximab doses should ideally be prepared. Many NHS compounding centres have little spare capacity. Any recommendation that this review makes should bear in mind the consequence of the extra cost involved in increasing the workload of aseptic units or the consequence of patient safety should the practicalities of administration be overlooked.	Comments noted. The scope does not provide an exhaustive overview of the methods for economic analysis or the impact of recommendations on capacity. No changes made to the scope.
	Roche	It is appropriate in the first instance "to appraise the clinical and cost effectiveness of rituximab within its licensed indication for the first line treatment of chronic lymphocytic leukaemia".	Comments noted. It was agreed at the scoping workshop that the appraisal would be split into two single technology appraisals (STAs)
	Royal College of Physicians	None	Comments noted. No action required
Timing Issues	Chronic Lymphocytic Leukemia Support Association	It is appropriate that thiis proposed appraisal of rituximab should be carried out as soon as is feasible.	Comment noted. Following the final referral from the Department of Health, the appraisal will be planned into the technology appraisal schedule to allow as timely as possible guidance to the NHS
	Baxter Healthcare Ltd	No comment	Comments noted. No action required

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	Roche	No exact timings have been made known to Roche. Any timings should take into account the regulatory approval timelines. Roche anticipate being in a position to submit to NICE for the first line indication by November 2008. This is consistent with NICE's intention to review new technologies as close to the time of licence as possible. Given the anticipated timings for regulatory approval for the relapsed indication it is less urgent to consider this indication as part of this appraisal.	Comment noted. Following the final referral from the Department of Health, the appraisal will be planned into the technology appraisal schedule to allow as timely as possible guidance to the NHS
	Royal College of Physicians	None	Comments noted. No action required
Additional comments on the draft remit	Chronic Lymphocytic Leukemia Support Association	consider adding low dose rituximab to the schedule in view of the so-called shaving reaction? see J. Immunol, 2006, Feb, 15; 176 4,: 2006-9 The shaving readtion: rituximab/ C 20 complexes are removd from mantle cell lymphoma and chronic lymphocytic leukaemai cells by THP-1 monocytes. Beum P.V, et al.	Comments noted. NICE can only issue recommendations in accordance with the marketing authorisation. At the scoping workshop the manufacturer confirmed that the clinical trials were completed using a high dose of rituximab. No changes made to the scope.
	Baxter Healthcare Ltd	None	Comments noted. No action required
	Roche	None	Comments noted. No action required
	Royal College of Physicians	None	Comments noted. No action required

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Chronic Lymphocytic Leukemia Support Association	'Genetic subtypes'; this is an oversimplification, although there are 2 extreme types, there is in fact a whole spectrum of adverse factors some have greater wrighting than others. I am not aware that cyclophosphamide +/- corticosteroids is or ever was a common first line treatment. Chlorambucil is; is this statement a typographical error? .	Comments noted. The scope has been amended.
	Baxter Healthcare Ltd	No comment	Comments noted. No action required
	Roche	The background information appears somewhat inaccurate and incomplete. In general, failure of the blood to clot is not typically seen in CLL. The notion that there are two genetic subtypes of CLL is not true - it is a very complex and genetically heterogeneous cancer with numerous factors determining the disease course. Chlorambucil would have been a much more appropriate example to use as a commonly used alkylating agent.	Comments noted. The scope has been amended.
	Royal College of Physicians	None	Comments noted. No action required
The technology/ intervention	Chronic Lymphocytic Leukemia Support Association	Rituximab can be adminstered by subcutaneous injection at low dosages. this is probably a rare route of administration.	Comments noted. NICE can only issue recommendations in accordance with the marketing authorisation. At the scoping workshop the manufacturer confirmed that the clinical trials were completed using IV administration of rituximab. No changes made to the scope.
	Baxter Healthcare Ltd	No comment	Comments noted. No action required

Section	Consultees	Comments	Action
	Roche	Rituximab combination treatments have been widely investigated in CLL clinical trials: examples include PCR (pentostatin, cyclophosphamide and rituximab); rituximab plus chlorambucil (trial still recruiting) and also other fludarabine combinations (eg FCM-R: fludarabine, cyclophosphamide, mitoxantrone and rituximab; and CFAR: cyclophosphamide, fludarabine, alemtuzumab and rituximab)	Comments noted. No action required
	Royal College of Physicians	None	Comments noted. No action required
Population	Chronic Lymphocytic Leukemia Support Association	patients should be tested for working p 53 pathway before any treatment; patients without a working p53 pathway may require other treatment which is thought more effective.	Comments noted. It was agreed at the scoping workshop that the p53 pathway should be considered as part of this appraisal.
	Baxter Healthcare Ltd	No comment	Comments noted. No action required
	Roche	This appraisal should only include first line CLL patients.	Comments noted. To accommodate differing timelines for first-line and relapsed disease, it was agreed at the scoping workshop that the appraisal would be split into two single technology appraisals (STAs)
	Royal College of Physicians	None	Comments noted. No action required

Section	Consultees	Comments	Action
Comparators	Chronic Lymphocytic Leukemia Support Association	Choice of chlorambucil or fludarabine cyclophosphamide combination therapy for first line treatment; normally this depends on the co-morbidities of the patient. Fludarabine is most commonly used in combination with cyclophosphamide which increases the efficacy and helps protect against AIHA; see; Blood, 2007, Nov 30; The prognostic significance of a positive direct antiglobulin test in chronic lymphocytic leukaemia- a beneficial effect of the combination of fludarabine and cyclophosphamide on the incidence of haemolytic anaemia; Dearden, C, et al. Relapsed patients; again fludarabine monotherapy is unlikely to be used; CHOP and stem cell transplant are more likely to be used on multiply relapsed patients. .	Comments noted. It was agreed at the scoping workshop that fludarabine monotherapy was not an appropriate comparator for first line or subsequent treatment of CLL.
	Baxter Healthcare Ltd	No comment	Comments noted. No action required
	Roche	For a combination therapy such as rituximab, fludarabine and cyclophosphamide the most relevant comparator is fludarabine in combination with cyclophosphamide. Market research data shows that this treatment is used to treat around 40% of CLL patients in the UK. These patients are likely to represent those who are suitable for combination therapy, whereas around 47% receive chlorambucil monotherapy and these patients would be less likely to be suitable for combination therapy (although a certain proportion of these patients will be eligible for rituximab combination therapy) (Genactis Market Research, Q4 2007). The relapsed indication should not be included in this appraisal and as such cyclophosphamide monotherapy, doxorubicin, vincristine, prednisone (CHOP) combination therapy, and stem cell transplant are not relevant comparators.	Comments noted. To accommodate differing timelines for first-line and relapsed disease, it was agreed at the scoping workshop that the appraisal would be split into two single technology appraisals (STAs) Comment noted. It was agreed at the scoping workshop that CHOP and stem cell transplants were appropriate comparators for the appraisal of rituximab for the treatment of relapsed CLL, as they were included in clinical guidelines as possible treatment options.

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	Royal College of Physicians	The comparators should also include the combination of fludarabine with cyclophosphamide	Comments noted. The comparators in the scope include fludarabine combination therapies.
Outcomes	Chronic Lymphocytic Leukemia Support Association	Overall survival in CLL with a mean survival period of 8-16 years depending on modern markers is not an appropriate measure of success. The other 4 are more appropriate.	Comments noted. It was agreed at the scoping workshop that overall survival was an appropriate outcome as it was measured in the trials for rituximab for CLL
	Baxter Healthcare Ltd	No comment	Comments noted. No action required
	Roche	No comments	Comments noted. No action required
	Royal College of Physicians	None	Comments noted. No action required
Economic analysis	Chronic Lymphocytic Leukemia Support Association	This is difficult, since effective treatment of younger patients is likely to have a skewed effect on the economics of the situation. Many of the younger patients would appreciate an opportunity to continue their economic and social contributions to society to the overall gain of all. Patients with young children particularly.	Comments noted. No changes to the scope required.
	Baxter Healthcare Ltd	No further comment to above points	Comments noted. No action required
	Roche	No comments	Comments noted. No action required
	Royal College of Physicians	None	Comments noted. No action required

Section	Consultees	Comments	Action
Other considerations	Chronic Lymphocytic Leukemia Support Association	Effectiveness of low dose rituximab. see above. Cohort selection by diagnostic markers (excluding p53)	Comments noted. NICE can only issue recommendations in accordance with the marketing authorisation. At the scoping workshop the manufacturer confirmed that the clinical trials were completed using a high dose of rituximab. No changes made to the scope. It was agreed at the scoping workshop that the p53 pathway should be considered as part of this appraisal.
	Baxter Healthcare Ltd	No comment	Comments noted. No action required
	Roche	No comments	Comments noted. No action required
	Royal College of Physicians	None	Comments noted. No action required
Questions for consultation	Chronic Lymphocytic Leukemia Support Association	None	Comments noted. No action required
	Baxter Healthcare Ltd	No comment	Comments noted. No action required

Section	Consultees	Comments	Action
	Roche	Roche suggests that the most relevant comparator for first line therapy is fludarabine in combination with cyclophosphamide. Roche suggests that at this stage only first line treatment should be considered as a single technology appraisal ***CIC removed.*** CHOP combination therapy and stem cell transplant are not considered relevant comparators in the assessment of first-line treatment. It is unclear whether the clinical efficacy of rituximab will differ markedly between patient sub-groups as data from the pivotal Phase III trial which will be used to support the licence has not yet been published	Comments noted. To accommodate differing timelines for first-line treatment and relapsed disease, it was agreed at the scoping workshop that the appraisal would be split into two single technology appraisals (STAs) Comment noted. It was agreed at the scoping workshop that CHOP and stem cell transplants were appropriate comparators for the appraisal of rituximab for the treatment of relapsed CLL, as they were included in clinical guidelines as possible treatment options.
	Royal College of Physicians	None	Comments noted. No action required
Additional comments on the draft scope.	Chronic Lymphocytic Leukemia Support Association	A sound start.	Comments noted. No action required
	Baxter Healthcare Ltd	None	Comments noted. No action required
	Roche	None	Comments noted. No action required
	Royal College of Physicians	None	Comments noted. No action required

Comment 4: Regulatory issues

Section	Consultees	Comments	Action
Remit			
	Roche	The wording is acceptable, but given the differing regulatory timelines for the first line and relapsed indications Roche suggests that the relapsed indication be removed from the remit. ***CIC removed***	Comments noted. To accommodate differing timelines for first-line and relapsed disease, it was agreed at the scoping workshop that the appraisal would be split into two single technology appraisals (STAs)
Current or proposed marketing authorisation	Roche	MabThera is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy. MabThera maintenance therapy is indicated for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without MabThera. MabThera monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy. MabThera is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's Lymphoma in combination with CHOP chemotherapy. MabThera in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs including one or more tumour necrosis factor (TNF) inhibitor therapies.	Comments noted. No action required
		CIC removed	Comments noted. No action required

Section	Consultees	Comments	Action
		CIC removed	Comments noted. No action required
		CIC removed	Comments noted. No action required
		CIC removed	Comments noted. No action required
		CIC removed	Comments noted. No action required

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

- Bayer Schering Pharma
- GlaxoSmithKline
- Macmillan Cancer Support
- Marie Curie Cancer Care
- NHS Quality Improvement Scotland
- Royal College of Nursing
- Royal Pharmaceutical Society
- Sanofi-aventis