National Institute for Health and Clinical Excellence

Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Roche Products	We feel that it is appropriate for this topic to be referred to NICE for appraisal.	Comment noted. No changes to the remit requested.
	Royal College of Pathologists	Yes this is an appropriate topic. Follicular lymphoma is the second commonest Non-Hodgkin lymphoma representing approximately 22 % cases. Rituximab has made a significant impact on the treatment of this disease.	Comment noted. No changes to the remit requested.
Wording	Roche Products	PROPOSED REVISED REMIT: To appraise the clinical and cost-effectiveness of rituximab within its proposed licensed indication for maintenance treatment following response to first-line chemotherapy with or without rituximab for follicular non-Hodgkin lymphoma. Please note, this wording combines both the anticipated first-line and existing relapsed-refractory rituximab maintenance licences. Please also note, (with specific reference to the draft remit) that rituximab is currently not yet licensed in previously untreated follicular lymphoma patients as maintenance therapy.	Comment noted. Discussed at scoping workshop. Rituximab does not yet have a marketing authorisation for the indication. The remit will not specify that first-line chemotherapy could be with or without rituximab.
	Royal College of Pathologists	Yes	Comment noted. No changes to the remit requested.
Timing Issues	Royal College of Pathologists	Appropriate timing with a planned scoping workshop on Friday 16th January 2009	Comment noted. No changes to the remit requested.

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	NCRI/RCP/RCR/ACP/JCCO	The general feeling is that this appraisal is premature: the definitive study to determine the role of maintenance rituximab in first remission has not yet reported, and there are only two other studies which do not provide relevant evidence, since neither used rituximab as part of initial therapy, as is recommended by NICE already.	Comment noted. Discussed at scoping workshop. Consultees thought that outcomes from the key registration trial are likely to be included in the appraisal, and that the timing is appropriate to ensure timely guidance.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Roche Products	This section appears accurate and sufficiently complete. Our only comment is that the final sentence "Observation or 'watchful waiting' is currently the only option for maintenance after first-line induction therapy" does not read well. Can we suggest as a clearer more accurate alternative "Observation or 'watchful waiting' is the current standard treatment option for stage III-IV follicular lymphoma patients who achieve remission with first line induction therapy"?	Comment noted. This has been amended in the scope.
	Royal College of Pathologists	The background information is accurate but there is limited information on the types of treatment given beyond first relapse. Follicular lymphoma is readily treatable but is characterised by a recurring and remitting course over several years with each successive response becoming more difficult to achieve and of shorter duration. In considering the cost benefit of rituximab maintenance it is important to also factor in the cost saving of avoiding other salvage treatments and associated costs such as repeat biopsies and hospital admissions etc.	Comment noted. The scope is intended to only provide a brief background to the condition. Complete details of the condition will be incorporated within the framework of an appraisal.

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The technology/ intervention	Roche Products	Suggested amendments: "Rituximab does not have a UK marketing authorisation for maintenance treatment following first-line chemotherapy for follicular lymphoma. It is currently being studied as maintenance therapy following response to first-line chemotherapy plus rituximab in comparison to observation in patients with stage III-IV follicular lymphoma" "Rituximab has a marketing authorisation for maintenance therapy in patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without rituximab, and for the first line treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy. Rituximab is also licensed for the treatment of patients with CD20-positive diffuse large B-cell non-Hodgkin lymphoma in combination with CHOP chemotherapy, and as monotherapy for patients with stage III-IV follicular lymphoma patients who are chemoresistant or are in their second or subsequent relapse after chemotherapy. Licences are also anticipated for rituximab in previously untreated and relapsed/refractory CLL patients in Q1 and Q4 2009 respectively."	Comment noted. Discussed at the scoping workshop. It was highlighted that the population in the trial protocol is “advanced” NHL. Therefore, this has not been changed in the scope. Other suggested changes have been amended in the scope. Comment noted. The scope has been amended accordingly.
	Royal College of Pathologists	Yes	Comment noted. No changes to the scope requested.
Population	Roche Products	This is broadly correct. Specifically this should read "Adults with symptomatic stage III-IV follicular lymphoma who have responded to first line induction chemotherapy with or without rituximab".	Comment noted. Discussed at scoping workshop. As the inclusion criteria for the registration trial includes people with ‘advanced stage NHL’, the population will remain unchanged.
	Royal College of Pathologists	Yes the population is defined appropriately	Comment noted.

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Comparators	Roche Products	This is the correct standard comparator. Standard management for patients obtaining a remission after initial chemotherapy in this setting would be "watch and wait" in remission until progression, at which point further treatment would be initiated.	Comment noted. Discussed at scoping workshop. It was agreed that ibritumomab tiuxetan is an appropriate comparator. Scope has been amended to reflect this.
	Royal College of Pathologists	Induction with combination chemotherapy such as R-CVP (rituximab, cyclophosphamide, vincristine and prednisolone) is a standard treatment within the NHS. This scope will be considering rituximab maintenance versus observation or "watchful waiting" following standard induction. Maintenance or consolidation with zevalin (Yttrium-90-ibritumomab tiuxetan) has not been discussed. Although this drug is currently licensed for relapsed or refractory follicular lymphoma, the FDA has granted a priority review to extend this license to consolidation therapy after first remission. A phase III trial of 414 patients, who achieved either a complete (CR) or partial response (PR) after first line induction treatment , compared zevalin treatment to no further treatment has recently been published (JCO Vol26, no 32 (November 10), 2008. Zevalin prolonged progression free survival by 2 years (36.5 versus 13.4 months in control arm, p<0.0001). After zevalin, 77 % patients with a PR were converted to CR/CRu, resulting in a final CR rate of 87%. In many lymphomas achieving a CR correlates with an improved overall survival. For follicular lymphoma, prolonged follow up will be required to detect overall survival differences. Once licensed for this indication in the near future, zevalin may be considered as alternative care.	Comment noted. Discussed at scoping workshop. It was agreed that ibritumomab tiuxetan is an appropriate comparator. Scope has been amended to reflect this. It was noted that current marketing authorisation states that ibritumomab tiuxetan is indicated as consolidation therapy after remission induction in previously untreated patients with follicular lymphoma. The benefit of ibritumomab tiuxetan following rituximab in combination with chemotherapy has not been established.
Outcomes	Roche Products	These outcomes are entirely appropriate. • progression free survival • overall survival • response rates • adverse effects of treatment • health-related quality of life.	Comment noted. No changes to the scope required.

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	Royal College of Pathologists	The outcome measures are appropriate particularly progression free survival, response rates, adverse effects of treatment and quality of life measures. Prolonged follow up is required to detect differences in overall survival in low grade lymphoma.	Comment noted. No changes to the scope required.
Economic analysis	Roche Products	No comments.	Comment noted.
	Royal College of Pathologists	Appropriate	Comment noted. No changes to the scope requested.
Equality and Diversity	Roche Products	No comments.	Comment noted.
	NCRI/RCP/RCR /ACP/JCCO	No	Comment noted.
	Royal College of Pathologists	No issues apparent at present	Comment noted.
Other considerations	Roche Products	Please note, the subgroup noted will not exist ie - all patients in the registration trial will have received rituximab in combination with chemotherapy first-line.	Comment noted. It was suggested during the scoping workshop that there is evidence available from trials where participants had not received rituximab in combination with first-line chemotherapy. Therefore, the subgroup in the scope has not been changed. During the scoping workshop it was agreed that subgroup by type of first-line immunochemotherapy (i.e. R-CHOP vs R-CVP vs R-FCM) and type of response induced by first-line therapy (i.e. complete vs partial) would be added to the scope.

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	Royal College of Pathologists	No comment	Comment noted. No changes to the scope requested.
Questions for consultation	Roche Products	We do not anticipate any subgroups of patients in whom rituximab is expected to be more clinically or cost-effective. We feel that appraisal of this technology through the NICE STA process is entirely appropriate. (Please note, all other questions have already been addressed in the main body of this document).	Comment noted.

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	NCRI/RCP/RCR /ACP/JCCO	Should the population be defined in more detail (for example stage III or IV follicular lymphoma)? No, “patients with follicular lymphoma requiring systemic therapy, to which they have responded” is sufficient definition. Some patients may receive only rituxmab without chemotherapy to achieve remission. Have any appropriate comparators for the maintenance treatment of follicular lymphoma following first line induction therapy been excluded from the scope? Recent data suggesting that 90Y-Ibritumomab tiuxetan (Zevalin) can improve progression-free survival in first remission (the ‘FIT’ trial) suggest that Zevalin may be a legitimate comparator: Morschhauser F et al. Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. . J Clin Oncol. 2008 Nov 10;26(32):5156-64. Are the subgroups suggested in ‘other considerations appropriate? Are there any other subgroups of patients in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? Yes. The only reliable evidence concerning the role of rituximab maintenance in first remission at present comes from studies in which initial treatment did not include rituximab: - Hochster, et al. (2004) Results of E1496: a phase III trial of CVP with or without maintenance rituximab in advanced indolent lymphoma (NHL). J Clin Oncol 22 , s6502; - Ladetto, M et al. (2007) Prospective, multicenter, randomized GITMO-IIL trial comparing intensive (R-HDS) to conventional chemoimmunotherapy (CHOP-R) in high-risk follicular lymphoma (FL) at diagnosis. J Clin Oncol 25 , s 8006. The definitive trial to determine the place of maintenance rituximab after initial therapy comprising chemotherapy plus rituximab (‘PRIMA”) has not yet been reported, which may make this appraisal premature.	Comment noted. Discussed at the scoping workshop. Comment noted. It was agreed at the scoping workshop that ibritumomab tiuxetan is an appropriate comparator. Comment noted. It was suggested during the scoping workshop that there is evidence available from trials where participants had not received rituximab in combination with first-line chemotherapy. Therefore, the subgroup in the scope has not been changed. During the scoping workshop it was agreed that subgroup by type of first-line immunochemotherapy (i.e. R-CHOP vs R-CVP vs R-FCM) and type of response induced by first-line therapy (i.e. complete vs partial) would be added to the scope.

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	Royal College of Pathologists	No comment	Comment noted.

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

NHS Quality Improvement Scotland

National Public Health Service for Wales

Research Institute for the Care of Older People

Royal Pharmaceutical Society

Welsh Assembly Government