NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Rituximab for the treatment of recurrent or refractory stage III or IV follicular non-Hodgkin's lymphoma (Review of TA 37)

Response to consultee and commentator comments on the provisional matrix of consultees and commentators and provisional scope

Section	Consultee	Comment	Response
Background	Roche	It is stated that the percentage of follicular lymphomas that are follicular is in the range 22%-40% depending upon the system used to classify them. This is true. However, the REAL classification has been used in the UK and internationally for some years now. Under this system follicular lymphoma represents 22% of NHL (Non-Hodgkin's Lymphoma Classification Project, 1997). As such 22% is the only figure relevant to current UK practice.	Scope amended.
	Roche	The statement that current therapeutic interventions have not been shown to improve overall survival in follicular lymphoma is no longer correct. In recent years, it has been demonstrated that the addition of rituximab to first-line treatment of follicular lymphoma significantly improves overall survival. This has been demonstrated in both individual clinical trials (Herold et al. 2005; Hiddemann et al. 2005; Marcus et al. 2006) and meta-analysis (Schultz et al 2005)	Scope amended accordingly.
	Lymphoma Association	If the appraisal must consider these two applications simultaneously, then further background explanation is required in an attempt to make clear a notoriously complex and potentially confusing therapeutic situation.	Comment noted and scope amended. The background section of the scope aims to give a clear definition of the

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		The use of single agent rituximab in relapsed or refractory disease is quite distinct from its use as a maintenance therapy. Although still relevant for some patients, the original guidance on this application predates an understanding of the other potential applications of the technology, new applications that have had an impact on the treatment pathways for many people with the disease. An explanation of the recent history of follicular lymphoma treatments, and the addition of rituximab to first line chemotherapy treatments, might attempt to clarify the terms of the discussion.	spectrum of disease relevant to the new technology. The focus is on recurrent or refractory stage III or IV disease since this the indication under the remit.
	Lymphoma Association	The background information also fails to convey the significance of the age of this patient population. Follicular lymphoma is very largely a disease of old age, meaning that patients have far more potential problems with co-morbidity, and a reduced tolerance of chemotherapy. It is essential that the Appraisals Committee has an understanding of this fact. It is important that NICE recognises the importance of enabling a clinician to have a number of treatment options - to be chosen according to individual needs - rather than a pressing need to standardise treatment pathways.	Comment noted. The median age of incidence and increasing incidence with age are included in the background section. No change to scope.
	WAG	A fair summary.	Noted.
The Technology / Intervention	Roche	Yes, except that it should perhaps be made explicit that rituximab has an additional licensed indication to those listed: use in combination with CVP chemotherapy for the first-line treatment of Stage III/IV follicular lymphoma.	The indication for first-line use is included in the background section of the scope.

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	Lymphoma Association	Once again, this description falls far short of explaining the application of the technology. The individual applications, in particular the maintenance application, need to be more fully explained.	The technology section reflects the therapeutic indications that fall within the remit. These are stated as set out in section 4.1 of the Summary of Product Characteristics. No change to scope.
	WAG	Yes	Comment noted.
The Population	Roche	The description of the "induction of remission" population fails to identify a significant and recent group covered by the current Marketing Authorisation - those patients requiring reinduction with cytotoxic chemotherapy (when rituximab may be given in combination with CHOP chemotherapy)	No change to scope. The scope reflects the population described in therapeutic indications in the marketing authorisation.
	Roche	The scope correctly reports the licensed indication for rituximab monotherapy used as a re-induction treatment. However, it should be noted that in the light of the original guidance given in TA37 and the acceptance that combination treatment with cytotoxic drugs and rituximab is the optimum approach to remission induction, rituximab monotherapy for remission induction is usually reserved for patients considered unsuitable for further chemotherapy (by virtue of their having chemotherapy resistant disease or being intolerant of cytotoxic drugs) Therefore, when considering induction with rituximab monotherapy patients unsuitable for further cytotoxic chemotherapy should be considered separately.	See 'Other considerations' section. Where evidence allows, subgroups of patients will be considered, and this is likely to include consideration of comparators particularly relevant to such subgroups.

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	Roche	Roche suggests that as no new data has emerged for the monotherapy license since publication of TA37, that this particular element of the relapsed indication is not re-evaluated. Instead the evaluation of the new elements of the relapsed indication (2^{nd} line induction and maintenance would be more appropriate as the focus of this STA).	This is a review of NICE guidance TA 37 and this includes all licensed indications within the remit.
	WAG	It is probable that bulky, progressive stage 2 disease should be considered as well as stages 3 & 4.	The remit specifies stage III and IV disease.
Comparators	Roche	The proposed list of comparators can be shortened and, additionally, different comparators are relevant to each of the sub-populations included in this review.(market research data were provided)	The order of the comparators in the table has been amended. It is understood that CVP, chlorambucil and fludarabine are used in clinical practice in the NHS in England and Wales in this patient group.
	Lymphoma Association	If the appraisal is to consider the two applications simultaneously, the comparators need to be listed separately for each application. Single agent rituximab in chemoresistant disease or second or subsequent relapse: There are few comparators for someone with chemoresistant disease, as by definition they are no longer responding to chemotherapy. Comparators would include ibitrumomab tiuxetan (radioimmunotherapy) or best supportive care. Some patients might have treatment with another type of chemotherapy depending on treatment history, or with a fludarbine based regimen if they had only had alkylating agents or anthracyclines previously.	Noted. Following consultation radioimmunotherapy has been removed from the list of comparators.

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		Radiotherapy to affected nodes also has a potential role.	
	Lymphoma Association	People in second or subsequent relapse will be offered treatment on the basis of previous treatments, degree of response to those treatments, and duration of response. Adults with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without rituximab: The only other treatment given after induction with the aim of prolonging remission is autologous stem cell transplant and high dose chemotherapy. This is not suitable for many patients due to age and co-morbidity. Interferon has been used, and is used in countries such as France, but this is less common practice in the UK. The other comparators listed are used for patients with relapsed or refractory disease, depending on individual history and circumstance - they would be given with the intention of inducing remission but without a maintenance component.	Noted.
	WAG	These are fair comparators. Recently closed UK trial compared CMD vs FMD - the results could have a bearing on the "best alternative care". Otherwise choice is goverened by age/clinical state and rate of disease progression - young/fast =CHOP, frail/slow = Chlorambucil.	Noted.
Outcomes	Roche	With [redacted]% of patients receiving CHOP as induction in first or second relapse it is the key comparator for R-CHOP induction therapy. After CHOP, fludarabine alone or in combination with rituximab is the next most widely used regimen second- or third-line. However, fludarabine based regimens are not	Comments noted. No change to scope.

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		appropriate comparators for R-CHOP - clinicians who choose to use fludarabine at a given stage have already made a decision not to use CHOP, but may still choose to use rituximab. Thus the appropriate comparator for a fludarabine-based regimen is the same regimen plus rituximab. Such a combination is not included in the current rituximab Marketing Authorisation and so cannot be the subject of NICE appraisal.	
	Roche	For rituximab maintenance administered after induction of remission using chemotherapy (+/- rituximab) the only appropriate comparator is no treatment. Patients in remission not receiving rituximab would not receive any maintenance therapy and, in addition, they are in remission and so Best Supportive Care is an inappropriate description of their care suggesting, as it does, treatment to relieve the symptoms of active disease.	Comment noted. No change to scope.
	Roche	For chemotherapy refractory/intolerant patients receiving rituximab monotherapy for remission induction, the most relevant comparator to UK practice is Best Supportive Care. Further chemotherapy is clearly not an option. Radioimmunotherapy with ibritumomab is, theoretically, a comparator for rituximab in this patient group. However, this treatment can only be given in a few specialist centres and Roche market research suggests that ibritumomab represents less than [redacted]% of all treatment courses given for relapsed follicular lymphoma in the UK. Additionally, the Marketing Authorisation resitricts the use of ibritumomab to rituximab relapsed and refractory patients and so it is usually reserved for patients in whom rituximab is no longer considered a reasonable treatment option. Overall,	Comments noted. Following consultation ibritumomab has been removed from the list of comparators.

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		ibritumomab cannot therefore be considered a relevant comparator for rituximab in this appraisal.	
	Lymphoma Association	Adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy. Outcome measures should be confined to quality and duration of response, and quality of life. Overall survival is not relevant in this application, as the objective in this setting is to achieve as good a remission as possible for as long as possible.	Comments noted. Overall survival as an outcome of interest is part of standard methodology in the appraisal of health technologies.
	Lymphoma Association	Adults with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without rituximab: Outcomes should include those listed. There is evidence that overall survival is influenced when the technology is used in that context.	Noted.
	WAG	Diseases with a long natural history like FCL are difficult to assess. PFS/TTF measures will give an answer reasonably quickly but OS will take decades and be blurred by co-morbidities. The other measures are standard research tools and should provide comparative data.	Noted
Economic Analysis	Roche	The current license for rituximab permits its use as an induction agent in the second line setting and also as a maintenance therapy following second line induction therapy. It is therefore possible to perform 2 separate economic analyses depending upon the assumption of the starting timepoint of treatment. Firstly, one may evaluate rituximab plus CHOP as an induction therapy followed by	Comments noted. The technology will be appraised within the remit and within the boundaries of the marketing authorisation.

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		rituximab as a maintenance therapy compared to CHOP induction therapy with no maintenance therapy. Secondly one may just compare maintenance threapy compared to no maintenance for those patients who have responded to second-line induction therapy. As the current license permits both scenarios, Roche will estimate the ICER for rituximab in both scenarios.	
	Roche	As no new data has arisen in the monotherapy setting for last line use - no economic model is planned on being included within our submission.	This appraisal is a review NICE guidance TA 37 and this includes all licensed indications within the remit.
	Roche	As stated above in the comparators section, there is evidence to suggest that CHOP is highly representative of standard of care in second line induction therapy for follicular lymphoma treatment. Consequently this will be used as the economic comparator for 2nd line induction use of rituximab as it also has the added benefit of being the comparator in the pivotal phase III study. For the maintenance use of rituximab, a fair assumption of standard of care is observation or best suportive care only and will represent the comparator in this scenario.	The appraisal will need to consider all appropriate comparators. The technology is to be appraised in accordance with its marketing authorisation.
	Lymphoma Association	Again, the economic analysis will need to be separated for each application.	Noted.
Other Considerations	Lymphoma Association	In the consideration of rituximab as maintenance therapy, subgroups of patients should be identified on the basis of previous treatment.	Noted. See subgroups.
	WAG	The inclusion of the question of Rituximab maintenance is welcome - there is a growing body of evidence for its use.	Noted.

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Questions for consultation	Roche	In the draft scope, the question is raised on the current place of rituximab in chemotherapy. Preliminary results from Roche's latest cycle of market research suggests that chemotherapy plus rituximab as induction therapy is used widely at all treatment lines ……. Monotherapy is hardly used at first-line.. but rises steadily with treatment line,. In accordance with existing NICE guidance, rituximab monotherapy is reserved for patients who have reached a point where they will not tolerate further chemotherapy or have disease that is considered chemotherapy refractory. Rituximab maintenance is currently little used in England and Wales.	Noted.
	Lymphoma Association	Rituximab is being used in combination with chemotherapy as initial therapy for eligible patients. Its use is under continued investigation, including its use as a single agent in remission induction, its use as a single agent in previously untreated asymptomatic patients, and its use in conjunction with various combination regimens. Its use as a single agent for relapsed or chemoresistant follicular lymphoma is still relevant, particularly for the frail elderly who are unable to tolerate the toxicities of chemotherapy. Re treatment pathway: it is difficult to generalise because of the diversity of treatment options and the considerations demanded for the individual. Since last year, following the publication of NICE's guidance, R-CVP is a fairly standard first line therapy for eligible patients. Beyond first line, the situation is likely to be too variable to make a reliable generalisation.	This appraisal is a review NICE guidance TA 37 and this includes all licensed indications within the remit.

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	WAG	In Wales Rituximab is usually used in combination for induction thereapy and as monotherapy for maintenance - if the latter is ever given. Prior to its closure some hospitals enetered patients into the CMD/FMD trial and some frail, elderly patients will receive chlorambucil with or without prednisolone.	Noted.
Additional comments on draft scope	Lymphoma Association	The Lymphoma Association is anxious that the work of NICE supports and promotes optimum treatment for those with lymphoma. To this end, we support the Institutes proposal to appraise two lymphoma applications simultaneously, as this will limit the delay that would result from separate appraisals. However we would like to stress that the different applications of rituximab each deserve careful consideration, and that the differing clinical situations should be acknowledged. The Lymphoma Association would like to stress the complexity of this disease and the need for careful explanation of the principles of management, the history of developments in treatment, and the clinical diversity of the illness. We would also like to stress the importance of individual patient and clinician choice and that the options for management need to accommodate a wide array of clinical situations. This is of particular pertinence in follicular lymphoma because it is a disease largely of old age, and older people are faced with far more barriers to potential therapies. The question of choice is further complicated by differing clinical opinions on the use of the various treatment options.	Comments noted. This appraisal is a review NICE guidance TA 37 and this includes all licensed indications within the remit.

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		With reference to standard comparators, it may be difficult to find information that makes the specific comparison in question. Furthermore, there is likely to be little new information on the use of single agent rituximab in second or subsequent relapse or chemoresistant disease. This is partly because there are often no other treatment options other than supportive care, and because the introduction of rituximab to chemotherapy earlier in the pathway has changed the experience of potential cohorts of patients.	
	WAG	The question of relapse is complicated. Early relapse (<6/12) would suggest the disease was partially resistant and may even be transforming to a high-grade NHL. Such cases would carry a poor prognosis and should be analysed separately from those wth late relapse. There is a need for data to show whether Rituximab continues to be as efficacious in patients relapsing after Rituximab-containing induction.	See 'Other considerations' section; where evidence allows, subgroups of patients will be considered, and this is likely to include consideration of comparators particularly relevant to such subgroups. Indolent lymphomas that transform to more aggressive types are not within the remit.
Comments on provisional matrix of commentators and consultees	Roche	Roche would like to request that an ERG group other than Liverpool is appointed to critique our submission for this appraisal. This request is being made in the light of our feedback provided to NICE in relation to our three previous STA submissions involving Liverpool. Roche does not believe that either a fair and balanced critique of its submission is likely to be produced by Liverpool for this appraisal which will be fit-for-purpose to appropriately support the deliberations of the Appraisal Committee.	No change to matrix. Evidence Review Groups are allocated by the NCCHTA.
	Roche	The list of comparator manufacturers could be simplified by	Following consultation

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		removing generic manufacturers of cytotoxics - rituximab is an adjunct to chemotherapy and usage of their product will generally be unaffected by guidance on rituximab.	ibritumomab has been removed from the list of comparators.
NO COMMENTS	RCN		
	SCHERING		
	PFIZER		
	NHSQIS		
	MARIE CURIE CANCER CARE		
	MCMILLAN CANCER SUPPORT		
	DOH		
	AAH PHARMACEUTICALS LIMITED	Do not wish to be included in the consultation list for any HTA.	