rituximab, 100mg and 500mg concentrate for solution for infusion (MabThera®) No. (540/09)
Roche

08 May 2009

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

rituximab (MabThera®) is accepted for restricted use within NHS Scotland for first-line treatment of patients with chronic lymphocytic leukaemia (CLL) in combination with fludarabine and cyclophosphamide.

Rituximab in combination with fludarabine and cyclophosphamide resulted in significantly longer progression free survival than fludarabine and cyclophosphamide alone. The patient population in the pivotal clinical study had an Eastern Cooperative Oncology Group Performance Status of 0 or 1 and was a younger population than that generally seen in practice. Evidence in patients over 70 years of age is limited.

Rituximab is restricted to use by specialists in haematology and haemato-oncology.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

First-line treatment of patients with chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.

Dosing information

375mg/m^2 body surface area on Day 1 of the first treatment cycle followed by 500mg/m^2 body surface area administered on Day 1 of each subsequent cycle for six cycles in total. Chemotherapy should be given after rituximab infusion.

Rituximab infusions should be administered under the close supervision of an experienced physician, and in an environment where full resuscitation facilities are immediately available.

Product availability date

Licence extension approved February 2009

Summary of evidence on comparative efficacy

CLL is a chronic incurable disease and the most common form of leukaemia in the UK. It is characterised by a progressive accumulation of monoclonal B lymphocytes, expressing CD5 and CD23 molecules. Rituximab is a chimeric monoclonal antibody that binds specifically to the trans-membrane antigen, CD20, located on mature B lymphocytes.

The evidence to support the extended marketing authorisation for rituximab is from one unpublished phase lll, open-label, randomised study comparing rituximab in combination with fludarabine and cyclophosphamide with fludarabine and cyclophosphamide alone in 817 adult patients with previously untreated CD-20 positive, symptomatic and progressive CLL (according to National Cancer Institute [NCI] criteria). Four phase ll studies were also submitted to support the wider use of rituximab in combination with other cytotoxic agents and regimens.

Patients with a life expectancy >6 months, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1, Binet stage B (plus the presence of at least one other sign or symptom) and stage C disease were randomised to six cycles of iv fludarabine 25 mg/m^2 plus iv cyclophosphamide 250 mg/m^2 on days 1, 2 and 3 of the 28 day cycle (FC, n=407) or iv rituximab 375 mg/m^2 on day 0 of cycle 1, 500 mg/m^2 on day 1 of cycles 2 to 6 plus fludarabine and cyclophosphamide in the above schedule (R-FC, n=403). After three cycles, at a protocol defined interim staging, patients with progressive or stable disease discontinued study treatment. All patients with at least a partial response (PR) continued through to six cycles. In the FC and R-FC groups, 267 patients and 300 patients, respectively, completed six cycles of treatment. Patients were followed for up to five years.

The primary endpoint was progression free survival (PFS) defined as the time between randomisation and disease progression, relapse or death from any cause, in the intention-to treat (ITT) population which included all randomised patients. Secondary endpoints included event-free survival, overall survival (OS) rate and duration of response.

It was planned that the main analysis would be performed after 357 events (disease progression or death) had occurred with a pre-specified interim analysis after 238 events. The Drug and Safety Monitoring Board concluded that the interim analysis results demonstrated a significant difference in PFS in favour of the R-FC group and that the

statistical significance crossed the threshold for early stopping of the study (critical p-value for the two-sided Log-Rank test: p = 0.012). The results of the secondary endpoints were in keeping with the primary endpoint and were internally consistent. Therefore the study was formally stopped and the interim analysis became the main analysis.

At the time of analysis and with a median follow-up of 20.7 months there had been 254 PFS events (152 patients (37%) in the FC group and 102 patients (25%) in the R-FC group). Of these, 127 patients in the FC group and 85 patients in the R-FC group had progressed and 25 patients in the FC group and 17 patients in the R-FC group had died. Efficacy outcomes for this analysis are presented in Table 1. At two years, 77% of the patients in the R-FC group and 60% in the FC group were progression-free.

Table 1. Summary of progression free survival and duration of response in the ITT population for the interim analysis

Progression Free Survival (Kaplan-Meier estimate)		
	Fludarabine and cyclophosphamide N=407	**Rituximab plus fludarabine and cyclophosphamide N=403**
Median (months)	32.2	39.8
p value (Log-Rank test)	p <0.0001	
HR (95% CI) Unstratified (adjusted)	0.56 (0.43; 0.72)	
Duration of Response		
Median (months)	34.7	40.2
p value (Log-Rank test)	p = 0.004	
HR (95% CI) Unstratified (adjusted)	0.61 (0.43; 0.85)	

Results of the secondary endpoints supported the primary outcome. Some patients whose primary outcome was progression had subsequently died and at the time of analysis a total of 81 patients had died: 48 patients (12%) in the FC group and 33 patients (8.2%) in the R-FC group. The Kaplan-Meier estimated 24-month OS rate was 87% in the FC group and 92% in the R-FC group. Response rate was also higher in the R-FC group with significantly more patients achieving an objective response (complete response (CR/PR), 86% (347/403) versus 73% (296/407) in the FC group. The CR rate was doubled in the R-FC group (145/403; 36%) compared with the FC group (70/407; 17%), increasing the possibility of achieving a minimal residual disease response.

An additional analysis with median follow-up of 25.4 months, reported that a total of 296 patients had died or progressed (171 patients in the FC group, 125 patients in the R-FC group). The Kaplan-Meier estimate of median PFS was significantly longer for patients in the R-FC group than in the FC group (43 months and 32 months, respectively), thus significantly reducing the risk of death or progression by 40% (adjusted HR 0.60; 95% CI (0.48 to 0.76)). The difference in OS between treatment groups at 25.4 months was not significant (HR 0.72; 95%CI (0.48 to 1.09)). However, with 59% of patients in the FC group subsequently receiving rituximab either in combination or as monotherapy, survival outcomes were likely to be confounded.

Four phase II studies were submitted to support the use of rituximab in combination with three other alternative chemotherapy regimens: rituximab in combination with fludarabine, rituximab in combination with pentostatin plus cyclophosphamide and rituximab in combination with fludarabine, cyclophosphamide, mitoxantrone and pegfilgrastim.

Summary of evidence on comparative safety

The safety profile of rituximab in CLL was consistent with the known safety profile of rituximab used in combination with chemotherapy in other indications with no new safety concerns reported in the phase lll study.

Only grade 3 or 4 adverse events or serious adverse events were reported in this study. The proportion of patients reporting at least one grade 3 or 4 adverse event was higher in the R-FC group (77%) compared with the FC group (62%), due mainly to a higher incidence of blood and lymphatic system disorders (57% R-FC versus 41% FC), which were mostly neutropenia and leucopenia. The incidence of grade 3 and 4 adverse events increased with age in both groups. In the FC group, 60% of patients <65 years compared with 76% of patients >70 years and in the R-FC group 74% of patients <65years compared with 91% of patients >70 years reported a grade 3 or 4 event.

Adverse events leading to dose modifications were more frequent in the R-FC group but treatment discontinuation due to adverse events was the same in both groups (18%).

There were more deaths in the FC group than in the R-FC group (12% (n=47) versus 8% (n=33)). In eight FC patients and six R-FC patients, the investigator judged the death to be related to study treatment. At the time of a later analysis when the median observation time was 25.5 months, treatment related mortality had occurred in 2.0% in the R-FC and 1.5% in the FC groups.

The March 2009 issue of Drug Safety Update from the Medicines and Healthcare products Regulatory Agency (MHRA), lists rituximab, cyclophosphamide and fludarabine as having a suspected association with progressive multifocal leukoencephalopathy (PML). Warnings about PML are included in the product information for rituximab but at present the evidence for a causal relationship for cyclophosphamide is inconclusive.

Summary of clinical effectiveness issues

CLL is, for most patients, an incurable malignancy and treatment for younger and fitter patients in Scotland is usually fludarabine in combination with cyclophosphamide, with more frail and elderly patients receiving chlorambucil. The aim of treatment is to increase the time without signs and symptoms of the disease, with response to treatment being a prognostic factor. Addition of rituximab to the FC regimen in the phase lll study, doubled the CR response rate and increased median PFS by about 7.6 months.

However, the median age in the phase lll study was 61 years; 70% of patients were less than 65 years, 23% were between ≥ 65 and ≤ 70 years and 7% were over 70 years. Therefore patients were a younger population than generally seen in practice where the median presenting age is 70 years. The patients included in the study were also fit with an ECOG PS of 0 or 1 with little co-morbidity. Due to the relatively small patient numbers, evidence in patients over 70 years of age is limited and although based on a sub-analysis, the results in this population were less good than the whole population and the incidence of adverse events was higher.

The Binet disease stage also had an impact on the outcomes as patients with stage B disease had a greater reduction in the risk of disease progression or death than patients with stage C, where the risk reduction did not reach statistical significance. As a possible explanation for this finding, the European Medicines Agency Public Assessment report

(EPAR) notes that in patients with Binet stage C disease there were more patients with negative prognostic factors in the R-FC group compared to the FC group. There were also more safety problems with rituximab in patients with stage C disease, leading EMEA to conclude that the balance of risks and benefits in this patient group is doubtful.

In the follow-up analysis, survival outcomes were likely to be confounded as 59% of patients in the FC group subsequently received rituximab either in combination or as monotherapy, The EMEA considered the total study duration of 25 months to be short for a disease with a mean course of several years and have requested the submission of updated survival results as a follow up measure.

Although in the phase III study all components of the regimen were given intravenously, fludarabine and cyclophosphamide can both be given orally, therefore addition of rituximab to this regimen may require an additional once monthly hospital visit for administration of the intravenous infusion.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing R-FC with FC as first-line treatment for patients with CLL. FC was assumed to be given orally in the base case analysis. An analysis comparing R-FC with chlorambucil was also included. A Markov model was used to estimate the costs and benefits over a 15 year time horizon. Direct comparative study data were available for the comparison with FC whereas a mixed treatment comparison was carried out for the chlorambucil analysis. Utility values were taken from a published health technology assessment and were based on a combination of expert opinion and a study using a cancer-specific quality of life instrument.

The addition of rituximab to FC was estimated to result in a cost per QALY of £13,107 based on an increased cost of £11,545 and a QALY gain of 0.88. For the analysis comparing R-FC with chlorambucil the manufacturer estimated a cost per QALY of £6,279 based on an increased cost of £11,978 and a QALY gain of 1.91.

Expert replies indicated that the main comparison of interest was R-FC vs FC as chlorambucil would continue to be used in older frailer patients unable to tolerate FC. The model used was appropriate and a key assumption was that rituximab delayed the progression of the disease but did not impact on time to death once progression occurred. Extrapolation beyond the end of the clinical study was necessary which introduced uncertainty; however the method used was appropriate and was tested in the sensitivity analysis. Resource use estimates and utility values used in the analysis were mainly based on assumption but the sensitivity analysis showed that the results were not sensitive to changes in these parameters.

No costs or disutility associated with adverse events were included in the base case analysis but the cost of treating febrile neutropenia was included in the sensitivity analysis which resulted in the ICER increasing slightly to £13,201. In the clinical study both regimens were delivered intravenously, however in practice patients would be moving from oral FC to a partly intravenous regimen with the addition of rituximab. The manufacturer provided a sensitivity analysis which included an additional £500 in cycle 1 of the R-FC arm to account for infusion-related costs and this increased the cost per QALY slightly to £13,675. Although this analysis did not include any disutility associated with adverse events, the sensitivity analysis showed that the results were not sensitive to changes in utility values.

The manufacturer was also asked to provide some sensitivity analysis on the overall survival benefit estimated in the R-FC model as the difference in overall survival between treatment

groups in the clinical study was not significant. When the difference in overall survival was removed from the model the cost per QALY increased to £33,694. This analysis involved increasing the post-progression monthly mortality rate in the R-FC arm of the model by over 300% and the manufacturer argued that there was no evidence to suggest that patients who progressed on R-FC would die at a higher rate than patients who progressed in the FC arm.

The R-FC model relies on a number of assumptions but the sensitivity analysis provided reassurance that the results were robust to changes in these parameters, with the probabilistic sensitivity analysis showing a 98.6% probability that rituximab would be cost-effective at a willingness to pay of £30,000. Only when the very conservative assumption of no overall survival benefit was explored did the ICER increase to over £30,000 per QALY. The economics case versus FC has been demonstrated.

Summary of patient and public involvement

Patient Interest Group Submissions were received from:

- The Chronic Lymphocytic Leukaemia Support Association
- Leukaemia CARE

Additional information: guidelines and protocols

The British Committee for Standards in Haematology published guidelines in 2004 entitled Guidelines on the diagnosis and management of chronic lymphocytic leukaemia. For patients ineligible for a transplant procedure, these recommended entry into a study assessing fludarabine alone, chlorambucil alone or fludarabine in combination with cyclophosphamide, provided fludarabine is not contraindicated. These guidelines are being updated.

The European Society for Medical Oncology published guidelines in 2007 entitled Chronic lymphocytic leukaemia: ESMO clinical recommendations for diagnosis, treatment and follow-up. These recommend fludarabine and cyclophosphamide as the first option for fit patients being treated for the first time, and either a dose-adjusted fludarabine regimen or chlorambucil for the less fit.

The National Comprehensive Cancer Network in the United States published updated clinical practice guidelines for non-Hodgkin's lymphoma in 2008. These included treatment recommendations for patients with CLL and 17p-deletion.

Additional information: comparators

Rituximab for this indication is add on treatment and as such has no direct comparator but other regimens are available for use in this patient population and are listed in the cost comparator table below.

Cost of relevant comparators

Drug	Dose regimen	Cost per cycle (£)	Cost per 6 cycles (£)
Rituximab Fludarabine injection Cyclophosphamide injection	375mg/m^2 Day 1 of first cycle then 500mg/m^2 Day 1 in subsequent cycles 25mg/m^2 Days 1, 2, 3 of each cycle 250mg/m^2 Days 1, 2, 3 of each cycle	**2,223**	**12,814**
Rituximab Fludarabine tablets Cyclophosphamide tablets	375mg/m^2 Day 1 of first cycle then 500mg/m^2 Day 1 in subsequent cycles 24mg/m^2 Days 1, 2, 3, 4, 5 of each cycle 150mg/m^2 Days 1, 2, 3, 4, 5 of each cycle	**2,121**	**12,202**
Fludarabine tablets	40mg/m^2 Days 1, 2, 3, 4, 5 of each cycle	651	3906
Fludarabine injection	25mg/m^2 Days 1, 2, 3, 4, 5 of each cycle	780	4680
Fludarabine injection cyclophosphamide injection	25mg/m^2 Days 1, 2, 3 of each cycle 250mg/m^2 Days 1, 2, 3 of each cycle	477	2,860
Fludarabine tablets Cyclophosphamide tablets	24mg/m^2 Days 1, 2, 3, 4, 5 of each cycle 150mg/m^2 Days 1, 2, 3, 4, 5 of each cycle	375	2248
*Chlorambucil tablets 2mg	10mg/m^2 Days 1, 2, 3, 4, 5, 6, 7 of each 28 day cycle up to 12 cycles	21	Up to 252

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 03 March 2009. Costs for cyclophosphamide from BNF 57 (March 09). Doses are based on body surface area of 1.8m^2. *The dosing regimen and length of treatment was taken from the study comparing fludarabine, fludarabine plus cyclophosphamide and chlorambucil by Catovsky et al, 2007.

Additional information: budget impact

The manufacturer estimated the budget impact of rituximab would be £1.57m in year 1 rising to £1.59m in year 5. It was assumed that 118 patients would receive rituximab in year 1 rising to 120 in year 5. These figures were based on the number of patients who receive first-line treatment who are eligible for rituximab combination therapy. The manufacturer assumed 100% uptake in order to estimate the maximum budget impact to NHS Scotland.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 17 April 2009.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission. The reference shaded grey is in addition to those supplied with the submission.

Clinical Study Report. Phase lll trial of combined immunochemotherapy with fludarabine, cyclophosphamide and rituximab versus chemotherapy with fludarabine and cyclophosphamide alone in patients with previously untreated chronic lymphocytic leukaemia. July 2008

Catovsky D, Richards S, Matutes E, Oscier D, Dyer MJ, Bezares RF et al. Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): a randomised controlled trial. Lancet 2007; 370(9583):230-239.

Drug Safety Update Adverse drug reactions in focus: progressive multifocal leukoencephalopathy. March 2009 vol 2, issue 8 www.drugsafetyupdate@mhra.gsi.gov.uk

The European Medicines Agency (EMEA) European Public Assessment Report. Rituximab (MabThera) 25/03/2009 HC-165-II-63. www.emea.europa.eu