rituximab, 100mg and 500mg concentrate for solution for infusion (MabThera®) No. (493/08)

Roche

8 August 2008

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 the treatment of previously untreated patients with stage III to IV follicular lymphoma in combination with chemotherapy.

Rituximab added to a number of different chemotherapy regimens produced statistically significant improvements in the primary study endpoints when compared with the chemotherapy regimens alone. Rituximab is restricted to use only by haematologists or oncologists who have expertise in treating lymphoma. It should be administered in a healthcare environment where full resuscitation facilities are available.

SMC issued advice in December 2004 regarding the use of rituximab in combination with cyclophosphamide, vincristine and prednisolone (CVP) chemotherapy for the treatment of previously untreated patients with stage III to IV follicular lymphoma. The current advice extends the range of chemotherapy regimens that can be used in combination with rituximab for this indication.

Overleaf is the detailed advice on this product.

Vice Chairman
New Drugs Committee

Indication

The treatment of previously untreated patients with stage III to IV follicular lymphoma in combination with chemotherapy.

Dosing information

375mg/m^2 body surface area per cycle, for up to 8 cycles. Rituximab should be administered on day 1 of each chemotherapy cycle by intravenous (IV) infusion, after IV administration of the glucocorticoid component of the chemotherapy if applicable.

Pre-medication with glucocorticoids should be considered if rituximab is not given in combination with glucocorticoid-containing chemotherapy.

Product availability date

18th January 2008

Summary of evidence on comparative efficacy

Rituximab is a chimeric mouse / human monoclonal antibody that binds specifically to the trans-membrane antigen, CD20, located on pre-B and mature B lymphocytes and expressed on greater than 95% of all B-cell non Hodgkin's lymphomas. It induces cell death via apoptosis induction, complement dependent cytotoxicity and antibody dependent cellular cytotoxicity.

In December 2004 the Scottish Medicines Consortium (SMC) accepted rituximab for use within NHS Scotland for the treatment of previously untreated patients with stage III to IV follicular lymphoma in combination with cyclophosphamide, vincristine and prednisolone (CVP) chemotherapy. This decision reflected the UK marketing authorisation for rituximab at that time. In January 2008 the UK marketing authorisation for rituximab was broadened to include the use of rituximab in combination with any chemotherapy regimen for the treatment of previously untreated patients with stage III to IV follicular lymphoma. This current submission relates to this broader therapeutic indication.

The chemotherapy regimens used most frequently in Scotland for the treatment of follicular lymphoma are CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) and CVP. The most relevant clinical data provided as part of the current submission relates to comparisons of a CHOP plus rituximab regimen (R-CHOP) with CHOP alone and a CVP plus rituximab regimen (R-CVP) with CVP alone. The latter study was presented in the previous SMC assessment and the current submission considers two updated survival analyses of the initial study. The current submission also contained clinical data for a comparison of MCP (mitoxantrone, chlorambucil and prednisolone) plus rituximab (R-MCP) with MCP alone and CHVP (cyclophosphamide, doxorubicin, etoposide and prednisolone) plus rituximab (R-CHVP) and interferon-α with CHVP plus interferon-α. These data are less relevant to clinical practice in Scotland and will only be discussed briefly.

The R-CHOP versus CHOP study was a prospective, randomised, open-label multicentre phase III study involving 630 patients ≥ 18 years old from 200 participating centres of the German Low-Grade Lymphoma Study Group (GLSG) with previously untreated advanced stage III to IV follicular lymphoma requiring treatment, enrolled between May 2000 and August 2003. The CHOP combination consisted of cyclophosphamide 750mg/m^2, doxorubicin 50mg/m^2 and vincristine 1.4mg/m^2 (maximum 2mg) all administered IV on day 1, and prednisone 100mg/m^2 daily administered orally on days 1 to 5. Patients who were randomly assigned to the R-CHOP arm received a single IV dose of rituximab 375mg/m^2 the

day before the CHOP course. Treatment cycles were repeated every 3 weeks for a total of 6 to 8 cycles. The number of total cycles administered depended on the response to the first 4 cycles. Patients achieving a complete remission (CR) after 4 cycles were treated with a total of 6 cycles, whereas all other patients received 8 cycles. Patients from either arm with progressive disease at any time were taken off study.

All analyses were performed on an intention-to-treat basis without censoring for patients refusing the scheduled treatment, in remission, or receiving other unplanned therapies. In June 2003 the applied sequential test showed a significantly longer time to treatment failure (TTF) for the R-CHOP arm and the trial was stopped early. At this stage only the patients who had completed induction therapy (n=428, 223 in the R-CHOP arm and 205 in the CHOP arm) were eligible for analysis of efficacy and safety.

Overall response rate (CR + partial response (PR)) was significantly greater in the R-CHOP arm (96%) than in the CHOP arm (90%). CR rates were not statistically different (20% versus 17% for R-CHOP and CHOP, respectively). After a median observation time of 18 months (range 1 to 38 months), 28 patients in the R-CHOP arm experienced treatment failure compared to 61 in the CHOP arm. This translated into a significant reduction in the risk for treatment failure (by 60%) and a significantly longer TTF in the R-CHOP arm. A significant overall survival (OS) advantage for R-CHOP was apparent after 18 months. This equated to 6 deaths in the R-CHOP arm compared with 17 in the CHOP arm (at 3 years), with 1 death due to progressive lymphoma in the R-CHOP arm compared with 9 in the CHOP arm. The estimated probability of survival at 2 years was 95% for those treated with R-CHOP and 90% for those treated with CHOP.

In the R-CVP versus CVP randomised controlled study, 321 untreated patients (162 in the R-CVP arm and 159 in the CVP arm) with symptomatic stage III to IV follicular lymphoma received a total of 8, three-weekly, cycles of a combination of 750mg/m^2 cyclophosphamide and 1.4mg/m^2 of vincristine (maximum 2mg) IV on day 1 and 40mg/m^2 of oral prednisone per day on days 1 to 5. Patients treated with R-CVP also received 375mg/m^2 of rituximab IV on day 1 of each therapy cycle. With a median follow up of 53 months, the median time to progression, relapse or death (TTP) was significantly greater in the R-CVP arm (34 months) than in the CVP arm (15 months). The difference in number of deaths between the arms (19% in the R-CVP arm versus 29% in the CVP arm) translated into a significant improvement in OS for the R-CVP arm compared to the CVP arm (p=0.03, log rank; hazard ratio 0.60 (95% Confidence Interval: 0.38 to 0.96)). This benefit in OS was not statistically significant in the initial study report published in 2005 (with a median follow up of 30 months).

Overall response rate was the primary endpoint for the R-MCP versus MCP study, with a statistically significant improvement seen in the R-MCP arm (92%) compared with the MCP arm (75%). Secondary endpoints such as median progression-free survival and 4-year OS were also significantly improved in the R-MCP arm. Event-free survival (EFS) was the primary endpoint of the R-CHVP versus CHVP study where five-year follow-up confirmed the benefit of adding rituximab to the combination of CHVP plus interferon-α compared to CHVP plus interferon-α alone (53% versus 37%, respectively for EFS). A statistically significant OS benefit for those with high-risk disease (Follicular Lymphoma International Prognostic Index ≥3) was also seen in the rituximab arm but OS for the total study population was not statistically different between treatment groups.

Summary of evidence on comparative safety

The addition of rituximab to chemotherapy led to an increase in the total number of adverse events of all grades in the R-chemotherapy arms compared to the chemotherapy arms. This was mainly due to a higher incidence of leucopenia / neutropenia and infection but there was no increase in the incidence of grade 3 or 4 infections and there were no previously un-encountered or unexpected toxicities in the studies being considered.

In the R-CHOP versus CHOP study, myelosuppression, particularly granulocytopenia, was the commonest encountered toxicity. There was a statistically significant difference in grade 3 or 4 granulocytopenia between the treatment arms (63% versus 53% in the R-CHOP and CHOP arms, respectively). However the grade 3 or 4 infection rates after R-CHOP (7%) and CHOP (5%) were not statistically different. Non-haematological adverse events occurred at similar frequencies in both arms and were generally mild to moderate; with the exception of grade 3 or 4 alopecia (67% versus 61% in the R-CHOP and CHOP arms, respectively). Consistent with the incidence in routine clinical practice, infusion related reactions were observed in 7% of rituximab courses.

No additional safety concerns were raised in the updated survival analyses in the R-CVP versus CVP study. After 53 months follow-up, grade 3 or 4 leucopenia occurred in 12% of the 162 R-CVP patients compared to 19% of the 159 CVP patients and grade 3 or 4 neutropenia occurred in 24% of the R-CVP patients compared to 14.5% of the CVP patients.

Summary of clinical effectiveness issues

The marketing authorisation for rituximab now allows it to be used in combination with any chemotherapy regimen for the treatment of previously untreated patients with stage III to IV follicular lymphoma. However, it is not practical to conduct randomised phase III clinical studies in combination with all such chemotherapy regimens. This submission included randomised phase III studies utilising four different chemotherapy regimens, two of which (CHOP and CVP) appear to be most relevant to Scottish clinical practice. All of the studies were open-label with no specific placebo infused instead of rituximab in the control arms.

The R-CHOP versus CHOP study and the R-CVP versus CVP study used TTF as the primary endpoint. This increased time to treatment failure in previously untreated patients is clinically relevant as the first remission is usually the longest when treating follicular lymphoma and therefore prolonging this time is of particular importance. Response to treatment (CR, PR and overall response) and OS were assessed as a secondary endpoint in both studies. The European Medicines Agency (EMEA) European Public Assessment Report (EPAR) states that the achievement of a complete response is the single most important prognostic factor in follicular lymphoma regardless of the treatment regimen utilised. Evidence from clinical trials suggests there is a relationship between time-dependent efficacy endpoints and OS in follicular lymphoma. However, in a chronic disease characterised by multiple relapses and progressions it is difficult to assess the contribution of first-line therapy to OS especially due to the influence of multiple subsequent therapies.

None of the studies detailed in this submission specifically collected data on health-related quality of life (HR-QoL). A HR-QoL assessment has been carried out using 30 months survival data from the R-CVP versus CVP study using quality-adjusted time without disease symptoms or treatment toxicity. A further analysis using the 53 months survival data is planned.

Some of the data presented with this submisison have not been published in peer reviewed journals and the abstracts supplied provided limited information.

Summary of comparative health economic evidence

The manufacturer presented three related cost-utility analyses to estimate the costs and benefits of adding rituximab to CHOP, to MCP and to CHVP-plus-interferon in previously untreated patients with stage III-IV follicular lymphoma. Data from the three clinical trials were used, extrapolated beyond the end of the clinical trial follow-up period. The time horizon of the model was 25 years. It was assumed that (i) rituximab had a protective effect that did not extend beyond the end of the follow-up period from the relevant RCT and (ii) while rituximab delayed progression, it did not affect mortality rates once progression had occurred. On this basis, adding rituximab to:

- CHOP cost an extra £8,980 per patient and yielded 0.86 QALYs at a cost per QALY gained of £10,472
- MCP cost an extra £9,074 per patient and yielded 1.22 QALYs at a cost per QALY gained of £7,417
- CHVP cost an extra £3,973 per patient and yielded 0.47 QALYs at a cost per QALY gained of £8,549.

The economic study reflected the licensed use and considered adding rituximab to a range of appropriate regimens. Responses from clinical experts consulted by SMC suggests there is most interest in adding rituximab to CHOP. The submission made a number of assumptions but these were clearly explained and tested in a sensitivity analysis. The results of these sensitivity analyses provided adequate reassurance that the assumptions made were acceptable and that the results held under most plausible scenarios.

The manufacturer also submitted an estimate of the cost-effectiveness of adding rituximab to chlorambucil of £12,475 per QALY. However, this used the CHOP versus R-CHOP model and simply replaced the costs of CHOP with those of chlorambucil. This assumes chlorambucil is as effective as CHOP and no supporting evidence was submitted to demonstrate this.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The National Institute for Health and Clinical Excellence (NICE) has not assessed the use of rituximab in the indication under consideration in this SMC submission. However, in September 2006 NICE recommended the use of rituximab (given with CVP) as a possible treatment for people with symptomatic stage III to IV follicular lymphoma who haven't been treated before (TA110). NICE also issued guidance on the use of rituximab to treat aggressive non-Hodgkin’s lymphoma (TA65) in September 2003 and to treat relapsed or refractory stage III to IV follicular non-Hodgkin's lymphoma (TA137) in February 2008.

The British Committee for Standards in Haematology published guidelines on the diagnosis and therapy of Nodal non-Hodgkin's lymphoma in August 2002 that were revised in 2005.

The European Society of Medical Oncology published clinical recommendations for diagnosis, treatment and follow-up of newly diagnosed follicular lymphoma in 2007. This guideline recommends the use of rituximab combination chemotherapy (R-CVP, R-CHOP, and R-FCM (fludarabine, cyclophosphamide, mitoxantrone)) for symptomatic stage III to IV patients.

Additional information: previous SMC advice

Following a full submission, SMC published advice dated March 2003: Rituximab is accepted for restricted use within NHS Scotland for the treatment of patients with CD20 positive diffuse large B-cell non-Hodgkin's lymphoma. It is recommended for use by oncologists or haematologists in Scotland who have expertise in treating lymphoma. It should be administered in a hospital environment where full resuscitation facilities are available.

Following a full submission, SMC published advice dated December 2004: Rituximab is accepted for use within NHS Scotland for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with cyclophosphamide, vincristine and prednisolone (CVP) chemotherapy. Rituximab is for use only by oncologists or haematologists who have expertise in treating lymphoma. It should be administered in a hospital environment where full resuscitation facilities are available. Limited results show that rituximab plus CVP significantly increased the time to treatment failure compared with CVP alone.

Following a full submission, SMC published advice dated December 2006: Rituximab 10mg/ml concentrate for infusion (MabThera®) is accepted for restricted use within NHS Scotland as maintenance therapy for patients with relapsed / refractory follicular lymphoma responding to induction therapy with chemotherapy with or without rituximab. In a phase lll, randomised, open-label study, rituximab maintenance treatment significantly increased the median progression-free survival from 15 months in the observation arm to 52 months in the rituximab arm with an increase in overall survival at three years. This prolonged survival requires to be confirmed in longer term follow up. Rituximab is restricted for use only by oncologists or haematologists who have expertise in treating lymphoma.

Additional information: comparators

CVP and CHOP are commonly used base regimens in Scotland, whilst MCP and CHVP are rarely used. As both arms of the reported studies included the base chemotherapy regimens there are no active comparators in this submission.

Cost of relevant comparators

Drug	Dose regimen	Cost per cycle (£)	Cost per 8 cycles (£)
Rituximab	375mg/m^2 body surface area on day 1 of each cycle, for up to 8 cycles	**1,222**	**9,776**

Cost calculated based on a body surface area (BSA) of 1.7m^2 and the use of one 500mg/50mL vial and two 100mg/10mL vials for each cycle (assuming no vial sharing and disposal of excess drug after each administration). Cost of a 100mg/10mL vial (£174.63) and a 500mg/50mL vial (£873.15) obtained from the 55th edition of the British National Formulary (BNF). The above cost is additional to that for the CHOP and CVP chemotherapy regimens, which is approximately £1,559 and £32 respectively per cycle and £12,472 and £256 respectively for 8 cycles, assuming a BSA of 1.7m^2 (and maximum dose of 2mg for vincristine) and no vial sharing (disposal of excess drug after each administration). Cost obtained from eVadis on 22nd May 2008 and 55th edition of the BNF.

Additional information: budget impact

The net drug budget impact was estimated by the manufacturer at £321k in year 1 rising to £328k in year 5. This was based on 33 patients. The assumptions used by the manufacturer were broadly confirmed by one clinical expert. It should be noted that the budget impact may be over-estimated as some patients will already be receiving R-CHOP.

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 18 July 2008.

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 additional to those supplied with the submission.

Hiddemann W, Kneba M, Dreyling M *et al*. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood* 2005;106:3725-32.

Herold M, Haas A, Srock S et al. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: An East German Study Group Hematology and Oncology Study. *J Clin Oncol* 2007;25:1986-92.

European Medicines Agency (EMEA) European Public Assessment Report (EPAR) for rituximab. Revision 15 published 02/04/08.
http://emea.europa.eu/humandocs/Humans/EPAR/mabthera/mabthera.htm.