PUBLIC SUMMARY DOCUMENT

Product: RITUXIMAB, solution for IV infusion, 100 mg in 10 mL and 500 mg in 50 mL, Mabthera®

Sponsor: Roche Products Pty Limited

Date of PBAC Consideration: March 2010

1. Purpose of Application

The submission sought an extension to the current listing of rituximab to include a general schedule Authority required listing and inclusion in the Chemotherapy Pharmaceutical Access Program (CPAP) for the treatment of CD20 positive, chronic lymphocytic leukaemia, in combination with chemotherapy.

2. Background

Rituximab had not previously been considered by the PBAC for the treatment of CD20 positive, chronic lymphocytic leukaemia.

Rituximab is currently listed for:

- Relapsed or refractory low grade B-cell non Hodgkin's lymphoma;
- Relapsed or refractory follicular B-cell non-Hodgkin's lymphoma
- Treatment of previously untreated, CD20 positive, diffuse large B-cell non-Hodgkin's lymphoma, in combination with chemotherapy;
- Treatment of symptomatic patients with previously untreated, CD20 positive, Stage III or IV, follicular, B-cell non-Hodgkin's lymphoma, in combination with chemotherapy.
- Treatment of adult patients with severe active rheumatoid arthritis.

3. Registration Status

Rituximab was registered for first-line treatment of patients with CD20 positive chronic lymphocytic leukaemia (CLL) in combination with chemotherapy by the Therapeutic Goods Administration (TGA) as at 26 August 2009.

At the time of PBAC consideration, rituximab was not registered for the treatment of patients with CD20 positive chronic lymphocytic leukaemia in combination with chemotherapy, other than as first-line.

4. Listing Requested and PBAC's View

Authority Required

Treatment of CD20 positive, chronic lymphocytic leukaemia, in combination with chemotherapy.

The PBAC considered that there was a significant risk of leakage (i.e. use of a medicine for a purpose outside its PBS restriction) for use as monotherapy. The PBAC, however, did not consider that restricting rituximab prescription to combination with FC only, as was the recommendation by NICE, was clinically appropriate. Although the evidence for survival benefit of combination use with other chemotherapies is less certain, depriving patients for whom FC is not the chemotherapy backbone of choice of a potentially effective treatment option was not clinically acceptable. *See Recommendations and Reasons.*

5. Clinical Place for the Proposed Therapy

Chronic lymphocytic leukaemia (CLL) is the most common chronic leukaemia and comprises 30 % of all adult leukaemias. The majority of patients with CLL are asymptomatic at diagnosis. Symptoms appear with disease progression and are generally related to cytopenias due to bone marrow infiltration of malignant cells. Treatment is usually initiated when patients become symptomatic, when there is a high tumour burden or evidence of rapidly progressive disease.

Rituximab in combination with chemotherapy would provide an additional treatment option for CLL.

6. Comparator

The submission nominated chemotherapy alone (fludarabine plus cyclophosphamide) as the main comparator. This was considered appropriate.

7. Clinical Trials

The submission presented two randomised trials comparing rituximab with fludarabine and cyclophosphamide (R-FC) with fludarabine plus cyclophosphamide (FC) in patients with chronic lymphocytic leukaemia (CLL). Trial CLL-8 was a randomised open-label controlled trial in 817 treatment naive patients and REACH was a randomised open-label controlled trial in 552 treatment experienced patients. Both trials assessed progression-free survival as the primary outcome.

Trial ID / First author	Protocol title / Publication title	Publication citation
CLL-8		
Hallek M et al. (2008)	Immunochemotherapy with Fludarabine (F), Cyclophosphamide (C), and Rituximab (R) Versus Fludarabine and Cyclophosphamide (FC) Improves Response Rates and Progression-Free Survival of Previously Untreated Patients with Advanced Chronic Lymphocytic Leukaemia (CLL).	50th ASH Annual Meeting and Exposition.
Beottcher S et al. (2008)	Quantitative MRD Assessments Predict Progression Free Survival in CLL Patients Treated with Fludarabine and Cyclophosphamide with or without Rituximab – a Prospective Analysis in 471 Patients from the Randomized GCLLSG CLL8 Trial.	50th ASH Annual Meeting and Exposition.
Stilgenbauer S et al. (2008)	Genomic Aberrations, VH Mutation Status and Outcome after Fludarabine and Cyclophosphamide (FC) or FC Plus Rituximab (FCR) in the CLL8 Trial.	50th ASH Annual Meeting and Exposition.
Hallek M et al. (2009)	First-Line Treatment with Fludarabine (F), Cyclophosphamide (C), and Rituximab (R) (FCR) Improves Overall Survival in Previously Untreated Patients (pts) with Advanced Chronic Lymphocytic Leukemia (CLL): Results of a Randomized Phase III Trial On Behalf of An International Group of Investigators and the German CLL Study Group. Analysis of individual patient data from the 22 June 2009 data cut-off for the CLL-8 trial.	Presented as a paper at the 51st ASH Annual Meeting and Exposition, December 5-8 2009, New Orleans, USA.

REACH Robak T et al. (2008)	Rituximab, Fludarabine, and Cyclophosphamide (R-FC) Prolongs Progression Free Survival in Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL) Compared with FC Alone: Final Results from the International Randomized Phase III REACH Trial.	50th ASH Annual Meeting and Exposition.

The PBAC considered that the two key clinical trials presented, CLL-8 (treatment naïve) and REACH (treatment experienced), which compared rituximab with fludarabine and cyclophosphamide (R-FC) with FC in patients with chronic lymphocytic leukaemia were appropriate.

The PBAC noted that eleven single arm studies were presented in the submission in which rituximab was used in combination with several chemotherapy regimens other than FC. The PBAC considered that in routine clinical practice rituximab would definitely be used concurrently with chemotherapy regimens other than FC, and also that rituximab would be used in patients whose prior treatments differ from the population in REACH. However, the PBAC considered that because of the limited evidence available, the efficacy of rituximab used in these circumstances remains uncertain. The PBAC noted that the submission did not present evidence of benefit if combined with the most common alternative chemotherapy, chlorambucil, and that this was a source of additional uncertainty. In addition, no evidence of single agent activity was presented and the PBAC considered that there was a significant risk of leakage for use as monotherapy. The PBAC, however, did not consider that restricting rituximab prescription to combination with FC only, as was the recommendation by the National Institute for Clinical Excellence (NICE), was clinically appropriate. Although the evidence for survival benefit of combination use with other chemotherapies is less certain, depriving patients for whom FC is not the chemotherapy backbone of choice of a potentially effective treatment option was not clinically acceptable.

8. Results of Trials

Both trials were designed to assess the efficacy of rituximab on the primary outcome of progression-free survival (PFS) and both found a significant improvement in this outcome attributable to rituximab. PFS was defined as the time to the first occurrence of disease progression or death.

The PBAC noted that in both trials the rituximab plus fludarabine plus cyclophosphamide arm had a statistically significant increase in PFS compared with fludarabine plus cyclophosphamide only.

The PBAC considered that the outcome of PFS measured in the CLL-8 and REACH trials concurred with the clinical claim of superiority but the trials are in disagreement over the statistical significance of an improvement in overall survival (OS) due to rituximab treatment. The CLL-8 trial, which involved treatment naïve patients, found a statistically significant improvement in overall survival for patients treated with rituximab (HR 0.65; 95 % CI: 0.46-0.94; p = 0.0116). The REACH trial, which assessed treatment experienced patients, did not find a statistically significant difference in overall survival with the addition of rituximab (HR 0.83; 95 % CI: 0.59-1.17; p = 0.2874). The PBAC noted that the difference in overall survival outcomes between the trials may relate to whether prior therapy was received by the patients.

The meta-analysis for OS combining the CLL-8 and REACH trials produced a hazard ratio for overall survival of 0.74 - approximately midway between the individual results of CLL-8 and REACH. The PBAC agreed that, as for the PFS data, combining the OS data from trials CLL-8 and REACH was reasonable as there was no significant heterogeneity in this analysis and that it reasonable to assume that treatment with rituximab would improve survival.

Rituximab was described in the submission as more toxic than chemotherapy alone. This was supported by the clinical evidence.

Adverse events were very common in both clinical trials. Rituximab treatment was associated with significantly more Grade 3 and 4 adverse events in both trials and a significantly higher likelihood of treatment interruption or dose modification due to an adverse event. The increased number of Grade 3 and 4 adverse events was driven largely by a higher proportion of patients experiencing neutropenia and febrile neutropenia and leucopenia when treated with rituximab. These adverse events were serious and may impact on quality of life for patients treated with rituximab and the costs associated with listing rituximab on the PBS.

The submission provided the most recent Periodic Safety Update Report for rituximab for the period June 2008 – May 2009 as an extended assessment of comparative harms. It was claimed that the incidents of adverse event recorded are in line with expectations for rituximab. This was correct but the very high prevalence of adverse events underscored that the use of rituximab is often toxic and can lead to fatalities. Much of this was not adequately captured in the economic evaluation.

The PBAC agreed that rituximab is more toxic than chemotherapy alone and that this is supported by the clinical evidence which demonstrated that there was increased neutropenia and febrile neutropenia with R-FC and no unexpected toxicities.

9. Clinical Claim

The submission described the addition of rituximab to chemotherapy regimens of fludarabine plus cyclophosphamide as superior in terms of comparative effectiveness and inferior in terms of comparative safety over fludarabine plus cyclophosphamide alone.

The PBAC considered that the outcome of PFS measured in the CLL-8 and REACH trials concurred with the clinical claim of superiority but the trials are in disagreement over the statistical significance of an improvement in OS due to rituximab treatment.

The PBAC agreed that rituximab is more toxic than chemotherapy alone and that this is supported by the clinical evidence which demonstrated that there was increased neutropenia and febrile neutropenia with R-FC and no unexpected toxicities.

10. Economic Analysis

A modelled economic evaluation was presented in a five step process. The model contained two health states (unprogressed and progressed disease) and a state capturing death. Five transitions were possible between these states and their relative hazards (between treatment groups) were determined from the individual patient data from the CLL-8 and REACH clinical trials:

- Unprogressed disease → progressed disease
- Unprogressed disease → new treatment
- Unprogressed disease → death
- Progressed disease → new treatment
- Progressed disease → death

The key driver of the model was the effectiveness of rituximab at retaining patients in the unprogressed disease health state and, in this way, preventing the reduced quality of life of the progressed disease health state and preventing the likelihood of death (which was higher when disease is assumed to have progressed). The model was very sensitive to changes in the relative transition rates (hazard ratios) between treatment groups from the unprogressed health state. The health outcome of QALYs incorporated by design a considerable effect of rituximab on overall survival, which was not unambiguously supported in the evidence. While the trial CLL-8, which assessed treatment naïve patients, showed a statistically significant improvement in overall survival with the addition of rituximab, there was no statistically significant difference in overall survival found in the REACH trial between R-FC and FC (which may reflect that the patients in this trial were treatment experienced).

Associated with the efficacy of rituximab, the model was sensitive to the utility values assigned to the health states.

There was some uncertainty with the true incremental cost difference assigned to rituximab treated patients as the administration costs (infusion costs) and the cost of adverse events may not have been wholly captured. It is likely that the cost difference was underestimated to a degree.

The length of the time horizon was shown as particularly influential on the results of the model. A shorter time horizon may be more conservative in that it reduces some of the uncertainty associated with extrapolation and the durability of the effect of rituximab. The argument against this was that patients with CLL can survive for a long time without disease progression and the benefits of rituximab occur in the future, while the costs occur up front.

The base-case ICER was estimated to be in the range of $15,000 - $45,000/QALY which the PBAC considered to be high but acceptable for the R-FC combination.

11. Estimated PBS Usage and Financial Implications

The likely number of patients/year was estimated by the submission to be less than 10,000 in year 5 after listing.

The financial cost/year to the PBS was estimated by the submission to in the range of $10 – 30 million in year 5 after listing.

12. Recommendation and Reasons

The PBAC considered that the two key clinical trials presented, CLL-8 (treatment naïve) and REACH (treatment experienced), which compared rituximab with fludarabine and cyclophosphamide (R-FC) with FC in patients with chronic lymphocytic leukaemia were appropriate.

The PBAC noted that in both trials the rituximab plus fludarabine plus cyclophosphamide arm had a statistically significant increase in PFS compared with fludarabine plus cyclophosphamide only.

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The PBAC agreed that rituximab is more toxic than chemotherapy alone and that this is supported by the clinical evidence which demonstrated that there was increased neutropenia and febrile neutropenia with R-FC and no unexpected toxicities.

The PBAC noted that eleven single arm studies were presented in the submission in which rituximab was used in combination with several chemotherapy regimens other than FC. The PBAC considered that in routine clinical practice rituximab would definitely be used concurrently with chemotherapy regimens other than FC, and also that rituximab would be used in patients whose prior treatments differ from the population in REACH. However, the PBAC considered that because of the limited evidence available, the efficacy of rituximab used in these circumstances remains uncertain. The PBAC noted that the submission did not present evidence of benefit if combined with most common alternative chemotherapy, chlorambucil, and that this was a source of additional uncertainty. In addition, no evidence of single agent activity was presented and the PBAC considered that there was a significant risk of leakage for use as monotherapy. The PBAC, however, did not consider that restricting rituximab prescription to combination with FC only, as was the recommendation by NICE, was clinically appropriate. Although the evidence for survival benefit of combination use with other chemotherapies is less certain, depriving patients for whom FC is not the chemotherapy backbone of choice of a potentially effective treatment option was not clinically acceptable.

The base-case ICER was estimated to be in the range of $15,000 - $45,000/QALY which the PBAC considered to be high but acceptable for the R-FC combination. However, there were some uncertainties around the economic issues identified which could not be resolved during the evaluation due to the structure and design of the model. The PBAC noted the sponsor's argument that the model is robust because for all scenarios tested in

sensitivity analyses, the ICER remains less than a certain value in the range of $45,000 - $75,000/QALY. However, the PBAC considered that a major uncertainty that could not be tested in the model is the effect of using R with non-FC chemotherapy, especially chlorambucil. The PBAC considered that ICER per QALY would be higher and was uncertain for rituximab in combination with other chemotherapy.

The PBAC also noted that most of the patients in CLL-8 trial were less than 70 years of age (mean age 60 years) with only 6 – 8 % of patients greater than 70 years. However, international and Australian registries show that in patients with CLL, 53 % are older than 70 years and 25 % are older than 80 years. The PBAC noted that a 15-year time horizon was used in the economic model and at 15 years, 18 % of R-FC patients and 6 % of FC patients are still alive, assuming the average age was 60 years. If a shorter time horizon of 10 years was used to account for the older age groups seen in Australian clinical practice this could potentially increase the ICER to be in the range of $45,000 - $75,000/QALY. Therefore, there was uncertainty regarding the ICER arising from this issue.

The PBAC therefore deferred the submission for rituximab to request the sponsor recalculate the incremental cost-effectiveness in the modelled economic evaluation to include consideration of the uncertainties identified by the PBAC. These include the time horizon, ages of patients entering the model, the impact of reducing treatment effect over time and the effect of varying patients' baseline risk. These should be tested in sensitivity analysis, both univariate and multivariate. The PBAC noted that the base case used the age group included in the trial population and noted the high ICER in the univariate analysis where patients entered the model at 75. The PBAC considered that it was highly likely that rituximab would be used in older patients and in combination with chemotherapy other than FC. Therefore, the time horizon of 15 years does not reflect patients seen in clinical practice and that the time horizon should be shorter as older patients had other co-morbidities.

Any resubmission presented would need to be in the form of a major submission.

Recommendation:
Defer

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor has no further comment.