PUBLIC SUMMARY DOCUMENT
Product: Rituximab, solution for I.V infusion, 100 mg in 10 mL, 500 mg in 50 mL, Mabthera®
Sponsor: Roche Products Pty Ltd
Date of PBAC Consideration: November 2010

1. Purpose of Application

The submission sought to address concerns of the PBAC from the March 2010 meeting, regarding the cost-effectiveness of rituximab in the treatment of patients with CD20 positive chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.

2. Background

At the March 2010 meeting, the PBAC deferred a submission requesting an extension to the current listing for rituximab to include a Section 85 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, 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 included 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.

Full details are available in the March 2010 Public Summary Document available at http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-Rituximab-mar10

3. Registration Status

Rituximab was registered for first-line treatment of patients with CD20 positive CLL in combination with chemotherapy by the TGA on 26 August 2009.

On 8 January 2010, the TGA extended the registration of rituximab to include treatment of patients with CD20 positive CLL in combination with chemotherapy, other than as first line.

Rituximab is also TGA registered for the treatment of certain types of B-cell non-Hodgkin lymphoma and rheumatoid arthritis under certain conditions.

4. Listing Requested and PBAC's View

Authority Required
CD20 positive, chronic lymphocytic leukaemia, in combination with chemotherapy.

NOTE:
Not for use as monotherapy.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

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. The submission proposed that in the first line setting, rituximab would be added to fludarabine and cyclophosphamide (FC), chlorambucil, or cyclophosphamide, vincristine and prednisone (CVP) chemotherapy protocols, and in the relapsed/refractory setting to cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), CVP or FC chemotherapy protocols.

6. Comparator

The re-submission nominated chemotherapy alone (fludarabine plus cyclophosphamide) as the comparator. This was previously accepted by the PBAC.

The re-submission also presented the results of a sensitivity analysis to assess the incremental cost-effectiveness of the addition of rituximab to chlorambucil compared with chlorambucil alone.

7. Clinical Trials

The submission presented two randomised trials (CLL-8 and REACH) comparing the combination of rituximab with fludarabine and cyclophosphamide (R-FC) with fludarabine plus cyclophosphamide (FC) in patients with CLL. This was unchanged from the previous submission.

Citations for CLL-8 and REACH have been previously reported in the March 2010 Public Summary Document.

8. Results of Trials

Results from the trials have been previously reported in the March 2010 Public Summary Document.

The PBAC accepted that the combination of fludarabine with cyclophosphamide is the most effective chemotherapy for the treatment of CLL and that chlorambucil is less effective compared with FC by a factor of two (based on data from Catovsky et al. *Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): a randomised controlled trial,* Lancet 2007; 370: 230–39.

The PBAC considered that rituximab has benefits when used in combination with other chemotherapy but the magnitude and durability of such benefits were uncertain.

No new toxicity data were presented in the submission, with the exception of the additional note about the increased risk of progressive multifocal leukoencephalopathy (PML) with rituximab use reported in the latest Product Information.

At the March 2010 meeting, the PBAC agreed that rituximab was more toxic than chemotherapy alone and this was supported by the clinical evidence which demonstrated that there was increased neutropenia and febrile neutropenia. Significantly more Grade 3 and 4 adverse events occurred with the addition of rituximab in both key trials. Neutropenia, febrile neutropenia, and leucopenia were key drivers of safety concerns with rituximab and might affect patient quality of life.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The re-submission claimed that rituximab is more effective and more toxic than the comparator of chemotherapy alone.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The modelled economic evaluation presented at the March 2010 meeting, was a five-step process and remained unchanged in the re-submission.

The incremental cost per QALY gained in the base case was between $15,000 and $45,000 for the R-FC combination.

A sensitivity analysis assessed the incremental cost-effectiveness for combination R-FC of a patient entry age of 60 versus 70 years, assuming a continuing benefit of rituximab over the 10-year period. The incremental cost effectiveness ratio (ICER) for combination R-FC using a starting age of 60 years and a 15-year time horizon was in the range of between $15,000 and $45,000 per QALY (effect of rituximab maintained) to between $45,000 and $75,000 per QALY (progression curves converge rapidly).

A sensitivity analysis was conducted to assess the incremental cost-effectiveness of the addition of rituximab to chlorambucil compared to chlorambucil alone. The re-submission doubled the rate of progression (Catovsky et al) and with an increased patient age of 70, a time horizon of 15 years and continued benefit with rituximab, the cost-effectiveness in this setting was estimated to be in the range of $45,000 to $75,000 per QALY (base case analysis).

For the scenario of rituximab used in combination with chlorambucil and a starting age of 70 years, a 10 year time horizon and durability of benefit which tapered to control group over five years after year five, a rapid convergence of time unprogressed curves beyond 5 years and a doubled baseline rate of progression, the base case ICER was estimated to be in the range of $45,000 to $75,000 per QALY. With convergence of the time unprogressed and overall survival beyond 5 years, the base case ICER was estimated to be in the range of $75,000 to $105,000 per QALY.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the re-submission to be less than 10,000 (including first-line and relapsed patients) in year 5 after listing. This is unchanged from the previous submission.

The re-submission estimated the net financial cost per year to the PBS as a result of the listing to be in the range of $10 to $30 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended the listing of rituximab in combination with fludarabine and cyclophosphamide (R-FC) on the PBS as an Authority Required listing and in the Section 100 Chemotherapy Pharmaceuticals Access Program (CPAP) for CD20 positive, chronic

lymphocytic leukaemia on the basis of a high but acceptable cost-effectiveness ratio compared with FC.

The PBAC agreed that the NOTE stating that rituximab is not PBS-subsidised for monotherapy was appropriate and should be included.

The PBAC noted that no new clinical trial data were presented. However, the PBAC previously agreed in March 2010 that the outcome of progression-free survival (PFS) measured in the CLL-8 and REACH trials concurred with the clinical claim of superiority. Further, as for the PFS data, combining the overall survival (OS) data from trials CLL-8 and REACH was reasonable as there was no significant heterogeneity in this analysis and that it was reasonable to assume that treatment with rituximab would improve survival.

The PBAC agreed that for combination R-FC, a starting age of 60 years and a 15-year time horizon was appropriate in the economic model and that the ICER was most likely in the range of between $15,000 and $45,000 per QALY (effect of rituximab maintained) to between $45,000 and $75,000 per QALY (progression curves converged rapidly, which was considered by the PBAC to be high, but acceptably cost-effective.

The PBAC accepted that the combination of fludarabine with cyclophosphamide is the most effective chemotherapy for the treatment of CLL and that chlorambucil is less effective compared with FC by a factor of two (based on the data from Catovsky et al). The PBAC considered that if the PBS listing of rituximab was restricted to use with FC alone, there may be toxicity issues with use of this combination in the elderly and that there may be potential for leakage to use in combination with other chemotherapy despite being restricted to use with FC alone.

The PBAC considered that rituximab has benefits when used in combination with other chemotherapy but the magnitude and durability of such benefits were uncertain. The PBAC noted that a sensitivity analysis was conducted in the re-submission to assess the incremental cost-effectiveness of the addition of rituximab to chlorambucil compared chlorambucil alone. The re-submission doubled the rate of progression (Catovsky et al) and with an increased patient age of 70, a time horizon of 15 years and continued benefit with rituximab, the cost-effectiveness in this setting was estimated to be in the range of $45,000 to $75,000 per QALY (base case analysis).

However, the PBAC considered that the most plausible scenario analysis when rituximab is used in combination with chlorambucil was age 70 years, a 10 year time horizon and durability of benefit which tapered to control group over five years after year five. With those inputs, a rapid convergence of time unprogressed curves beyond 5 years and a doubled baseline rate of progression, the base case ICER was estimated to be in the range of $45,000 to $75,000 per QALY. With convergence of the time unprogressed and overall survival beyond 5 years, the base case ICER was estimated to be in the range of $75,000 to $105,000 per QALY. The PBAC concluded that the combination of rituximab with chlorambucil/other chemotherapy was not cost-effective unless the ICER for the combination with non-FC chemotherapy was in the same range as the ICER for R-FC. The PBAC noted that it may be prepared to consider the matter out of session should the ICER for combination with non-FC chemotherapy be reduced to within this range and would consider recommending the restriction be changed to allow use of rituximab “in combination with chemotherapy”.

The PBAC did not recommend rituximab for inclusion in the list of PBS medicines for prescribing by nurse practitioners as chemotherapy agents are excluded.

Further out-of-session PBAC consideration:
Further to the November 2010 PBAC recommendation for PBS listing of rituximab in combination with fludarabine and cyclophosphamide (R-FC), the PBAC recommended out-of-session the listing of rituximab in combination with non-FC chemotherapy on the PBS on the basis of a high but acceptable cost-effectiveness ratio. The PBAC recommended an Authority Required listing and listing in the Section 100 Chemotherapy Pharmaceuticals Access Program (CPAP) for CD20 positive, chronic lymphocytic leukaemia in combination with chemotherapy.

The PBAC noted the alternative proposal provided by the sponsor out-of-session for the use of rituximab in combination with non-FC chemotherapy, which resulted in ICERs in the same range as the ICERs for R-FC.

Recommendation:
RITUXIMAB, solution for I.V. infusion, 100 mg in 10mL and 500 mg in 50mL, Mabthera®

Extend the current restriction to include:

Restriction:	Authority Required CD20 positive, chronic lymphocytic leukaemia, in combination with chemotherapy. NOTE: Rituximab is not PBS-subsidised for use as monotherapy.
Maximum quantity:	2
Repeats:	5

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.