Public Summary Document

Product:	Rituximab, solution for I.V. infusion, 100 mg in 10 mL and 500 mg in 50 mL, Mabthera®,
Sponsor:	Roche Products Pty Ltd
Date of PBAC Consideration:	March 2006

1. Purpose of Application

The submission sought an extension to the current Pharmaceutical Benefits Scheme (PBS) authority restriction to include symptomatic patients with previously untreated, CD20 positive, Stage III or IV, follicular, B-cell non-Hodgkin's lymphoma, in combination with chemotherapy.

2. Background

Rituximab is currently listed on the PBS as an authority required benefit 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.

At the March 2005 meeting, the Pharmaceutical Benefits Advisory Committee (PBAC) rejected a submission to extend the PBS indications to include the treatment of previously untreated patients with CD20 positive, follicular B-cell non-Hodgkin's lymphoma, in combination with chemotherapy, because of uncertain clinical benefit based largely on differences in events of doubtful clinical importance and the resulting uncertain cost-effectiveness including in the context of doubling the amount and cost of therapy in the first-line setting compared to the second-line setting.

3. Registration Status

Rituximab was registered on 6 October 1998 for treatment of patients with relapsed or refractory low grade or follicular, CD20 positive, B-cell non Hodgkin's lymphoma. In April 2004, rituximab was approved for registration for the treatment of CD positive, diffuse large B-cell non-Hodgkin's lymphoma, in combination with chemotherapy.

Rituximab was registered on 18 January 2005 for the additional indication for the treatment of CD20 positive, previously untreated, stage III/IV, follicular, B-cell non-Hodgkin's lymphoma, in combination with chemotherapy.

4. Listing Requested and PBAC's View

In this submission the sponsor proposed a more targeted patient population than in the submission considered at the March 2005 meeting, as follows:

<u>Authority required</u>

Treatment of symptomatic patients with previously untreated, CD20 positive, Stage III or IV, follicular, B-cell non-Hodgkin's lymphoma, in combination with chemotherapy.

The PBAC was of the view that points raised by the PBAC in the previous submission regarding the restriction for the extension to the current listing when used in combination with chemotherapy had been addressed adequately in the current submission.

5. Clinical Place for the Proposed Therapy

In previously untreated follicular non-Hodgkin's lymphoma, approximately 80% to 90% of patients present with advanced-stage disease, defined as Ann-Arbor Stage III or IV. These patients are responsive to chemotherapy, however most patients are not cured and show a continuous pattern of relapse and eventual disease-related death. This chronic disease is characterised by use of multiple salvage therapies after relapse and a median survival of 8 to 10 years.

6. Comparator

The submission nominated placebo in combination with chemotherapy (CVP) as the main comparator.

The submission argued that CVP was representative of all chemotherapies in this submission as rituximab was added to a wide range of chemotherapies in this patient population and regardless of the chemotherapy used, the addition of rituximab led to significant clinical benefits.

C = Cyclophosphamide 750 mg/m^2 day 1
V = Vincristine 1.4 mg/m^2 (maximum of 2 mg/day) day 1
P = Prednisolone 40 mg/m^2 days 1-5

However, the resubmission also compared the treatment algorithm for patients initiating treatment with rituximab plus CVP, with the current clinical practice algorithm for an "average" patient with follicular lymphoma in a second modelled evaluation.

7. Clinical Trials

The submission presented study M39021 as the key clinical evidence. This was a multicentre, randomised, parallel-group, phase III trial, which compared rituximab combined with CVP (R-CVP) with CVP alone in 321 patients with previously untreated stage III/IV follicular non-Hodgkin's lymphoma.

Patients were treated every three weeks for 8 cycles of CVP. Patients treated with R-CVP also received rituximab 375 mg/m^2 on day 1 of each of the 8 cycles of CVP. The submission reported an efficacy analysis that was conducted at a median follow-up of 42 months for all randomised patients.

The submission also presented three supportive trials.

All four studies had been published at the time of submission, as follows:

Trial/First author	Protocol/Publication title	Publication citation
Key trial		
Marcus R et al	CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma.	Blood 105 (4):1417-23
Supporting trials		
Herold et al (2004)	Results of a prospective, randomized, open-label, phase III study comparing rituximab plus mitoxantrone, chlorambucil, prednisolone chemotherapy (R-MCP) versus MCP alone in untreated advanced indolent non-Hodgkin's lymphoma and mantle cell lymphoma	Blood 2004; 104: abstract 584 American Society of Hematology (ASH) Annual Meeting Abstracts
Hiddemann et al (2005)	Front-line therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) significantly improves outcome of patients with advanced stage follicular lymphomas as compared to CHOP alone – results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG).	Blood 2005; (pre published online August 25, 2005; doi 10.1182/blood-2005-01-0016).
Salles et al (2004)	Rituximab added to IFNα + CHVP improves the outcome of follicular lymphoma patients with a high tumor burden: first analysis of the GELA-GOELAMS FL-2000 randomized trial in 359 patients.	American Society of Haematology Meeting 2004 (poster and abstract 160).

8. Results of Trials

The 42-month analysis of trial M39021 reported statistically significant differences in time to treatment failure (TTF) and time to progression, relapse or death (TTP) favouring R-CVP over CVP. However, the overall difference in survival was non-significant (p=0.0553) although the trend favoured R-CVP (and the confidence intervals around point estimates of difference in survival were narrowing compared to earlier analyses). The following are the mean time results reported:

Results from 42-month analysis of trial M39021

	CVP (N=159)	R-CVP (N=162)
Time to treatment failure (TTF)		
Mean time (in years) to event: Truncated 42-month analysis ± standard error (95% CI)[Φ]	1.05 ± 0.09 (0.87, 1.23)	2.38 ± 0.13 (2.13, 2.63)
Risk difference (years)[∞] (95% CI)	**1.33 (1.02, 1.64)**[Ψ]	
Time to progression, relapse or death (TTP)		
Mean time (in years) to event: Truncated 42-month analysis ± standard error (95% CI)[Φ]	1.77 ± 0.11 (1.55, 1.99)	2.76 ± 0.12 (2.52, 3.00)
Risk difference (years)[∞] (95% CI)	**0.99 (0.67, 1.31)**[Ψ]	
Overall survival		
Mean time (in years) to event: Truncated 42-month analysis ± standard error	4.21 ± 0.11	4.49 ± 0.08
Risk difference (years)[∞], p-value^	0.28, 0.0553	

[∞] R-CVP group minus CVP group
^ Based on log rank test
[Φ] For each treatment group, the lower and upper 95% CL were calculated by adding and subtracting respectively 1.96 × standard error of the Kaplan-Meier probability estimate to its point estimate
[Ψ] The 95% CI was estimated as point estimate ± 1.96 × standard error of the difference (SE_{diff}) whereby SE_{diff} is the square root of the sum of squared standard errors from each treatment groups.

The toxicity profile of rituximab remained unchanged from the previous submission. In that submission, the comparative toxicity was based on data from the 18-month analysis. R-CVP patients reported a higher incidence of neutropenia and infusion-related toxicities than CVP

patients. No new unexpected adverse events were reported in the updated 42 month analysis. of trial M39021. Infusion-related adverse events, which occurred within 24 hours of the infusion of treatment, were higher in R-CVP patients (71%) than CVP patients (51%).

9. Clinical Claim

The submission claimed that rituximab in combination with chemotherapy had significant advantages in effectiveness over chemotherapy alone, but had more toxicity.

The PBAC noted that although there is a trend in support of rituximab from the available results of trial M39021, only the first 42 months of survival data from this 20 year program is currently available.

10. Economic Analysis

The submission presented two preliminary economic evaluations, both of which were cost-effectiveness analyses. The first analysis used median values and the second used mean values for event-free survival, progression-free survival and overall survival estimates from the 42 month analysis of Study M39021.

For the median time-to-event data, the discounted cost-effectiveness ratio for R-CVP was estimated to be <$15,000 per event-free year gained and to fall in the range $15,000 - $45,000 per progression-free year gained. As median overall survival had not been reached in either treatment arm, a cost-effectiveness ratio using this as a denominator could not be calculated. For the mean time-to-event data, the discounted cost-effectiveness ratios for R-CVP per event-free year gained and per progression-free year gained were in the range $15,000 - $45,000 and in the range $105,000 - $150,000 per life-year gained.

Two modelled evaluations were presented. Model A extrapolated the survival curves from study M39021 over a 20-year time period to estimate the incremental cost-effectiveness of R-CVP compared with CVP, in terms of cost per life-year gained. Model B assessed the impact of first-line treatment with R-CVP versus CVP on the usage and efficacy of subsequent salvage therapy regimens. The incremental cost-effectiveness ratios predicted by both models fell in the range $15,000 - $45,000 per life year gained and for Model B only, per quality adjusted life-year (QALY) gained.

11. Estimated PBS Usage and Financial Implications

The submission estimated the number of patients with follicular lymphoma treated with rituximab as first-line therapy to be <2,000 in year 4 of listing at a cost to the PBS of $30- $40 million. However, when total health care expenditure was considered, the listing of rituximab was expected to result in savings of >$5 million in year 4 of listing.

12. Recommendation and Reasons

The PBAC recommended extension to the current listing on a cost-effectiveness basis as compared to placebo when used in combination with chemotherapy, noting that points raised by the PBAC in the previous submission, had been addressed adequately in the current submission.

The only outstanding issue relates to survival gain. The PBAC noted that although there is trend in support of rituximab therapy from the available results of trial M39021, only the first

42 months worth of survival data from this 20 year program is currently available. The Committee therefore requested that the sponsor be approached to provide annual updates on survival as they become available, with a view to reviewing the cost-effectiveness on an ongoing basis. In the event that there is a deterioration in the cost-effectiveness of this treatment, a number of options would be available to government including seeking a price reduction.

Recommendation
Add to restriction:

Restriction	Authority required Treatment of symptomatic patients with previously untreated, CD20 positive, Stage III or IV, follicular, B-cell non-Hodgkin's lymphoma, in combination with chemotherapy.
Maximum Quantity	2 (100mg), 1 (500 mg)
Repeats	7 (both strengths)

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

No further comment.