6.07 RITUXIMAB injection for infusion, 500mg/50mL; Mabthera®, Roche Products Pty Ltd.

The March 2015 rituximab Public Summary Document is reproduced below with the addition of an 'ADDENDUM' at the end of the document to convey the July 2015 PBAC consideration.

1 Purpose of Application

1.1 The submission sought Section 100 Authority Required listing for rituximab for remission induction in patients with severe active granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).

2 Requested listing

2.1 The requested listing is outlined below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
RITUXIMAB 500 mg/50 mL injection, 1 x 50 mL vial	2	1	Private ($4,112.58) Public ($4,065.82)	Mabthera RO

Category / Program	Section 100 – Highly Specialised Drugs Program (Public/Private)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Granulomatosis with polyangiitis (GPA/*Wegener's granulomatosis*) ~~also known as Wegener's granulomatosis~~ or microscopic polyangiitis (MPA)~~) according to the Chapel Hill Consensus Conference Nomenclature of the Vasculitides with ANCA-positive serology~~.
PBS Indication:	Granulomatosis with polyangiitis (GPA/*Wegener's granulomatosis*) or microscopic polyangiitis (MPA)
Treatment phase:	Induction of remission
Restriction Level / Method:	☒Authority Required - In Writing
Clinical criteria:	The treatment must be for the induction of remission ~~(NOT maintenance of remission)~~; AND The treatment must be in combination with glucocorticoids; AND Patient must have severe active GPA with risk of end-organ damage or mortality

	~~such as~~ • ~~Glomerulonephritis with risk of progression~~ • ~~Risk to sight including scleritis/episcleritis, sudden visual loss, uveitis, retinal changes (vasculitis/thrombosis/exudates/haemorrhage)~~ • ~~Bronchial/subglottic obstruction~~ • ~~Pulmonary haemorrhage~~ • ~~Parenchymal lung disease~~ • ~~Sensory neural hearing loss~~ • ~~Recurrent sinonasal disease requiring recurrent surgical interventions~~ • ~~Meningitis, organic confusion, seizures, stroke, cord lesion, cranial nerve palsy, sensory peripheral neuropathy, motor mononeuritis multiplex~~ AND Patients must be ~~contradicted or refractory~~ *unable* to *use* cyclophosphamide
Definitions	*Risk of end-organ damage or mortality is defined as:* • *Glomerulonephritis with risk of progression* • *Risk to sight including scleritis/episcleritis, sudden visual loss, uveitis, retinal changes (vasculitis/thrombosis/exudates/haemorrhage)* • *Bronchial/subglottic obstruction* • *Pulmonary haemorrhage* • *Parenchymal lung disease* • *Sensory neural hearing loss* • *Recurrent sinonasal disease requiring recurrent surgical interventions* • *Meningitis, organic confusion, seizures, stroke, cord lesion, cranial nerve palsy, sensory peripheral neuropathy, motor mononeuritis multiplex*
Prescriber Instructions	*1. Diagnosis should be made according to the Chapel Hill Consensus Conference Nomenclature of the Vasculitides with ANCA positive serology.* *2.Patients are considered unable to use cyclophosphamide for the following reasons:* • *Cyclophosphamide is contraindicated as per the approved Australian Product Information;* *OR* • *Cyclophosphamide is not recommended due to the need to preserve gonad function;* *OR* • *Patient experiences severe toxicity to cyclophosphamide that warrants cessation of treatment;* *OR* • *Patient has life- or organ-threatening deterioration at any time during treatment with cyclophosphamide, where the deterioration is thought to be due to severe uncontrolled active vasculitis;* *OR* • *Commencing a further treatment cycle with cyclophosphamide would exceed the maximum cumulative dose of cyclophosphamide of 25g;* *OR* • *Patient has persistent severe active GPA despite at least 3 months therapy with cyclophosphamide.*
Administrative Advice	*Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).*

	Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au *Written applications for authority to prescribe should be forwarded to:* *Department of Human Services* *Prior Written Approval of Complex Drugs* *Reply Paid 9826* *GPO Box 9826* *HOBART TAS 7001* *Increased maximum quantities and/or repeats should be based on a dosing regimen of 375mg per meter squared once weekly to provide sufficient supply for 4 weeks treatment.* ~~*A patient may only qualify for PBS-subsidised treatment under this restriction once in a lifetime.*~~

2.2 The Pre-Sub-Committee Response (PSCR) stated that given the relapsing-remitting nature of the diseases, rituximab use should not be restricted to once per lifetime. The ESC and DUSC both agreed that use should not be limited to once per lifetime in patients who successfully achieve an initial response and remission, noting additional clinical evidence to support retreatment provided in the PSCR.

2.3 The submission sought PBS listing on the basis of a cost analysis compared with cyclophosphamide (CYC) and salvage therapies.

2.4 The requested restriction is for a fixed dosing regimen of rituximab of either 500mg administered every 2 weeks, 500mg administered every week, or 1g administered every 2 weeks, instead of the TGA-approved weight-based dosing that was used in the pivotal clinical trial.

2.5 The DUSC considered there is potential for use beyond the requested restriction, particularly in interpretation of the restriction criterion where CYC is not recommended. The DUSC considered there may be clinician and/ or patient preference to use rituximab over CYC and that this criterion may be used to gain access for a variety of patients. The DUSC also considered there is potential for use in maintenance treatment, in milder forms of GPA and MPA and for other forms of ANCA-associated vasculitis (AAV).

2.6 The PBAC noted that the submission proposed an Authority Required listing under the Section 100 Highly Specialised Drugs Program with applications made in writing. The PBAC considered that a written authority might reduce the potential for use of rituximab outside the listing requested.

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

3.1 TGA status: Rituximab was TGA registered on 13 May 2013 for the induction of remission in patients with severely active GPA also known as Wegener's granulomatosis, and MPA, in conjunction with glucocorticoids.

3.2 Rituximab is currently PBS-listed for non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, and rheumatoid arthritis. It has not been considered for the treatment of GPA/MPA by the PBAC previously.

4 Clinical place for the proposed therapy

4.1 ANCA-associated vasculitis (AAV) is a potentially life-threatening disease where the body's immune system causes inflammation of the blood vessels, depriving affected tissues and organs of blood supply. Rituximab is proposed for use for patients with two severe forms of AAV, GPA and MPA. Listing is requested for remission induction in those patients who are contraindicated or refractory to CYC. The ESC noted the rare and fatal nature of these diseases and that there is a genuine clinical need for alternatives in the treatment of these conditions.

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

5.1 Cyclophosphamide was nominated as the comparator for patients with relative contraindications to cyclophosphamide (i.e. patients who need preservation of gonad function, patients who are close to the maximum cumulative dose of CYC of 25g, and patients for whom CYC is contraindicated as per the Approved Product Information but for whom the need to treat outweighs the risk). The evaluation considered that CYC may be an appropriate comparator for patients where the need to treat with CYC outweighs the risk. However, for patients who are close to the maximum cumulative dose of CYC, and in whom starting another cycle would push them over this limit, the evaluation considered that intravenous immunoglobulin (IVIg) may be a more appropriate comparator.

5.2 Salvage therapies (IVIg, mycophenolate mofetil (MMF), anti-thymocyte globulin (ATG) and alemtuzumab) were nominated as comparators for patients strictly contraindicated to or refractory to treatment with CYC: that is, patients with persistent severe active GPA or MPA despite at least 3 months treatment with CYC; patients who experience severe toxicity from CYC that warrants cessation of treatment; patients who have life- or organ- threatening deterioration at any time during treatment with CYC where deterioration is thought to be due to severe uncontrolled active vasculitis; and patients where CYC is strictly contraindicated according to the TGA-approved Product Information. The evaluation considered that salvage therapies are an appropriate comparator for this group of patients. Other salvage therapies that are used, which may also be appropriate comparators include chlorambucil, and etoposide, with or without plasma exchange. Based on the advice of the sponsor's Advisory Board, CYC may also be an appropriate comparator for this group of patients.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (6) and health care professionals (6) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with rituximab for GPA/MPA including fast and effective disease remission, the opportunity to avoid use of cyclophosphamide with associated risks, and improved quality of life.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Clinical trials

6.3 The submission was based on one head-to-head trial (RAVE) comparing rituximab to CYC (n=197) and 35 supplementary studies, the majority of which were single arm studies, retrospective reviews or case series, and did not directly compare rituximab with the salvage therapies.

6.4 Details of the trials and studies presented in the submission are provided in the table below.

Trials and associated reports for the analysis of rituximab vs. CYC for patients relatively contraindicated to CYC

Trial ID/First author	Protocol title/ Publication title	Publication citation
Direct randomised trial		
(RAVE) ITN021AI	Rituximab therapy for the induction of remission and tolerance in ANCA-associated vasculitis. National Institute of Allergy and Infectious Diseases. Report Date 14 October 2010 (Data cut-off 9 January 2009). Pages 1-239.	14 October 2010
	Stone JH, Merkel PA, Spiera R et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis.	*NEJM* 2010; 363 (3):p221-232
	Specks U, Merkel PA, Hoffman GS et al. Design of the rituximab in ANCA-associated vasculitis (RAVE) trial.	*Open Arthritis Journal* 2011; 4 (1):1-18
	Specks U, Merkel PA, Seo P et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis.	*NEJM* 2013; 369 (5):417-427
	Miloslavsky EM, Specks U, Merkel PA et al. Clinical outcomes of remission induction therapy for severe anti-neutrophil cytoplasmic antibody-associated vasculitis	*Arthritis and Rheumatism* 2013; 65 (9):2441-2449
	Miloslavsky EM, Specks U, Merkel PA et al. Rituximab for the treatment of relapses in ANCA-associated vasculitis.	*Arthritis and Rheumatism* 2014; accepted 15 July 2014
Supplementary studies		
Rituximab		

Trial ID/First author	Protocol title/ Publication title	Publication citation
Aries	Aries PM, Hellmich B, Voswinkel J et al. Lack of efficacy of rituximab in Wegener's granulomatosis with refractory granulomatous manifestations	*Annals of the Rheumatic Diseases*. 2006;65(7):853-58
Brihaye	Brihaye B, Aouba A, Pagnoux C et al. Adjunction of rituximab to steroids and immunosuppressants for refractory/relapsing Wegener's granulomatosis: A study on 8 patients	*Clinical and Experimental Rheumatology*. 2007;25(1 SUPPL. 44):S23-S27
Calich	Calich AL, Puechal X, Pugnet G et al. Rituximab for induction and maintenance therapy in granulomatosis with polyangiitis (Wegener's). Results of a single-center cohort study on 66 patients	*Journal of Autoimmunity. 2014;50:135-41*
Cartin-Ceba	Cartin-Ceba R, Golbin JM, Keogh KA et al. Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener's): Ten-year experience at a single center	*Arthritis and Rheumatism. 2012;64(11):3770-78*
Charles	Charles P, Neel A, Tieulie N et al. Rituximab as induction and maintenance therapies for anca-associated vasculitis: A multicenter retrospective study on 80 patients	*Arthritis and Rheumatism. 2012;64:S1004*
Erikkson	Eriksson P. Nine patients with anti-neutrophil cytoplasmic antibody-positive vasculitis successfully treated with rituximab. *Journal of Internal Medicine.* 2005;257(6):540-48	Eriksson P. Nine patients with anti-neutrophil cytoplasmic antibody-positive vasculitis successfully treated with rituximab. *Journal of Internal Medicine.* 2005;257(6):540-48
Gregersen	Gregersen JW, Chaudhry A, Jayne DR. Rituximab for ANCA-associated vasculitis in the setting of severe infection	*Scandinavian journal of rheumatology. 2013;42(3):207-10*
Henes	Henes JC, Kanz L, Koetter I. Rituximab and leflunomide for Wegener's granulomatosis: A long-term follow-up	*Rheumatology International. 2011;31(3):425-26*
Holle	Holle JU, Dubrau C, Herlyn K et al. Rituximab for refractory granulomatosis with polyangiitis (Wegener's granulomatosis): Comparison of efficacy in granulomatous versus vasculitic manifestations	*Annals of the Rheumatic Diseases. 2012;71(3):327-33*
Jones	Jones RB, Ferraro AJ, Chaudhry AN et al. A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis and Rheumatism.* 2009;60(7):2156-68.	*Arthritis and Rheumatism.* 2009;60(7):2156-68.
Joshi	Joshi L, Lightman SL, Salama AD et al. Rituximab in refractory ophthalmic Wegener's granulomatosis: PR3 titers may predict relapse, but repeat treatment can be effective	*Ophthalmology. 2011;118(12):2498-503*
Keogh	Keogh KA, Wylam ME, Stone JH et al. Induction of remission by B lymphocyte depletion in eleven patients with refractory antineutrophil cytoplasmic antibody-associated vasculiti	*Arthritis and Rheumatism*. 2005;52(1):262-68
Keogh	Keogh KA, Ytterberg SR, Fervenza FC et al. Rituximab for refractory Wegener's granulomatosis: Report of a prospective, open-label pilot trial	*American Journal of Respiratory and Critical Care Medicine*. 2006;173(2):180-87
Lovric	Lovric S, Erdbruegger U, Kumpers P et al. Rituximab as rescue therapy in anti-neutrophil cytoplasmic antibody-associated vasculitis: A single-centre experience with 15 patients	*Nephrology Dialysis Transplantation*. 2009;24(1):179-85
Martinez Del Pero	Martinez Del Pero M, Chaudhry A, Jones RB et al. B-cell depletion with rituximab for refractory head and neck	*Clinical Otolaryngology. 2009;34(4):328-35*

Trial ID/First author	Protocol title/ Publication title	Publication citation
	Wegener's granulomatosis: A cohort study	
Omdal	Omdal R, Wildhagen K, Hansen T et al. Anti-CD20 therapy of treatment-resistant Wegener's granulomatosis: favourable but temporary response	*Scandinavian Journal of Rheumatology* 2005;34:229-32.
Rees	Rees F, Yazdani R, Lanyon P. Long-term follow-up of different refractory systemic vasculitides treated with rituximab	*Clinical Rheumatology*. 2011;30(9):1241-45
Roccatello	Roccatello D, Baldovino S, Alpa M et al. Effects of anti-CD20 monoclonal antibody as a rescue treatment for ANCA-associated idiopathic systemic vasculitis with or without overt renal involvement Roccatello D, Sciascia S, Rossi D et al. Long-term effects of rituximab added to cyclophosphamide in refractory patients with vasculitis	*Clinical and Experimental Rheumatology*. 2008;26(3 SUPPL. 49):S67-S71 *American Journal of Nephrology*. 2011;34(2):175-80
Roll	Roll P, Ostermeier E, Haubitz M et al. Efficacy and safety of rituximab treatment in patients with antineutrophil cytoplasmic antibody-associated vasculitides: Results from a German registry (GRAID)	*Journal of Rheumatology. 2012;39(11):2153-56*
Sanchez-Cano	Sanchez-Cano D, Callejas-Rubio JL, Ortego-Centeno N. Effect of rituximab on refractory Wegener granulomatosis with predominant granulomatous disease	*Journal of Clinical Rheumatology*. 2008;14(2):92-93
Seo	Seo P, Specks U, Keogh KA et al. Efficacy of rituximab in limited Wegener's granulomatosis with refractory granulomatous manifestations	*Journal of Rheumatology*. 2008;35(10):2017-23.
Smith	Smith KGC, Jones RB, Burns SM, Jayne DRW et al. Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: Remission, relapse, and re-treatment	*Arthritis and Rheumatism*. 2006;54(9):2970-82.
Taylor	Taylor SRJ, Salama AD, Joshi L et al. Rituximab is effective in the treatment of refractory ophthalmic Wegener's granulomatosis	*Arthritis and Rheumatism. 2009;60(5):1540-47*
Stasi	Stasi R, Stipa E, Del Poeta G et al. Long-term observation of patients with anti-neutrophil cytoplasmic antibody-associated vasculitis treated with rituximab	*Rheumatology*. 2006;45(11):1432-36
Wendt	Wendt M, Gunnarsson I, Bratt J et al. Rituximab in relapsing or refractory ANCA-associated vasculitis: A case series of 16 patients Wendt M, Gunnarsson I, Bratt J, Bruchfeld A. Rituximab in ANCA-associated Vasculitis (AAV), a case series	*Scandinavian Journal of Rheumatology*. 2012;41(2):116-19 *APMIS. 2009;117:80*
Alemtuzumab		
Walsh	Walsh M, Chaudhry A, Jayne D. Long-term follow-up of relapsing/refractory anti-neutrophil cytoplasm antibody associated vasculitis treated with the lymphocyte depleting antibody alemtuzumab (CAMPATH-1H)	*Annals of the Rheumatic Diseases.* 2008;67(9):1322-27
Anti-thymocyte globulin		
Schmitt	Schmitt W, Hagen E, Neumann I et al. Treatment of refractory Wegener's granulomatosis with antithymocyte globulin (ATG): An open study in 15 patients	*Kidney International*. 2004; 65(4):1440-48
Intravenous immunoglobulin		
Jayne	Jayne, DR, Davies, MJ, Fox, CJ, et al. Treatment of systemic vasculitis with pooled intravenous immunoglobulin	*Lancet*. 1991; 337(8750):1137–39

Trial ID/First author	Protocol title/ Publication title	Publication citation
Jayne	Jayne DRW, Chapel H, Adu D et al. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity	*QJM - Monthly Journal of the Association of Physicians.* 2000;93(7):433-39
Kamali	Kamali S, Cefle A, Sayarlioglu M et al. Experience with monthly, high-dose, intravenous immunoglobulin therapy in patients with different connective tissue diseases	*Rheumatology International*. 2005;25(3):211-14
Martinez	Martinez V, Cohen P, Pagnoux C et al. Intravenous immunoglobulins for relapses of systemic vasculitides associated with antineutrophil cytoplasmic autoantibodies: Results of a multicenter, prospective, open-label study of twenty-two patients	*Arthritis and Rheumatism.* 2008; 58(1):308-17
Richter	Richter C, Schnabel A, Csernok E et al. Treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis with high-dose intravenous immunoglobulin	*Clinical and Experimental Immunology.* 1995;101(1):2-7
Mycophenolate mofetil		
Kazderova	Kazderova M, Jancova E, Rysava R et al. Mycophenolate Mofetil in Low Doses Stabilizes and Improves Antineutrophil Cytoplasmic Antibody-associated Vasculitis and Lupus Nephritis	*Archives of Medical Research*. 2008; 39(1):115-19
Silva	Silva F, Specks U, Kalra S et al. Mycophenolate mofetil for induction and maintenance of remission in microscopic polyangiitis with mild to moderate renal involvement - A prospective, open-label pilot trial	*Clinical Journal of the American Society of Nephrology.* 2010;5(3):445-53
Stassen	Stassen P, Tervaert J, Stegeman CA. Induction of remission in active anti-neutrophil cytoplasmic antibody-associated vasculitis with mycophenolate mofetil in patients who cannot be treated with cyclophosphamide	*Annals of the Rheumatic Diseases*. 2007; 66(6):798-802

Source: Table B.2.3, p7-8, Section B-DRT of the submission and Table B.2.10x, p16-19 of Section B-Supp of the submission

6.5 The key features of the RAVE trial and the supplementary studies are summarised in the table below.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome
RAVE	197	R, DB, MC trial comparing rituximab and CYC 6 months	Low	Patients with severe active GPA or MPA; either newly diagnosed or with relapsing disease at baseline	Complete remission at 6 months
Salvage therapy comparison	35 studies 864 patients	Variety of designs, including RR, CS, SA, OL with one DB trial; durations varied from 6 months to 5 years	High	Severe active GPA/MPA refractory (or intolerant) to CYC, or in some cases new onset disease where CYC was contraindicated.	Varied: complete and partial remission, and relapse rates

Source: Compiled during the evaluation

Abbreviations: CS=case series; CYC=cyclophosphamide; DB=double blind; GPA=granulomatosis polyangiitis MPA=microscopic polyangiitis; MC=multi-centre; OL=open label; R=randomised; RR=retrospective review; SA=single arm

Comparative effectiveness

6.6 Results from the RAVE trial are presented in the table below. The results demonstrated a similar rate of complete remission for patients treated with rituximab

compared to CYC, supporting the clinical claim made in the submission that rituximab is non-inferior to CYC for patients relatively contraindicated to CYC. A sub-group analysis also showed that more patients with relapsing disease at baseline achieved complete remission with rituximab (67% for rituximab versus 42% for CYC, p=0.01).

Results of the RAVE trial

	Rituximab (n=99) n with event/N (%)	Cyclophosphamide (n=98) n with event/N (%)	Absolute difference (95% CI)	p-value
Complete remission at 6 months - ITT without worse case imputation*	63 (64.3%)	52 (54.7%)	9.5% (-4.3% to 23.4%)	0.18
Complete remission at 6 months – ITT with worse case imputation	63 (63.6%)	52 (53.1%)	10.6% (-3.2% to 24.3%)	0.13
Complete remission at 6 months in patients with relapsing disease at baseline - ITT	34/51 (67%)	21/50 (42%)	25% (5.8% to 44.2%)	0.01
Complete remission at 6 months in newly diagnosed patients - ITT	29/48 (60.4%)	31/48 (64.6%)	-4.2% (-23.6% to 15.3%)	0.67

Source: Table B.2.5, Table B.6.1, B.6.2, B.6.7, p12 and pp38-39 and p43 of Section B-DRT of the submission, CSR p146, p154, p174

Abbreviations: SD = standard deviation

Note: * For worst case imputation patients with missing values were deemed to have failed treatment. All ITT analyses assume worst case imputation apart from those designated ITT without worst case imputation

6.7 The submission presented a weighted average of the proportion of patients with remission across the 25 rituximab studies and the 10 comparator studies. Presentation of weighted average results across each group of studies was not appropriate since the outcomes reported and the patient populations in the studies were not comparable. The evaluation considered that the results do not allow any meaningful conclusions to be made.

6.8 The ESC considered that the clinical evidence submitted did not provide an estimate of the comparative effectiveness of rituximab against the salvage therapies for patients who are strictly contraindicated or refractory to treatment with CYC.

6.9 Further, the ESC considered that fixed dosing of rituximab may not be appropriate given the lack of comparative data to show that this is as effective as the higher TGA-approved weight-based dosing used in the comparative trial (RAVE).

Comparative harms

6.10 Based on the results of the RAVE trial, rituximab had a similar adverse event profile to CYC in the first 6 months of follow-up. A similar proportion of patients experienced any adverse event, any severe (grade 3 or above) adverse event and any serious adverse event. Rituximab and CYC are likely to have a comparable adverse event profile.

6.11 It was not possible to make a comparison of harms between rituximab and the salvage therapies (alemtuzumab, ATG, IVIg and MMF) based on the data provided.

Clinical claim

6.12 For patients relatively contraindicated to CYC, the submission described rituximab as non-inferior to CYC in terms of comparative effectiveness and comparable in terms of short to medium term safety. The evaluation considered that this claim was adequately supported. The ESC agreed that results of the RAVE trial indicate that rituximab is non-inferior to CYC in this patient population. The ESC considered that the submission's suggestion that rituximab is associated with better long-term safety than CYC, which forms the basis of the submission's use of a cost analysis, could not be substantiated.

6.13 For patients strictly contraindicated or refractory to CYC, the submission did not make a claim in terms of superior or similar efficacy and safety. Instead it stated that there is a large body of evidence to support efficacy and safety of rituximab compared to a small body of evidence to support the efficacy of the salvage therapies. The statement made by the submission did not constitute a clinical claim and the assessment of available evidence made by the submission did not provide an indication of the comparative efficacy and safety of rituximab versus the salvage therapies. While the submission acknowledged the limitations of the data, the methods applied were not adequate. Appropriate assessment of the available salvage therapy evidence, including use of the available rituximab meta-analysis (Mejia 2012[1]) as well as consideration of possible statistical analysis of data for the other salvage therapies may have been informative. The ESC considered that this additional data was unlikely to make a large impact on the assessment of the overall clinical claim being made.

6.14 The PBAC considered that the claim of non-inferior comparative effectiveness and safety of rituximab compared to cyclophosphamide is reasonable.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Economic analysis

6.15 The submission presented a cost analysis. The evaluation considered that a cost analysis was not appropriate for either the relatively contraindicated to CYC or strictly contraindicated to CYC patient groups. The ESC considered that it may have been appropriate to conduct separate economic analyses for the two patient groups (relatively contraindicated to CYC and strictly contraindicated to CYC).

6.16 The evaluation considered that a cost-minimisation analysis versus CYC would have been more appropriate for patients relatively contraindicated to CYC, However, since the administration costs of rituximab ($1,262) exceed the total cost of oral CYC ($608.90/91 day cycle) a cost-minimisation analysis is not feasible.

[1] Mejia C, Lozada CJ. Rituximab for ANCA-Associated Vasculitis: A Meta-Analysis of Randomized Trials. *Arthritis and Rheumatism* 2012; 64: S660-S660

6.17 The evaluation further considered that a cost effectiveness analysis would have been more appropriate for patients strictly contraindicated or refractory to CYC treatment, however there was inadequate evidence presented to determine comparative efficacy and safety versus salvage therapies.

6.18 The submission had made an error in its calculation of administration costs for CYC in the cost analysis. While the submission correctly applied 50% use for oral CYC and 50% use for IV CYC to calculate treatment costs, administration costs for IV use of CYC were applied to 100% of patients when it should only be applied to 50% of patients. Correcting this decreased administration costs from $4,283 to $2,142 and therefore increased the rituximab incremental cost to $5,941 compared to the $3,800 estimated by the submission. The table below provides the corrected CYC administration cost and resultant incremental cost versus rituximab. The submission applied ex-manufacturer costs to determine treatment costs of rituximab and IV CYC, which is appropriate.

Summary of incremental cost

Type of resource item	Rituximab^	CYC^	AMB*	ATG	IVIg*	MMF
Cost of treatment	$7,756	*$935*	$14,000	$33,210	$4,741	$1,659
Administration cost	$1,262	*$2,142***	$2,677	$5,354	$5,354	$0
Total cost	$9,018	*$3,077*	$16,677	$38,564	$10,094	$1,659
Incremental cost per induction	**-**	***$5,941***	**-$7,659**	**-$29,546**	**-$1,076**	**$7,359**

Source: Table D.2.1, p6 of Section D of the submission

Abbreviations: CYC = cyclophosphamide; ATG = anti-thymocyte globulin; AMB = alemtuzumab; IVIg = intravenous immunoglobulin; MMF = mycophenolate mofetil

^ 500mg ex-manufacturer cost of rituximab is $2,032.91; CYC 500mg $19.23, 1000mg $29.42, 2000mg $58.85, 170mg tablet $83.64 (DPMQ)

* The submission stated that the costs for alemtuzumab and IVIg were provided as commercial in confidence [redacted]. *The cost of these products could not be verified and given that drug costs may vary across hospitals, the costs used by the submission may not provide a precise representation of cost.*

** For CYC administration cost cell I20 of the 'results_cost analysis' worksheet had the following formula: =c_weighted_admin_CYC_IV*cyc_CYC_IV. The formula should be: =(c_weighted_admin_CYC_IV*cyc_CYC_IV)*pCYC_IV. Variable names are: c_weighted_admin_CYC_IV='Administration costs'!E20 which is $535.38; cyc_CYC_IV='General inputs'D50 which is 8 cycles; pCYC_IV='General inputs'D25 which is 50%.

6.19 Non-inferiority in the RAVE trial was established using doses of rituximab 375mg/m^2 once per week for 4 weeks over 6 months and oral CYC 2mg/kg/day for 3 months as opposed to the fixed dosing regimen used in the submission's cost analysis. An additional sensitivity analysis undertaken during the evaluation using weight-based rituximab dosing showed that the incremental cost per induction was most sensitive to this change, with the regimen of 375mg/m^2 once per week as recommended in the PI increasing the incremental cost per induction of rituximab by approximately $9,400 compared to each of the comparators.

6.20 The evaluation considered that appropriate assessment of the available salvage therapy evidence would have provided a basis on which to make a clinical claim for treatment of strictly contraindicated patients. Depending on the clinical claim made, i.e. superiority or non-inferiority, the type of economic evaluation to be used could then be determined. The evaluation noted that it may be feasible to consider cost per remission induction for the economic analysis. The PSCR provided the incremental

cost per complete remission at 6 months for relapsed patients from the RAVE trial. This is presented in the table below.

Incremental cost per complete remission at 6 months

	Rituximab	CYC
Proportion of patients with relapsed disease achieving complete remission at 6 months	66.7%	42.0%
Mean total cost per induction of remission	$9,018	$3,077
Incremental cost per additional complete response at 6 months	$24,086	

Source: PSCR Table 1, p5

6.21 The ESC agreed that a pragmatic approach for assessing value for money for rituximab in GPA and MPA may be reasonable due to the genuine clinical need and the lack of comparative data and considered it relevant to compare the price per milligram of rituximab requested for this indication to other PBS indications, noting the proposed listing is for 1g fixed dose regimen. Prices for PBS indications are shown in the table below. Note that the price requested in this submission is the current price for rituximab, which has been weighted across all of rituximab's listed indications.

Rituximab indication-specific pricing

Indication	Ex-man 500 mg	Ex-man 100 mg	Comment	Listing Date
Price requested for GPA and MPA	$2,032.91	-	This is the published ex-man price, which is weighted for the prices outlined below.[a]	
FNHL RR- induction	$	$	First indication listed	1-Feb-99
FNHL RR- maintenance	$	$		1-Dec-14
DLBCL previously untreated in combination with chemotherapy	$	$		1-Jul-03
DLBCL RR	$	$		Between Mar-06 and Mar-07 PBAC
CLL in combination with FC	$	$		1-Apr-12
CLL non-FC	$	$		1-Dec-14
FNHL previously untreated in combination with chemotherapy- induction	$	$		Considered Mar-06 PBAC
FNHL previously untreated in combination with chemotherapy- maintenance	$	$		1-Dec-14
Rheumatoid arthritis				1-Mar-08

Source: compiled by Department at request of ESC

[a]Price is current as of 1 December 2014, at which time a was applied.

GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; FNHL = follicular B-cell non-Hodgkin's lymphoma; RR = relapsed or refractory; DLBCL = diffuse large B-cell non-Hodgkin's lymphoma; CLL = chronic lymphocytic leukaemia; FC = fludarabine and cyclophosphamide; bDMARD = biological disease-modifying anti-rheumatic drug.

6.22 The ESC noted that a Markov model for rituximab in GPA/MPA was presented to NICE but agreed with the PSCR that a cost-effectiveness model is unlikely to be informative for PBAC decision-making in this instance because of the lack of comparative data for most of the patient subgroups in the proposed PBS restriction.

Drug cost/patient/course: $7,756

6.23 The drug cost was based on fixed dosing. If weight-based dosing is used by clinicians the cost of rituximab will be substantially higher, at $15,390 per 4-week course. The DUSC considered that use of weight based dosing is likely given that the recommended course of rituximab in the Australian PI and the dose used in the

pivotal (RAVE) trial is 375 mg/m^2 once per week for four weeks for induction of remission.

6.24 The cost presented in the submission was based on a weighted average of 2.36 scripts per patient, assuming 9.7% use of the 500mg x 2 regimen, 17.9% use of the 500mg x 4 regimen and 72.4% use of the 1g x 2 regimen. Should a patient not achieve complete remission by month 3, the requested PBS listing does not preclude a further course of therapy. The ESC considered that only patients who achieve a complete initial response and have a subsequent relapse should receive a further course of therapy. The cost of a further course of therapy was not included in the cost estimates. The approved PI states that the efficacy and safety of retreatment with rituximab has not been established.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Estimated PBS usage & financial implications

6.25 The submission was considered by DUSC. The estimate of the total cost of rituximab in the first five years of listing on the PBS for this indication in the submission is presented in the table below.

Total cost of rituximab in the first five years of PBS listing

	Year of PBS listing				
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Number of patients treated	229	233	237	241	245
Total cost of rituximab to PBS	$1,776,703	$1,807,591	$1,838,496	$1,869,295	$1,899,997
PBS patient co-payments	$5,034	$5,121	$5,209	$5,296	$5,383
Total cost of rituximab to RPBS	$34,873	$35,479	$36,086	$36,690	$37,293
RPBS patient co-payments	$30	$31	$31	$31	$32
Net cost of rituximab to PBS and RPBS	$1,806,512	$1,837,919	$1,869,342	$1,900,658	$1,931,875

Source: Table E.2.2 Comm., p.56, based on Table E.2.1 and E.4.1, pp15-16 of Section E of the submission
Note: Cost for rituximab is the dispensed cost

6.26 The DUSC noted that the submission underestimated the number of treated patients, particularly in the first year. The DUSC agreed with the Commentary that it is likely that the number of eligible new patients contraindicated to CYC will be substantially higher than 5% of the incident population. The DUSC considered the 20% used in the additional sensitivity analysis undertaken during the evaluation to be a better estimate, but that the true estimate is likely to be higher still.

6.27 The DUSC agreed with the Commentary that the proportion of prevalent patients that relapse is a large underestimate in Year 1 due to a large pool of patients who are

currently relapsed who would be switched to rituximab if it is listed on the PBS. The DUSC considered the 25% used in the additional sensitivity analysis undertaken during the evaluation to be a more appropriate estimate. The DUSC considered 10% was reasonable for years 2-5.

6.28 The PBAC noted that revised estimates were presented in the pre-PBAC response and considered that these estimates provided a closer estimate of use, however were still overall an underestimation. The PBAC noted that the revised estimates had the following changes compared to those presented in the submission:

- a higher proportion of GPA/MPA incident patients contraindicated to cyclophosphamide. The revised estimate was 20%, as used in the evaluation, increased from 5% in the submission.
- a small increase to the proportion of prevalent patients in Year 1. The revised estimate was 15%, increased from 10% in the submission, and;
- a change in the prevalence calculation for MPA to 39.1 per million from 33 per million in the submission. This corrects the inconsistency identified by the DUSC (39.1/million is the prevalence figure for adults from Ormerod 2008, consistent with the other prevalence figures for adults used in the submission).

6.29 The PBAC also noted that the sponsor expressed its willingness to enter into a risk sharing arrangement with a cap based on the revised utilisation estimates in the pre-PBAC response.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Financial Management – Risk Sharing Arrangements/Other Relevant Factors

6.30 The submission indicated that the 'rule of rescue' should apply. The evaluation considered that rituximab does not meet criterion one for 'rule of rescue' since a number of alternative therapies are available, including CYC, IVIg, chlorambucil and etoposide. In addition, as the submission does not provide any indication of whether rituximab is better or worse than the salvage therapies, it is not clear that rituximab provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition (criterion four). The PSCR (p6) argued that salvage therapies are theoretical comparators only based on their mechanism of action and are rarely used due to the lack of RCT data to support their efficacy and safety.

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

7.1 The PBAC deferred its consideration of rituximab for the treatment of CYC-contraindicated or resistant severe active GPA and MPA because it could not determine whether rituximab was cost-effective at the price proposed. Given that no further data is likely to become available to inform this consideration, the PBAC deferred the submission to enable the Department to negotiate an appropriate price.

7.2 The PBAC considered that the restriction should allow rituximab to be used for re-treatment due to the relapsing-remitting nature of the disease. The re-treatment should be limited to previous responders.

7.3 The PBAC welcomed and noted the input received from individuals and health care professionals in support of the submission. The comments outlined the benefits of rituximab treatment in GPA and MPA including improvements in quality of life and the avoidance of CYC and its associated risks and harms.

7.4 The PBAC considered that there is a high clinical need for rituximab for rare and potentially life-threatening conditions such as GPA and MPA.

7.5 The PBAC agreed with the submission's nominated comparator, CYC, for the group of patients who are relatively contraindicated to CYC. The PBAC considered that best supportive care was the appropriate comparator for patients who are strictly contraindicated to, or refractory to, CYC.

7.6 The PBAC noted that the RAVE trial showed similar rates of complete remission for patients treated with rituximab compared with CYC. The PBAC accepted that rituximab is non-inferior to CYC for remission induction in patients with GPA and MPA.

7.7 The PBAC considered that it was difficult to assess comparative harms, but considered that rituximab is likely to have less toxicity than CYC.

7.8 The PBAC considered that it was not possible to determine whether rituximab was cost-effective for the treatment of GPA and MPA at the price proposed. The PBAC considered that a cost utility analysis against BSC in the group of patients strictly contraindicated or refractory to CYC would not be reliable because of the lack of comparative data. Further, a cost minimisation analysis versus CYC in the group of patients relatively contraindicated to CYC would not be feasible as the administration costs of rituximab exceed the total cost of oral CYC. The PBAC agreed with the ESC that a pragmatic approach for assessing the cost-effectiveness of rituximab for the treatment of GPA and MPA may be appropriate. In view of the high clinical need and given that it is unlikely that further information will become available in the future to inform the cost-effectiveness of rituximab in this setting, the PBAC requested that the Department negotiate a reduction to the proposed price.

7.9 The PBAC agreed with the DUSC that the utilisation is likely to have been underestimated noting that revised estimates were presented in the pre-PBAC response. The PBAC considered that the patient numbers are uncertain and there is a high risk of use of rituximab outside the requested restriction.

7.10 Further to its consideration of the submission, the PBAC also noted that rituximab is being used in a broad range of other non-cancer indications. The PBAC considered that it may be appropriate to consider all non-cancer indications in the same context and requested that the sponsor provide a list of other non-cancer indications in which rituximab is currently being used in Australian clinical practice.

Outcome:
Deferred

ADDENDUM

Subsequent to the March 2015 meeting, the sponsor provided the PBAC with the following information:

- acceptance of the restriction wording and written authority, as outlined in the PBAC minutes;
- a revised price for rituximab for the treatment of severe active granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) ([redacted]% rebate on the ex-manufacturer price of the 500 mg vial, as per the listing for [redacted]);
- revised financial estimates;
- the status of ongoing clinical trials with rituximab; and
- a list of non-cancer indications for which rituximab is currently being used off-label.

The PBAC recommended the listing of rituximab, on the basis that it should be available only under special arrangements under the Section 100 Highly Specialised Drugs Program, for remission induction in patients with severe, active GPA and MPA.

The PBAC noted that rituximab is the treatment of choice in patients who have contraindications to cyclophosphamide (CYC).

The PBAC accepted the revised price, noting that the rebate was equivalent to that provided for rituximab for the treatment of [redacted]. While the cost effectiveness of rituximab compared with CYC was unable to be determined, for the specific population included in the written authority where CYC is not the comparator, the PBAC pragmatically considered that the proposed reduced price was acceptable.

The PBAC requested the Department negotiate a Risk Share Arrangement with a cap based on the DUSC-revised utilisation estimates, in a manner that can be implemented and managed by the Department. The PBAC considered that as use in a broader than intended population would mostly include patients where CYC was a legitimate alternative, any additional rebate that is applied to any Government expenditure on rituximab beyond the financial cap should reduce the cost of rituximab further, at least to a level where the total cost per induction for rituximab does not exceed the total cost per induction of CYC.

The PBAC advised that rituximab is not suitable for prescribing by nurse practitioners.

The PBAC recommended that the Safety Net 20 Day Rule should not apply.

Outcome:
Recommended

8 Recommended listing

8.1 Amend existing listing. Restriction to be finalised.

9 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.

10 Sponsor's Comment

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The PBAC's decision to recommend rituximab for PBS listing is welcome news for patients with severe, active GPA/MPA, their families and clinicians.