Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Rituximab

Proprietary Product Name: MabThera

Sponsor: Roche Products Pty Limited

August 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission:	Extension of indications
Decision:	Approved
Date of Decision:	13 May 2013
Active ingredient:	Rituximab
Product Name:	MabThera
Sponsor's Name and Address:	Roche Products Pty Limited 4-10 Inman Road PO Box 255 Dee Why NSW 2099
Dose form:	Injection solution concentrated
Strengths:	100 mg/10 mL and 500 mg/50 mL
Container:	Vial
Pack sizes:	1 or 2
Approved Therapeutic use:	MabThera in combination with glucocorticoids is indicated for the induction of remission in patients with severely active Granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) and Microscopic polyangiitis (MPA). The efficacy and safety of retreatment with MabThera have not been established.
Route of administration:	Intravenous infusion
Dosage (abbreviated):	375 mg/m^2 body surface area, once weekly for 4 weeks.
ARTG Numbers:	60318 and 60319

Product background

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The antibody is a glycosylated IgG1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences (Fab domain) and human constant region sequences (Fc domain). It is produced by mammalian (Chinese hamster ovary) cell suspension culture. Rituximab binds specifically to the antigen CD20, a transmembrane molecule located on pre-B and mature B lymphocytes.

MabThera injection solution concentrate was first registered in 1998 and is currently approved for the following indications, involving Non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL), and rheumatoid arthritis (RA):

Non-Hodgkin's lymphoma

MABTHERA is indicated for treatment of patients with:

- CD20 positive, previously untreated, Stage III/IV follicular, B-cell non-Hodgkin's lymphoma
- CD20 positive, relapsed or refractory low grade or follicular, B-cell non-Hodgkin's lymphoma
- CD20 positive, diffuse large B-cell non-Hodgkin's lymphoma, in combination with chemotherapy.

Chronic lymphocytic leukaemia

MABTHERA is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia (CLL) in combination with chemotherapy

Rheumatoid arthritis

MABTHERA (rituximab) in combination with methotrexate is indicated for the treatment of adult patients with severe, active rheumatoid arthritis who have had an inadequate response or intolerance to at least one tumour necrosis factor (TNF) inhibitor therapy.

> *MABTHERA has been shown to reduce the rate of progression of joint damage as measured by x-ray when given in combination with methotrexate.*

This AusPAR describes the application by Roche Products Pty Limited (the sponsor) to extend the indications for MabThera to include the following:

> *MabThera in combination with glucocorticoids is indicated for the induction of remission in patients with severely active Granulomatosis with Polyangiitis (GPA also known as Wegener's granulomatosis) and Microscopic Polyangiitis (MPA).*

MabThera has been granted orphan drug designation for *"the induction of remission in patients with severely active Anti-Neutrophil Cytoplasmic Antibody (ANCA)-associated vasculitis".*

The two most common types of such anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitis are GPA and MPA. A third and very rare type of vasculitis, namely the Churg-Strauss Syndrome also fits under the collective term of ANCA associated vasculitis but the pathogenic link between Churg-Strauss Syndrome and the presence of ANCA is less established than with GPA and MPA. Patients with Churg-Strauss Syndrome were not involved in the pivotal trial submitted in the dossier. The sponsor is only applying for an indication involving GPA and MPA.

Regulatory status

The product received registration on the Australian Register of Therapeutic Goods in October 2010.

At the time this application was considered by the TGA, a similar application was approved in Canada (November 2011), Switzerland (March 2012) and the USA (April 2011), and was under consideration in the European Union (EU).

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

This application is a hybrid submission requesting an extension of indication for rituximab (RTX) to include the induction of remission in patients with severely active granulomatosis with polyangiitis (GPA, previously known as Wegener's granulomatosis) and microscopic polyangiitis (MPA) in combination with corticosteroids (CS).

Orphan drug designation has been granted for RTX use in this patient population. The hybrid submission contains a single pivotal controlled trial (the RAVE Study) with supporting efficacy and safety data provided by published investigator-sponsored studies, which have evaluated the utility of RTX for the treatment of severe GPA or MPA. The supporting trials are limited by small sample sizes, lack of blinding (open label design) and/or no appropriate comparator group. The methodology of the literature search part of this submission was approved by the TGA.

The proposed additional indication is

> *Mabthera in combination with glucocorticoids is indicated for the induction of remission in patients with severely active Granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) and Microscopic polyangiitis (MPA).*

Rituximab is administered by intravenous (IV) infusion. The sponsor has proposed a dosing regimen for the induction of remission in GPA and MPA of 375 mg/m^2 weekly for 4 weeks. This dose was used in the single pivotal trial (RAVE Study), and is consistent with the approved dose regimen for treating patients with NHL and CLL.

Clinical rationale

Anti-neutrophil cytoplasmic antibody associated vasculitis is a rare, multisystem, autoimmune disease characterised by small to medium sized vessel vasculitis, the production of ANCA, and the frequent occurrence of significant respiratory tract and kidney disease in its severe form. There are 3 types of ANCA associated vasculitis, but the 2 commonest sub-types are GPA and MPA. Cyclophosphamide (CYC) and CS have been the standard of care for inducing remission in these diseases for more than 40 years, however, both therapies are associated with significant potential toxicity (short and long-term), treatment failures and disease relapses (de Groot *et al*, 2009). There is a major unmet clinical need for alternative treatments in patients suffering from severe ANCA associated systemic vasculitis.

B-Lymphocytes play an important role in the pathogenesis of autoimmune diseases, including ANCA associated vasculitis, whereby the percentage of activated peripheral blood B-lymphocytes has been shown to correlate with disease activity, and certain effects

of CYC on B-cells are associated with a positive treatment response. Rituximab, an anti-CD20 monoclonal antibody approved for use in RA, NHL and CLL, depletes B-lymphocytes through several potential mechanisms including complement mediated toxicity, antibody-dependent cell mediated cytotoxicity, as well as the inhibition of B-cell proliferation and the induction of apoptosis. Furthermore, short-lived plasma cells are considered to be the primary source of various pathogenic autoantibodies (including ANCA), and these cells are the progeny of antigen-specific B-cell precursors. Hence, the administration of RTX may result in the disruption of pivotal B-cell contributions to disease pathogenesis and suppress autoantibody production. Moreover, preliminary open-label, small patient number experiences suggested a potential role for RTX in controlling severe refractory GPA and MPA, which subsequently led to the development of controlled trials such as the RAVE Study to more rigorously examine a potential treatment effect and safety profile for RTX use in this patient population (Stone *et al*, 2010).

Contents of the clinical dossier

The submission contained the following clinical information:

Module 5

- 1 clinical pharmacology sub-study of the pivotal RAVE Study, which provided pharmacokinetic (PK) and pharmacodynamic (PD) data collected from 97 subjects with ANCA associated vasculitis treated with RTX.
- 1 population PK analysis of that data.
- 1 pivotal efficacy/safety study called the RAVE Study (Stone *et al*, 2010).
- No dose-finding studies.
- 1 supporting efficacy/safety study called RITUXVAS (Jones *et al*, 2010).
- 12 published, investigator-initiated studies identified by a literature search.

Module 1

- Application letter, application form, draft Australian PI and Consumer Medicine Information (CMI), Pre-submission documents, literature search submission documents, FDA-approved product label, European Summary of Product Characteristics (SmPC), and Risk Management Plan (RMP)

Module 2

- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

Guidance

This submission is consistent with the pre-submission planning advice given to the sponsor by the TGA. There are no specific regulatory guidelines pertaining to the requested indication. However, two European guidelines, both adopted by the TGA, are noteworthy:

- CPMP/EWP/2330/99. Points to consider on application with 1. Meta-analyses; 2. One Pivotal Study
- CHMP/EWP/83561/2005. Guideline on Clinical Trials in Small Populations.

The TGA has approved the literature search strategy, including the exclusion criteria for identifying all relevant publications, as part of the hybrid submission. The literature search process for RTX use in ANCA associated vasculitis was conducted in November

2011. All types of publications including review articles, case reports, letters and commentaries were retained. In total, 643 citations were retrieved by the literature search, but 627 articles were excluded after the exclusion criteria were applied leaving a total of 16 references requiring evaluation. These citations will be considered as supportive data for the indication. The reasons for citation exclusion (n=627) from consideration were: no relevant reported safety of efficacy data (372; 59.3%), no relevant disease condition (111; 17.7%), case reports of efficacy only (57; 9.1%), editorial opinion (46; 7.3%), reviews of efficacy data (34; 5.4%) and retrospective efficacy reports (7; 1.1%).

An important omission from the literature-based submission is the retrospective study with standardised data collection published by Holle *et al* (2011), which examined the effectiveness of RTX in treating the granulomatous versus vasculitic manifestations of GPA. This publication may have post-dated the data cut-off time-point, as it does not appear to be excluded on the basis of the literature search process methodology. The results of this trial were included in both the efficacy and safety sections of the clinical evaluation report (CER).

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The 2 main studies (1 pivotal [RAVE], and the other [RITUXVAS] supportive) evaluating the use of RTX in adult subjects with GPA or MPA were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements was met. No major protocol deviations were recorded in either of the 2 main studies.

Pharmacokinetics

Studies providing pharmacokinetic data

The single pivotal RAVE Study was the only source of PK data for this submission. A summary of the key PK parameters of RTX in the ANCA associated vasculitis population is presented in Table 1.

Table 1. Key PK parameters of RTX in the ANCA associated vasculitis population

Descriptive Summary of Pharmacokinetic Parameters of Rituximab

PK parameter	N	Mean	SD	Median	Range
Clearance (mL/day)	97	313	131	281	116 - 726
Volume of Distribution (L)	97	4.50	1.08	4.40	2.25 - 7.39
Half-life (Days)	97	24.3	8.05	23.4	9.38–48.7
$AUC_{0\text{-}Inf}$ (mg/mL*day)	97	10.6	3.93	10.1	3.14–24.5

$AUC_{0\text{-}Inf}$ = area under concentration time curve from time 0 to infinity; PK = pharmacokinetic; SD = standard deviation

Evaluator's overall conclusions on pharmacokinetics

In this submission, the PK properties of RTX when used in patients with ANCA associated systemic vasculitis were assessed from data collected in a single pivotal clinical trial (RAVE Study) involving 97 patients who received a single induction course of RTX (375 mg/m^2 weekly, for up to 4 weeks of therapy). The majority of subjects were middle-aged

and Caucasian. Overall, the population PK analysis of the collected data demonstrated that RTX has PK characteristics in patients with ANCA associated vasculitis that are similar to those observed in adult patients with RA. In particular, the presence of Human Anti-Chimeric Antibodies (HACA) significantly increases RTX clearance, with a consequent reduction in half-life and overall exposure to the drug. Gender also has a moderate effect on clearance and volume of distribution, and volume of distribution is additionally impacted upon by the subject's body surface area. RTX demonstrates moderate inter-individual variability, the majority of which cannot be readily explained. There are significant deficiencies to the current known PK characteristics of RTX use in patients with autoimmune disease. This is reflected in the limited rationale provided by the sponsor in the justification of the RTX dose selected for assessment in the pivotal clinical study. In particular, no dose ranging studies have been performed to accurately determine the minimum effective dose to obtain effect (pharmacodynamic or clinical). Dosing studies after repeat courses of RTX (including those with extended intervals between dosing) have not been performed. This may be a potential problem in the future as it is biologically plausible that increased rates of HACA development may occur with repeat courses and/or extended dose intervals, which would then have significant implications for the PK characteristics of RTX.

Pharmacodynamics

Studies providing pharmacodynamic data

The single, pivotal, RAVE Study was the only source of PD data for this submission.

Mechanism of action

Rituximab binds specifically to the CD20 antigen located on the transmembrane of pre-B and mature B-cells. This action consequently results in B-cell lysis through several putative mechanisms including complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity.

Evaluator's overall conclusions on pharmacodynamics

For this submission, the PD properties of RTX when used in patients with ANCA associated systemic vasculitis were assessed from data collected in a single pivotal clinical trial (RAVE Study) involving 197 patients, 99 of whom received a single induction course of RTX (375 mg/m^2 weekly, for up to 4 weeks of therapy). The majority of subjects were middle-aged and Caucasian. The sponsor has appropriately nominated changes in peripheral blood CD19+ B-cell levels following RTX as the pivotal PD marker to support the biological plausibility of the drug in ANCA associated vasculitis. More than 90% of patients treated with RTX demonstrate B-cell depletion by 2-4 weeks following commencement of therapy, and most patients (83.3%; 70/84) maintained this effect until at least 6 months of follow-up. By 12 months, the majority of patients (80.5%; 66/82) showed signs of B-cell repletion. The relationship between achieving B-cell depletion and efficacy outcomes in the first 6 months following induction therapy with RTX is limited. However, with increasing rates of B-cell repletion 6 months after RTX induction, there appears to be a trend towards disease related flares (both severe and limited) suggesting a loss of effect with time for RTX beyond 6-12 months. The sponsor has not performed studies in patients with systemic vasculitis which may have examined the relationship between a reproduction of the desired PD effect with repeat RTX courses.

Dosage selection for the pivotal trials

The dose and administration frequency of RTX used in the pivotal RAVE Study (375 mg/m^2 weekly for 4 doses) is poorly justified by the sponsor and is a significant area of uncertainty requiring further examination. The sponsor states that previous studies (RITUXVAS) and case series/reports have utilised the same dose and regimen, but no dose-finding studies have been performed for this indication. The dose and regimen of RTX appears to have been extrapolated from that which is approved for the indication of treating lymphoma. However, there are several case reports/series in a diverse range of autoimmune conditions, such as idiopathic thrombocytopenia purpura, autoimmune haemolytic anaemia, pemphigus vulgaris, and myasthenia gravis, which indicate that substantially lower doses of RTX (for example, 100 mg weekly for 4 weeks, or 500 mg x 2 given a fortnight apart) are clinically effective, and are able to achieve the desired PD effect of prolonged CD19+ B-cell depletion (Barcellini *et al*, 2012; Horvath *et al*, 2012; and Blum *et al*, 2011). Furthermore, the design of the RAVE Study (that is, by using a single induction course of RTX) provides no information about repeat dosing (either scheduled maintenance, or on-demand for disease relapse) of RTX in patients with ANCA associated vasculitis. This is a major deficiency in the current knowledge regarding the utility of RTX treatment for patients with vasculitis, and requires further on-going studies or analysis by the sponsor.

The doses of CYC, azathioprine (AZA) and CS used in the pivotal RAVE study were appropriate, consistent with contemporary clinical practice, and based on several previous historical studies in patients with systemic vasculitis.

Efficacy

Studies providing evaluable efficacy data for the proposed indication

Table 2. Submitted efficacy and safety studies

Study	Treatment arms	Total n; Gender; Median Age	Patient Population	Concomitant Therapies	Primary Endpoint	Results
Pivotal, NIAID-sponsored, randomized, controlled study						
ITN021AI/ RAVE: 5.3.5.1.1/Vol.1/p.1	1. Experimental arm: IV RTX wkly × 4 2. Control arm: oral CYC daily	197; M: 99 F: 98; 52 years	Severe AAV (147 WG, 48 MPA)	GC	Complete remission (BVAS/WG score = 0) and successful taper of GC treatment at 6 months after randomization	64% of patients in the rituximab arm achieved complete remission at 6 months compared with 56% of patients in the CYC arm.
Investigator-initiated, randomized, controlled study						
RITUXVAS [10065: 5.4/Vol.15/p.529]	1. Experimental arm (n = 33): IV RTX weekly × 4 and 2 × IV CYC pulses 2. Control arm (n = 11): IV CYC and AZA	44; M: 23 F: 21; 68 years	Newly diagnosed AAV with renal involvement	GC	Sustained remission (BVAS/WG score = 0) at 12 months after randomization	Sustained remission achieved in: 25/33 patients (experimental arm); 9/11 patients (control arm)
Uncontrolled Studies and case series						
Aries et al. 2006 [10153: 5.4/Vol.18/p.1364]	RTX 375 mg/m^2 every 4 weeks × 4	8; M: 5 F: 3; 41 years *	WG with granulomatous manifestations refractory to standard therapy	CYC, MMF, MTX, GC	Remission defined as BVAS indicating absence of signs of new or worse disease activity and persistent activity for <=1 item	Remission: 2/8 patients
Brihaye et al. 2007 [10025: 5.4/Vol.14/p.34]	RTX 375 mg/m^2 weekly × 4	8; M:5 F: 3 50 years *	Refractory WG	GC, IS	Remission defined as BVAS 2003 = 0	Complete remission :3/8; Partial remission : 3/8
Eriksson et al. 2005 [10036: 5.4/Vol.14/p.110]	RTX 500 mg weekly × 4 (n = 6) RTX 500 mg weekly × 2 (n = 3)	9; M:5 F:4; 59 years	Therapy-resistant or relapsing ANCA-positive vasculitis (7 WG, 2 MPA)	MMF, AZA, CYC, GC	Complete remission (BVAS 1994 = 0) at 6 months after start of RTX.	Complete remission: 8/9; Partial remission: 1/9

Table 2 continued. Submitted efficacy and safety studies

Study	Treatment arms	Total n; Gender; Median Age	Patient Population	Concomitant Therapies	Primary Endpoint	Results
Jones et al. 2009 [10064: 5.4/Vol.15/p.516]	RTX 1 g×2, 2 weeks apart RTX 375 mg/m^2 weekly×4	65; M: 34 F: 31 47 years	Refractory AAV (46 WG, 10 MPA, 5 CSS, 4 unclassified)	GC, Anti-TNF, IVIG, AZA, MTX, MMF, CYC	Complete remission defined as absence of disease signs and symptoms, using DEI, with reduction in GC.	Complete remission: 49/65; Partial remission: 15/65
Keogh et al. 2005 [10066: 5.4/Vol.15/p.539]	RTX 375 mg/m^2 weekly×4	11; M: 6 F: 5; 31 years	Severe, refractory, active AAV (10 WG, 1 MPA)	Plasma exchange for nephritis, GC	Complete remission defined as BVAS/WG=0	Complete remission: 10/11; Partial remission: 1/11
Keogh et al. 2006 [10067: 5.4/Vol.15/p.546]	RTX 375 mg/m^2 weekly×4	10; M: 7 F: 3; 57 years	Severe, active AAV refractory to CYC	GC	Complete remission defined as BVAS/WG=0. Stable remission defined as BVAS/WG=0 for >6 months [b]	Complete remission: 10/10 patients, who remained stable for several months
Lovric et al. 2009 [10074: 5.4/Vol.16/p.631]	RTX 375 mg/m^2 weekly × 4	15; M:8 F: 7 45 years	Refractory or relapsing AAV (13 WG, 1 MPA, 1 CSS)	AZA, MMF, CYC, CsA, MTX, IFX, GC	Partial remission (reduction in BVAS 1994 – 0 by > 50%); Complete remission (BVAS 1994 – 0) b	Complete remission: 6/15; Partial remission: 8/15
Omdal et al. 2005 [10087: 5.4/Vol.16/p.714]	RTX 375 mg/m^2 weekly × 4	3; M:3 38 years a	Refractory WG	GC, MTX	Remission assessed via chest radiography, lab parameters (proteinuria, ANCA, ESR) b	Complete remission: 3/3
Sanchez-Cano et al. 2008 [10099: 5.4/Vol.16/p.837]	RTX 375 mg/m^2 weekly × 4	4; M:3 F: 1 45 years a	Refractory WG	CYC, GC, MTX	Remission monitored using BVAS/WG b	Complete remission: 2/4; Partial remission: 2/4

AZA – azathioprine, BVAS – Birmingham Vasculitis Activity Score; CsA – cyclosporine; CSS – Churg-Strauss Syndrome; CYC – cyclophosphamide; DEI – Disease Extent Index; GC – glucocorticosteroids; MMF – mycophenolate mofetil; IFX – infliximab; IVIG – intravenous immunoglobulin; MTX – methotrexate; RTX – rituximab; TNF – tumor necrosis factor; WG – Wegener's granulomatosis.
[a] Mean age.
[b] In some investigator-initiated studies, the primary efficacy endpoint was not clearly defined.

Evaluator's conclusions on clinical efficacy for induction of remission in patients with severely active GPA and MPA

In support of the extension of indication for induction of remission in patients with severely active GPA and MPA, the sponsor has provided data from 1 pivotal Phase II/III trial (RAVE Study) as the core evidence of efficacy for the claimed indication. Supportive evidence of efficacy is provided by a Phase II, open-label, randomised trial (RITUXVAS Study) of 12 months duration, and a TGA approved literature search strategy which identified 12 relevant, uncontrolled studies involving a total of 162 patients administered RTX for treatment refractory ANCA associated vasculitis. In addition to the sponsor provided information, the clinical evaluator has included another study examining the efficacy of RTX in patients with different disease manifestations of refractory GPA (granulomatous versus vasculitic manifestations). The submission meets the requirements of 2 European Medicines Agency (EMA) guidelines of relevance, both adopted by the TGA, which are CPMP/EWP/2330/99 *Points to consider on application with 1. Meta-analyses; 2. One Pivotal Study* and CHMP/EWP/83561/2005 *Guideline on Clinical Trials in Small Populations.*

In the pivotal RAVE Study, a total of 198 subjects were randomised to receive either an induction course of RTX (375 mg/m^2 weekly for 4 weeks; n=99), or oral CYC (up to 2 mg/kg/day) for 3-6 months (n=98). Both groups received a protocol-determined course of CS with dose tapering to be completed by 6 months. The study also had a maintenance of remission phase between 6-18 months, whereby patients given CYC in the 6-month induction phase were switched to AZA (2 mg/kg/day), but RTX treated subjects had no specific maintenance therapy. The choice of comparator in this study is appropriate and consistent with the current standard of care for patients with a severely active ANCA associated vasculitis. However, the choice of RTX dose and regimen selected for the pivotal trial is questionable, and appears to be justified by the sponsor on the basis of what dose

and regimen have been historically used. No dose-finding studies for this indication have been performed, and no dose-response relationship in terms of PD parameters of relevance (such as changes in CD19+ B-cells) has been examined. There is some evidence that lower doses of RTX may achieve the PD outcomes of interest in other autoimmune conditions.

The trial design of the pivotal RAVE Study is appropriate for the claimed indication of induction of remission in patients with severely active GPA and MPA. However, the duration of follow-up is insufficient to adequately determine relapse rate for a disease that has a natural history of involvement and treatment follow-up spanning several years. This is evident in the 18 month efficacy data for the RAVE Study, whereby more patients treated with RTX experienced severe flares between months 12-18 (8 for RTX versus 4 for CYC/AZA). Similarly, the number of limited disease flares after 6 months was higher in the RTX group (15 between months 6-12, and 9 between months 12-18) compared with the CYC/AZA arm (9 between months 6-12, and 7 between months 12-18). Although many of the supporting studies used a variety of concomitant immunosuppression medicines (particularly CYC, either intravenous (IV) or oral), the pivotal RAVE Study was not designed in this manner and therefore, there is limited, high quality information about the combination of RTX with other commonly used immunosuppression therapies. For the RAVE Study, randomisation procedures, strategies to maintain blinding and statistical analysis were appropriately performed. Efficacy in the pivotal RAVE Study was primarily analysed as a non-inferiority outcome, with a secondary analysis of treatment superiority. The RAVE and RITUXVAS studies were performed according to GCP, and the minor protocol amendments in the RAVE Study did not have a significant impact upon the results.

The population examined in the RAVE and supporting studies are similar in demographics to the subjects that would be treated with RTX for GPA and MPA in Australian clinical practice. The vast majority of subjects were middle-aged, Caucasian, and near equal gender distribution. The generalisability of the results is satisfactory with some noteworthy caveats. In general, the studies only enrolled patients with severe disease who were ANCA positive, and therefore it is unclear whether the results are generalisable to those who are ANCA negative or have milder forms of GPA and MPA. The RAVE Study also excluded patients with a serum creatinine > 4.0 mg/dL or respiratory failure requiring ventilator support, so it is difficult to determine the comparative efficacy of RTX versus CYC in the most fulminantly ill patients. The RITUXVAS specifically included patients with renal vasculitis, and administered concurrent low dose CYC with RTX induction therapy.

The choice of primary efficacy endpoints was acceptable, but not ideal. For the pivotal RAVE Study, the primary efficacy outcome was the percentage of patients in each treatment group who achieved complete remission at 6 months. Complete remission was defined as the obtaining a Birmingham Vasculitis Activity Score for Wegener Granulomatosis (BVAS/WG) score of 0 and a successful completion of CS taper. The use of the BVAS/WG is appropriate because it is a validated instrument capable of measuring disease activity. However, the nomination of a complete CS taper by 6 months is the incorrect efficacy endpoint of interest. Moreover, it may even be counter-productive to medium-long term efficacy outcomes (beyond 12 months of follow-up) as there is evidence of significantly higher disease relapse in those who don't continue to receive continuous low dose CS until at least 18 months of treatment. The primary endpoint in the RAVE Study focussed on the induction of remission (as per the sponsor's requested indication listing), but does not address the question of re-treatment with RTX (either empirical, or upon disease relapse).

All of the supporting studies used various efficacy endpoints that were relevant (and not dependent on a successful complete withdrawal of CS by a particular time point) such as changes in BVAS score, remission rates, and changes in CS dose requirements.

The primary efficacy endpoint in the pivotal RAVE trial was achieved. At 6 months, 64.3% (63/98) of patients in the RTX group achieved complete remission compared to 54.7% (52/95) of patients in the CYC group, which met the protocol-specified non-inferiority margin of treatment difference. Therefore, RTX demonstrated non-inferiority to CYC in the induction of complete remission for ANCA associated vasculitis. Treatment superiority was not demonstrated on the secondary analysis. A significantly higher proportion of patients with relapsing disease at baseline in the RTX group met the primary endpoint (66.7%, 34/51) compared with those in the CYC group (42%, 21/50; p=0.013), although, the rates of complete remission between the 2 groups in patients with newly diagnosed disease at baseline (60.4% [29/48] for RTX versus 64.6% [31/48] for CYC) were similar. Furthermore, RTX provided similar outcomes compared with CYC/AZA for patients with more severe vasculitic manifestations of GPA and MPA, such as renal disease. Various secondary and exploratory efficacy endpoints in the RAVE Study supported the non-inferiority of RTX to conventional treatment for the induction of remission in severe ANCA associated vasculitis.

The RITUXVAS Study is supportive of the key efficacy findings of the RAVE trial by demonstrating:

- Sustained remission (BVAS of 0 for 6 months) in 76% (25/33) of patients in the RTX + low-dose CYC group, and 82% (9/11) of subjects (82%) in the CYC group at 1 year, with an absolute treatment difference of -6% (95% confidence interval (CI): -33%, 21%) being non-significant.
- Among patients who reached 12 months of follow-up, 93% in the RTX + low-dose CYC group and 90% in the CYC group had sustained remission.
- The median time to remission was 90 days (inter quartile ratio (IQR), 79-112 days) in the RTX + low dose CYC group and 94 days (IQR, 91-100 days) in the CYC group.
- Renal function improved in both groups with the median increase in glomerular filtration rate (GFR) between baseline and 12 months being 19ml/min in the RTX + low-dose CYC group, and 15ml/min in the CYC group.

The literature search identified a total of 162 patients (121 of whom received the same dose of RTX being requested by the sponsor) with treatment refractory ANCA associated vasculitis that participated in 12 published investigator initiated studies. The majority of patients (93%, 151/162) were reported to have achieved either partial or complete remission at 6 months of follow-up. This data provides further support for the claimed indication. However, the study by Holle *et al* sheds insight into the utility and role of RTX in patients with refractory GPA. Complete remission was reported in 9.3% (7/59) of patients in this trial. Response was documented in 61.3% of patients (52% [39/59] showed objective improvement, and 9.3% [7/59] had unchanged disease activity), and refractory disease was observed in 26.7% (20/59). Of particular note in this retrospective study was that granulomatous disease manifestations such as orbital masses and meningitis were far less likely to respond than vasculitis features. For example, complete remission or improvement was only recorded in 44.4% (12/27) of patients with orbital granulomas compared with 88.5% (23/26) of patients with renal disease. The RAVE Study also showed a high rate of refractory, GPA-related laryngeal stenosis with the RTX treatment group. Furthermore, almost half of the patients (44.4%, 16/36) relapsed following RTX induction after a median period of 13.5 months (range: 3-54 months). The high rate of relapse in the study by Holle *et al* was observed despite 95% of patients continuing to receive some form of maintenance immunosuppression.

Overall, the data in this submission supports the efficacy of RTX in the induction of remission in patients with severely active GPA and MPA, but there is no evidence that it is superior to the currently available standard of care unless the patient has relapsed

severely active, systemic GPA. RTX offers another treatment strategy in area of medicine with a significant unmet therapeutic need.

Safety

Studies provided evaluable safety data

Pivotal efficacy studies

There is a single pivotal efficacy study (RAVE), which collected the following safety data:

- General adverse events (AEs) were assessed by AE reporting and physical examinations, both of which occurred weekly for the first 4 weeks; months 2, 4, and 6 for the treatment induction period; and then every 3 months thereafter.
- Nine categories of pre-specified AEs of particular interest, including death (all cause), leucopenia (at least grade 2), thrombocytopenia (grade 2 or more), infection (grade 3 or higher), haemorrhagic cystitis, malignancy, venous thromboembolic event, hospitalization, cerebrovascular accident and infusion reaction were assessed by their overall rate and number of individual events.
- Laboratory tests, including haematology, chemistry and urinalysis with microscopy were performed at baseline, weekly for the first 4 weeks of the trial; months 2,4, and 6 for the treatment induction period; and then every 3 months thereafter.
- Chest imaging (plain X-ray or computed tomography (CT) Scan) was performed at baseline; months 1, 4 and 6; and then every 3 months thereafter.

All adverse events were graded according to the National Cancer Institute's Common Terminology Criteria (version 3.0). Poisson regression was performed to compare the AE rates between the 2 treatment groups, adjusting for study centre and ANCA type (proteinase-3 (PR3), or myeloperoxidase (MPO)). The p-value was based on the Wald test of treatment effect.

Pivotal studies that assessed safety as a primary outcome

There were no studies that assessed safety as the primary outcome.

Dose-response and non-pivotal efficacy studies

No dose-response studies have been conducted but additional safety data was provided by the following non-pivotal efficacy studies:

- RITUXVAS (open-label, randomized study) provided data on 44 patients (33 of whom received RTX and 11 given CYC/AZA) with newly diagnosed, severe ANCA associated renal vasculitis.
- Published information from 12 investigator-initiated studies provided data on a total of 162 patients treated with RTX (all of whom received 375 mg/m^2 weekly for 4 weeks, except n=32 for a fixed dose of 1000 mg x 2, and n=9 for 500 mg x 2-4 infusions).
- Retrospective study using a standardised data collection methodology (Holle *et al* 2011) whereby 59 patients received a total of 75 cycles of RTX for GPA.

Evaluator's overall conclusions on clinical safety

The total clinical safety data (Common Close Out (CCO) date for RAVE Study is 27 January 2010, and the cut-off date for the Global Safety Database is 31 August 2011) consists of a patient exposure of 374 patients in 15 studies, of which 266 received RTX. Most of the RTX

treated subjects only received a single course of RTX therapy, at the sponsor's requested dose of 375 mg/m^2 weekly for 4 weeks. In the current submission, less than 40 subjects in total have been reported to be exposed to a repeat course of RTX.

At 18 months of follow-up, the pivotal RAVE Study safety dataset provides a total of 139.6 patient-years of observation for RTX, and 134.7 patient-years of observation for CYC/AZA. For the analysis through to the CCO date, there were 299.2 patient-years of follow-up in the RTX group, and 274.7 in the CYC group. For sensitivity analyses in which data were summarised until the point of treatment switch, patient-years of follow-up were 168.4 for the RTX group and 136.1 for the CYC group. The current safety dataset provides sufficient information about the short-term risk with RTX in this population such as haematological toxicity, infections, infusion reactions, and discontinuations due to AEs. However, the extent of long-term follow-up is not adequate to assess for some potential AEs of concern that may have a long latency between drug exposure and AE occurrence, particularly malignancy, some opportunistic infections (such as Progressive Multifocal Leukoencephalopathy (PML)) and cardiovascular safety. The study populations had baseline characteristics, disease activity and concomitant medications indicative of the intended target population for the claimed indication.

Key safety conclusions identified in the pivotal RAVE Study safety dataset are as follows:

- At 6 and 18 months, the overall incidence and rates per patient-year of exposure of any AE, AEs of pre-specified interest, grade 3 or higher AEs, and serious infections were similar in the RTX and CYC/AZA treatment groups.
- However, infections (of any severity) were numerically greater and occurred at higher rate in patients who received RTX compared with control treatment (CYC/AZA) for both the 6 month (61.6% for RTX versus 46.9% for CYC/AZA) and 18 month analysis (79.8% for RTX versus 70.4% for CYC/AZA) time points.
- The most frequent type of infectious AE in both treatment groups involved the respiratory tract (for example, there were 34 respiratory tract AEs in 22 RTX patients, and 28 corresponding AEs in 22 CYC subjects, at 6 months of follow-up).
- Various types of herpes (11% for RTX versus 3% for CYC) and fungal infections (15% for RTX versus 11% for CYC) were also more common at 6 months in the RTX versus CYC treatment group.
- Most common individual types of AEs (occurring in >10% of patients in either treatment group) showing a differential treatment related occurrence (>5% differential incidence) were diarrhoea, peripheral oedema, urinary tract infection and hypertension for RTX; and leucopenia, increased serum transaminases, and alopecia for CYC.
- Permanent discontinuations of study medication for AEs were more frequent in the CYC group (13.3% at 6 months) than the RTX arm (6.1% at 6 months).
- At 6 and 18 months of follow-up, the incidence of overall serious AEs (SAEs) were similar in the 2 treatment groups (33-34% at 6 months) with the most frequent type of SAE being infection (overall, 10.7% at 6 months; and 15.2% at 18 months).

The RAVE Study also clearly identifies a subset of patients at the highest risk of AEs from RTX (or any other treatment strategy). Older patients (aged > 65 years) or those with significant renal impairment are the most vulnerable to a broad spectrum of AEs, particularly infections.

In the supportive studies, a total of 254 subjects received treatment with RTX (mostly, a single fixed induction course of 375 mg/m^2 x 4 infusions), and treatment follow-up was limited to 6-12 months. It is unclear for most of these studies how systematic the reporting of safety outcomes was to detect any potential safety concerns, but SAEs

appeared to be recorded. In the RITUXVAS Study, 48% (16/33) patients who received RTX experienced 35 SAEs. Similarly, the largest of the studies identified by literature search (Jones *et al* Study) reported 45 SAEs in 25 subjects (38% of 65 affected) with 129 patient-years of follow-up. The study by Holle *et al* reported 24 SAEs in 59 individuals. The consistent, key safety finding from all of these supportive studies is that infections were the most common type of SAE, and that the respiratory tract was the most common site of those infections.

Death has been reported in at least 15 subjects with ANCA associated vasculitis exposed to RTX (2 in the RAVE Study, 6 in RITUXVAS, 5 in the published investigator initiated studies plus a further 2 deaths were reported in the Holle *et al* trial). Five deaths (and 2 unknown) have resulted from infections. Disease progression despite treatment appears to explain at least 5 of the other deaths and 2 RTX treated patients from cardiovascular disease. However, the mortality rates and types of deaths observed in the RAVE, RITUXVAS and other studies is consistent with those expected in the target population of ANCA associated vasculitis. A total of 6 malignancies in 5 RTX treated patients in the RAVE Study, and 4 patients treated with RTX + low dose CYC in the RITUXVAS trial developed cancers. No specific type of malignancy was observed. This result is within expectations for the target population.

RTX is associated with an increased risk of opportunistic infection, including pneumocystis pneumonia and PML (although no confirmed cases have been reported thus far in patients treated with GPA or MPA[1]), as well as significant viral reactivations (individual reports of hepatitis B, cytomegalovirus (CMV) and fulminant adenovirus infection have been recorded in the ANCA vasculitis population).

The RAVE Study specifically examined the rate of hospitalisations due to either disease activity or study medication. More patients in the RTX group (10 of 99) were hospitalised because of active disease or study drug problems by 6 months compared to the CYC group (4 of 98 subjects). The reasons for hospitalisation in both the RTX and CYC groups were typical for this population and included respiratory tract infections in 7 patients (pneumonia in 5 patients, upper respiratory tract infection in 1 patient, and bronchitis in 1 patient); and singular cases of Adult Respiratory Distress Syndrome (ARDS), pulmonary haemorrhage, pulmonary embolism, renal failure, osteomyelitis, and a hypersensitivity reaction (all with 1 patient each). Several of these hospitalisations appear related to active vasculitis, or concomitant therapies such as CS. Two of the patients with pneumonia also had significant leucopenia and/or neutropenia. The data at 18 months and through the CCO date was consistent with outcome observed at 6 months in that more patients were hospitalised for reasons related to disease activity or study drug (per the investigator's assessment) in the RTX group.

The RAVE Study demonstrates a higher frequency of leucopenia in the CYC versus RTX treatment groups at both the 6 (17.3% for CYC versus 5% for RTX) and 18 month time points (20.4% for CYC/AZA versus 7.1% for RTX). However, in both treatment groups no clear association between the occurrence of leucopenia and significant infections emerged. Thrombocytopenia of at least grade 2 severity by 18 months of follow-up was uncommon, but recorded in a higher number of RTX treated individuals (n=4; 2 with concurrent bleeding) compared with CYC/AZA managed subjects (n=1).

Infusion related reactions (IRR) occurred in 11.2-12.1% of subjects in the RAVE Study, with a similar proportion of reported AEs in each of the treatment groups (RTX versus RTX placebo infusions). RTX treated patients recorded a slightly different pattern of IRRs with features consistent with cytokine release syndrome being more common in the RTX group (5 patients in the RTX group versus 2 in the CYC arm). Only 1 subject in the RTX arm

[1] The sponsor advised TGA (in February 2013) that a case of PML in a patient with GPA has since been confirmed.

had to cease treatment due to an IRR. In the supportive studies, a small number of subjects (n=5) recorded significant IRRs.

Human Anti-Chimeric Antibodies (HACA) were only assessed in the RAVE Study, and developed in 28 subjects (22.6% of 124) as of the CCO date. The clinical relevance of positive HACA remains unclear with no discernible link to the risk of infection or acute infusion reactions. However, the presence does produce changes in PK behaviour with HACA positivity being clearly associated with increased clearance of RTX and reduced exposure to the drug.

In summary, the safety data indicates that RTX has an overall comparable safety profile to the current standard of care (CYC and/or AZA) in patients with severe systemic manifestations of GPA and MPA. There are some significant safety concerns including infection (particularly, involving the respiratory tract), hospitalisations for disease activity or medication side-effects, leucopenia, and thrombocytopenia. Of note, is the limited overall exposure to RTX for the target population, and no significant safety information has been presented for repeat dose exposure (which is currently beyond the sponsor's requested indication). Significant pharmacovigilance would be required if approval is granted for ANCA vasculitis. This would include vigilance for opportunistic infections, malignancy, all cause death, and cardiovascular AEs.

First round benefit-risk assessment

First round assessment of benefits

The benefits of RTX in the proposed usage of induction therapy for severe ANCA associated vasculitis are:

- RTX is non-inferior to the current standard of care treatment (CYC/AZA) for achieving the induction of remission in most patients with severe systemic GPA and MPA, particularly those with renal or pulmonary disease manifestations. Granulomatous disease manifestations of GPA such as orbital masses and tracheobronchial stenosis may be less responsive to RTX.
- RTX is superior to the current standard of care treatment (CYC/AZA) for the induction of remission in patients with relapsed, severely active GPA.
- RTX offers an alternative treatment strategy for life-threatening diseases (GPA and MPA) which currently have limited treatment options and a significant unmet therapeutic need.

First round assessment of risks

The risks of RTX in the proposed usage are:

- RTX has an equivalent safety profile to the current standard of care (CYC/AZA) in short-medium term follow-up with a moderately high incidence of SAEs, death and hospitalisations, particularly for those of older age (>65 years) and with significant renal impairment.
- Significant risk of infections, including a variety of opportunistic infections (such as PML and pneumocystis jiroveci pneumonia (PJP)) with RTX therapy for patients with ANCA associated vasculitis.
- Optimal dose and scheduling for RTX infusions has not been adequately defined, nor has the role of concomitant or maintenance immunosuppression been delineated.

- Sufficient numbers of treated patients with long-term (multi-year) follow-up has not been achieved. This may be important for issues such as malignancy development and cardiovascular disease.

First round assessment of benefit-risk balance

The benefit-risk balance of RTX, given the proposed usage (induction of remission) in the target population (severely active systemic forms of GPA and MPA), is favourable. However, the efficacy and safety of re-treatment with RTX has not been adequately evaluated to determine its role in this scenario. The natural history of ANCA associated vasculitis is that a significant proportion of patients will relapse and require additional treatment in the future (2-7 years after diagnosis).

First round recommendation regarding authorisation

The clinical evaluator recommended acceptance of the sponsor's proposed indication for RTX, subject to satisfactory response to the questions, below, and regular periodic safety update reports.

Recommended revisions to and comments on the draft PI and Consumer Medicine Information (CMI) are beyond the scope of the AusPAR.

List of questions and Second round evaluation of clinical data submitted in response to questions

The clinical evaluator's assessment of the sponsor responses to 9 clinical questions raised after the first round clinical evaluation appears below.

Pharmacokinetics

Question 1. Could the sponsor please provide PK data (other than historical use) justifying the dose/regimen of RTX utilised in the pivotal RAVE Study? In particular, have any dose-ranging studies been performed, or are they being considered for the future?

The sponsor response reiterates that the population PK analysis of the RAVE Study data indicates that the key PK parameters for RTX therapy in patients with GPA and MPA are similar to that observed in adult patients with rheumatoid arthritis. No dose-ranging studies have been performed for RTX in patients with systemic vasculitis, and none are planned by the sponsor. The sponsor acknowledges that some centres around the world and in some published case studies, beneficial efficacy outcomes have been achieved with RTX using alternative (that is, lower) dose regimens.

The clinical evaluator agreed with the sponsor in that the assessment of alternative dose regimens for RTX requires additional controlled prospective trials.

Question 2. ANCA associated vasculitis has a significant rate of disease relapse which may require re-treatment for induction of remission. Dosing studies after repeat courses of RTX (including those with extended intervals between dosing) have not been performed thus far for the requested indication. Is the sponsor considering further studies to examine the PK of RTX with repeat course of RTX in patients with ANCA associated vasculitis?

The sponsor acknowledges that a significant proportion of patients with GPA and MPA experience disease relapse (up to half within 2 years), and there is interest in evaluating the utility of maintenance RTX therapy for these patients. The MAINRITSAN Study is a prospective, open-label, investigator-initiated trial which has enrolled 114 patients in France to receive either RTX 500 mg every 6 months, or daily oral AZA (2 mg/kg) for up to 18 months, following induction of remission in newly diagnosed or relapsed GPA and MPA.

The data was accepted as an abstract at the recent American College of Rheumatology meeting in November 2012. At the cut-off date for the report, 73.7% (84/114) of patients had completed 28 months of follow-up with an interim analysis showing that major disease relapse had occurred in 3.6% (2/55) of patients in the RTX group, and 27.1% (16/59) of subjects in the AZA arm. The abstract conclusion states that the study demonstrates that treatment with RTX 500 mg every 6 months is superior to AZA for the maintenance of remission. However, no statistical analysis was provided in the abstract presentation. The incidence of SAEs and infection were similar in the 2 treatment groups. No PK or immunogenicity data has been reported for this study.

An additional, investigator-initiated trial (RITAZAREM Study) is proposed to commence in October 2012. This 24 month study, which aims to recruit 160 patients, will investigate the efficacy and safety, PK and rate of HACA development with RTX 1000 mg given every 4 months compared to oral AZA 2 mg/kg/day in the maintenance of GPA and MPA remission.

Question 3. Furthermore, it is biologically plausible that increased rates of HACA development may occur with repeat courses of RTX and/or extended dose intervals, which may then have significant implications for the PK characteristics of RTX. Could the sponsor please comment if there is a plan to examine this issue?

The sponsor re-affirms that in the RAVE Study dataset the overall number of HACA-positive patients is small (n=28; 22.6% of a possible 124 tested subjects), and the clinical relevance of HACA development in patients with vasculitis treated with RTX remains uncertain, as it is across other indications. The sponsor has provided an additional published report by Cartin-Ceba *et al* 2012[2] as supportive information in addressing this issue. The report pertains to a single centre, 10 year historical study of patients with treatment refractory, severe GPA treated with at least 2 course of RTX between January 2000 and May 2010. A total of 233 RTX courses were administered to 53 subjects over the follow-up period, with a median number of courses per patient of 4 (range of 2-12 courses; 38 patients received 3-5 courses). Most RTX courses (209; 90% of 233) consisted of 4 weekly doses at 375 mg/m^2, and 10% of courses were the 2 fixed RTX doses of 1000 mg given 2 weeks apart. The study authors report that they found no evidence of patients developing clinical resistance (i.e. non-response in terms of clinical outcomes) to RTX over time with repeat courses of therapy. The rates of HACA development were not reported in this study.

Pharmacodynamics

Question 4. Please elaborate on the utility of using a PD marker (such as CD19+ B-cells) to determine the likelihood of disease relapse? If so, can the same marker be used as an indicator for re-treatment including upon disease relapse (whereby a further induction course of RTX may be considered)?

The sponsor opines that changes in CD19+ B-cells are an exploratory PD response biomarker, which when considered in isolation does not possess predictive value for determining disease relapse. The clinical evaluator agreed with that opinion. The RAVE Study data does not provide evidence to justify the use of CD19+ B-cells in isolation as a predictive biomarker for relapse. At 18 months of follow-up in those patients who obtained remission by 6 months, 31 relapses were recorded in the RTX group and 23 relapses were identified in the CYC/AZA group. In the relapse population, 48% of those who received RTX and 61% of those in the CYC/AZA arm had evidence of B-cell reconstitution (CD19+ B-cell count >10 cells/µL) prior to clinical relapse. However, the

[2] Cartin-Ceba R., Golbin J., Keogh K *et al*. Rituximab for Remission Induction and Maintenance in Refractory Granulomatosis with Polyangiitis (Wegener's). Ten-Year Experience at a Single Center. *Arthritis & Rheumatism* 2012:64.

RAVE Study does indicate that when the achievement of B-cell depletion and ANCA seronegativity are considered together, the risk of disease relapse is low (10% in the RTX group, and 9% in the CYC/AZA arm). The sponsor acknowledges that there are conflicting opinions in the published literature as to the utility of B-cell depletion and reconstitution as a predictive biomarker of clinical response. The report by Cartin-Ceba *et al* (2012) suggests that pre-emptive, re-treatment with RTX in patients with relapsing GPA can be individualised based on serial B-cell and PR3-ANCA monitoring.

Question 5. Pease comment on whether or not genetic-related differences in PD response (e.g. polymorphisms of Fc gamma receptors) have been examined in the target population?

The sponsor indicates that investigation into genetic-related differences in PD response to RTX is planned by the Immune Tolerance Network, but this work has not yet commenced.

Question 6. Please comment on the evidence in other autoimmune conditions whereby significantly lower doses of RTX have achieved the primary PD (and clinical outcome) effect of CD19+ B-cell depletion, and how this may relate to the proposed indication in systemic vasculitis.

The sponsor is aware that several investigator-initiated studies have been performed in patients with autoimmune conditions (such as systemic lupus erythematosus (SLE) and Sjogren's syndrome) using various RTX dosing regimens. The sponsor concurs that peripheral B-cells are depleted at relatively low doses of RTX, but only a minority of the whole body B-cell population resides in the peripheral blood. Furthermore, the sponsor considers peripheral blood B-cell depletion to be an unreliable PD marker correlating with clinical efficacy. From the PD data, there is a limited relationship between B-cell depletion and efficacy outcomes in the first 6 months following induction therapy with RTX (RAVE Study). However, the data beyond 6 months suggests a different relationship outcome, in that many RTX treated patients had a significant return of CD19+ B-cell counts between 6 and 12 months. Peripheral B-cell repletion did not appear to impact upon the rate of complete remission over time (up to 18 months), but showed a signal towards recurrence of ANCA disease. The number of disease flares between 6 and 18 months were 17 severe and 24 limited flares for the RTX group compared with 13 severe and 16 limited for the CYC/AZA arm. This result suggests the loss of RTX treatment effect beyond 6-12 months, which may be associated with B-cell recovery.

Efficacy

Question 7. Given the small number (n=41) of patients in the published investigator initiated studies who received significantly lower doses of RTX were reported to obtain the same rate of remission as the proposed dose of 375 mg/m² x 4 infusions, has the sponsor explored the relationship between dose (over at least a limited dose range) and clinical outcomes?

The sponsor concurs that no relationship between RTX dose and clinical outcomes has been explored in dose ranging studies. The original submission explored the relationship between RTX area under the concentration time curve from zero to infinity ($AUC_{0-\infty}$) at or above the median value (10.2 mg/mL.day) and efficacy (complete remission) at 6 months in the RAVE Study. No correlation was observed in 94 PK-evaluable individuals who received RTX as per protocol. The sponsor has included an additional analysis in the response to a TGA request for further information, whereby the rates of remission outcomes (complete remission; and remission according to BVAS/WG score=0) at 6 months were assessed according to AUC_{0-inf} quartiles (n=24 for each quartile). Table 3 shows the newly presented data and has been taken without amendment from the sponsor's response. Complete remission rates were numerically lower in the first quartile (54.2%; 13/24), highest in the third quartile (75.0%; 18/24) and equivalent in the second and fourth quartiles (66.7%; 16/24). However, this relationship was not statistically verified as indicated by a Spearman correlation coefficient of 0.08.

Table 3. Remission Outcomes at 6 months in RAVE Study by AUC Quartiles in RTX treated patients

	PK AUC_{0-inf} <7.85 (n=24)	PK 7.85 ≤ AUC_{0-inf} <10.16 (n=24)	PK 10.16 ≤ AUC_{0-inf} <13.34 (n=24)	PK AUC_{0-inf} ≥13.34 (n=24)
Complete Remission	13 (54.2%)	16 (66.7%)	18 (75.0%)	16 (66.7%)
Remission (BVAS/WG=0)	15 (62.5%)	22 (91.7%)	19 (79.2%)	21 (87.5%)

BVAS = Birmingham Vasculitis Activity Score; PK = pharmacokinetics; WG = Wegener's granulomatosis.
The WOCF imputation was used for the as-defined definition of the primary endpoint.

Question 8. Please comment further on the literature (for example, Holle et al trial) and study findings in the RAVE trial whereby patients with vasculitic versus granulomatous disease manifestations of GPA appear to have a differential treatment response.

The sponsor opines that there are conflicting opinions in the published literature as to the effectiveness of RTX in treating vasculitic versus granulomatous disease manifestations of GPA, but that the weight of evidence suggests that RTX is effective for both granulomatous and vasculitic disease manifestations. The clinical evaluator agreed that the issue remains unclear and requires further investigation. The reasons for the differential efficacy observations in the literature are hypothesised to include patient-specific resistance mechanisms, use of lower RTX dosing regimens and the difficulty in histopathologically confirming granuloma formation versus fibrous tissue reaction at sites of granulomatous disease manifestation such as the orbit. The sponsor indicates that the results of the Cartin-Ceba *et al* 2012 Study are supportive of no significant differential treatment response to RTX according to predominant disease organ manifestation. Of the 53 patients in this study, all of whom achieved complete remission with RTX, 39% (21) had granulomatous disease and 61% (32) had vasculitic disease manifestations. The RAVE Study was not powered to determine a differential treatment response to RTX for granulomatous versus vasculitic disease presentations.

Question 9. Please provide an update on the patient with GPA in the Global Safety Database who experienced suspected (but unconfirmed) PML, in particular, clarifying whether or not the case remains unconfirmed.

The sponsor has not received any additional information on this case to verify the validity of the report.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of RTX in the proposed usage are unchanged from those identified in the *First round assessment of benefits*, above. The sponsor's response to the list of questions highlights that there is conflicting and limited literature on the relative benefit of RTX in inducing remission in patients with granulomatous versus vasculitic disease manifestations.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of RTX in the proposed usage are unchanged from those identified under *First round assessment of risks*, above.

Second round assessment of benefit-risk balance

The benefit-risk balance of RTX, given the proposed usage (induction of remission) in the target population (severely active systemic forms of GPA and MPA), is favourable.

However, as per the *First round assessment of benefit-risk balance* (above), the efficacy and safety of re-treatment with RTX has not been determined and the natural history of ANCA associated vasculitis is that a significant proportion of patients will relapse and require additional treatment in the future.

Recommendation regarding authorisation

The clinical evaluator recommend acceptance of the sponsor's proposed indication for RTX subject to regular periodic safety update reports (PSURs).

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a RMP, Version: 2.0, dated 16 March 2012, and Australian Specific Annex (ASA), Version: 1.0, dated 12 April 2012, which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the clinical aspects of the SS by the OMA, the summary of the Ongoing Safety Concerns as specified by the sponsor is as shown at Table 4:

Table 4. Summary of Ongoing safety Concerns

Important Identified Risks	• Acute Infusion-Related Reactions* • Infections* • Impaired Immunisation Response* • PML* • Neutropenia including prolonged** • HBV Reactivation** • Tumour Lysis** • Serious Viral Infections** • GI Perforation** • PRES** • Hypogammaglobulinaemia***
Important Potential Risks	• De Novo HBV*** • Opportunistic Infections* • Malignant Events*** • Impact on Cardiovascular Disease*** • GI Perforation *** • Prolonged B-cell depletion** • Grade 3/4 and serious blood and lymphatic system AEs in >70year patients** • AML/MDS** • Second malignancies** • Neutropenia***
Important Missing Information	• • Use in Pregnancy and Lactation* • Immunogenicity and Autoimmune Disease*** • Use in Paediatric populations **

* All indications
** NHL/CLL
*** RA and GPA/MPAonly

Pharmacovigilance plan

The sponsor states that routine pharmacovigilance activities, consistent with the activities outlined in 3.1.2 *Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities* (CPMP/ICH/5716/03), are proposed to monitor the specified ongoing safety concerns which pertain to the proposed ANCA associated vasculitis indication, including the use of guided questionnaires for the important identified risk:

'PML', the important potential risk: '*De Novo* hepatitis B virus (HBV), and HBV Reactivation' and the important missing information: 'Use in Paediatric populations'.

Additional pharmacovigilance activities (comprising ongoing registry and observational studies) are proposed for the important identified risks: 'Acute Infusion-Related Reactions' and 'Infections'; and the important potential risks: '*De Novo* HBV, and HBV Reactivation', 'Opportunistic Infections', 'Malignant Events', 'Impact on Cardiovascular Disease' and 'GI Perforation'.

Risk minimisation activities

The sponsor has concluded that at present routine risk minimisation activities are sufficient for the specified ongoing safety concerns which pertain to the proposed ANCA associated vasculitis indication.

Routine risk minimisation activities will comprise labelling, including a boxed warning[3], clinical trial information, special warning and precaution statements, instructions for use and/or notification of undesirable effects for the specified ongoing safety concerns which pertain to the proposed ANCA associated vasculitis indication.

Summary of recommendations

The OPR provides these recommendations[4] in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; the submitted Core RMP is applicable without modification in Australia unless so qualified; and the draft PI and CMI documents should not be revised until the Delegates overview has been received.

The sponsor is reminded that safety considerations may be raised by the clinical evaluator. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

The OPR recommended the sponsor address the following:

- In comparison to the AU-RMP Version 2 previously reviewed for these products, the following changes to the summary of ongoing safety concerns which pertain to the proposed ANCA associated vasculitis indication have been made:
  - 'Hypogammaglobulinaemia' has now been included as an important identified risk.
  - 'Neutropenia' has now been included as an important potential risk.
  - The important potential risk: 'Use in Pregnancy and Lactation' has now been categorised as important missing information.

  This is generally acceptable, although it is not clear why the important missing information: 'Use in Paediatric populations' has been restricted to the NHL/CLL indications. The sponsor should justify this position or delineate this ongoing safety concern as pertaining to all indications. If the latter course of action is taken the Core RMP and ASA will need to be amended accordingly when these documents are next updated.

[3] A boxed warning is a succinct warning statement printed at the start of the approved PI, designed to alert prescribers to an important safety issue with a medicine. The warning is highlighted by a bold black surround or "box".
[4] Note: Discussion of medication errors and revisions to the PI and CMI are beyond the scope of the AusPAR and therefore any recommendations relating to these are not included in this document.

- The apparent discrepancies between information in the Core RMP and the ASA should be corrected.
- In principle there is no objection to the sponsor implementing additional pharmacovigilance activities to further monitor the specified ongoing safety concerns. However, the ongoing studies are not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore the related study protocols have not been reviewed. Nevertheless an update on the progress/results/analysis of this study, as outlined in the Core RMP, will be expected in future PSURs.
- The sponsor should state if there are any material differences between the pharmacovigilance plan (PP) of the Core RMP, as adopted in Australia, compared to the PP of the updated EU-RMP submitted with the similar application in the EU. The sponsor should justify why any such material differences have not been adopted in Australia.
- The sponsor's conclusion that at present routine risk minimisation activities are sufficient for the specified ongoing safety concerns which pertain to the proposed ANCA associated vasculitis indication appears to be consistent with the US FDA not requiring a Risk Evaluation and Mitigation Strategy (REMS) for these products when it approved a similar application on 19 April 2011. Nevertheless Table 101: 'A Summary of Planned Risk Minimisation Actions' of the Core RMP states: *"additional risk minimisation activity in place"* for the important identified risk: 'PML'. However, it only refers to *"A guided questionnaire is currently in use for all suspected cases of PML",* which is considered to be a routine pharmacovigilance activity. Similarly Table 1: 'Australian Risk Management Plan' of the ASA refers on a number of occasions to the use of guided questionnaires and *"Enhanced PV practices"* under the table sub-heading: 'Proposed Australian risk minimisation activities'. These discrepancies should be corrected when these documents are next updated.
- The sponsor should state if there are any material differences between the Risk Minimisation Plan of the Core RMP, as adopted in Australia, compared to the Risk Minimisation Plan of the updated EU-RMP submitted with the similar application in the EU. The sponsor should justify why any such material differences have not been adopted in Australia.

The OPR reviewer's assessment of the sponsor's response to the above is as follows:

- It was drawn to the sponsor's attention that it was not clear why the important missing information: 'Use in Paediatric populations' had been restricted to the NHL/CLL indications. The sponsor has now agreed to extend the important missing information: 'Use in Paediatric populations' to cover all indications and commits to ensure this update is included in the next versions of the RMP and ASA submitted to the TGA. This is acceptable.
- The sponsor acknowledges the existence of numerous discrepancies within the Core RMP in regard to the delineation of the ongoing safety concerns along indication lines and has provided an assurance that the RMP will be amended and the updates included in the next version submitted to the TGA. This is acceptable.
- The sponsor has provided an assurance that relevant safety information from the ongoing studies will be included in future PSURs. This is acceptable.
- The sponsor has identified the numerous differences between the Pharmacovigilance Plan of the Core RMP and the Pharmacovigilance Plan of the EU-RMP (version 8.0) submitted with the similar application in the EU. In summary the sponsor has provided an assurance that the next version of the RMP submitted to the TGA will be updated to be consistent with the EU-RMP (version 8.0). This is acceptable.

- The sponsor agrees that the use of the guided questionnaires is now considered part of the routine pharmacovigilance activities for rituximab and has provided an assurance that the RMP and ASA will be amended and the updates included in the next versions submitted to the TGA. This is acceptable.
- The sponsor has identified the material differences between the Risk Minimisation Plan of the Core RMP and the Pharmacovigilance Plan of the EU-RMP (version 8.0) submitted with the similar application in the EU. Nevertheless the Risk Minimisation Plan of the Core RMP is consistent with the Australian RMP Version 2, dated September 2010, which was previously evaluated and accepted by the TGA. Therefore no PML Alert Card nor the supporting educational leaflets are utilised in Australia. This is acceptable.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Introduction

This is a hybrid submission for an extension of indications based on one pivotal study and a number of articles from the published literature. The TGA approved the literature search strategy and the exclusion criteria for identifying the relevant publications from the literature search output. An important omission from the literature-based submission was noted by the clinical evaluator. This was a retrospective study with standardised data collection published by Holle *et al* (2011), which examined the effectiveness of RTX in treating the granulomatous versus vasculitic manifestations of GPA. This publication may have post-dated the data cut-off time-point.

The clinical data in Module 5 consisted of:

- 1 clinical pharmacology sub-study of the pivotal RAVE Study which provided PK and PD data collected from 97 subjects with ANCA associated vasculitis treated with rituximab (RTX)
- 1 population PK analysis of the preceding data
- 1 pivotal efficacy and safety study called the RAVE Study (Stone *et al*, 2010)
- No dose-finding studies
- 1 supporting efficacy and safety study called RITUXVAS (Jones *et al*, 2010)
- 12 published, investigator-initiated studies identified by a literature search

There are no specific regulatory guidelines pertaining to the requested indication. Relevant EU Guidelines (beside other general guidelines) are as follows:

pp. 127 - 132 of Rules 1998 (3C) - 3CC6a (pdf,27kb)
Clinical Investigation of Medicinal Products for Long-Term Use
Effective: 12 February 2002
See also: pp. 121 - 125 of Rules 1998 (3C) - 3CC5a (Adopted by TGA with conditions)

CHMP/EWP/83561/2005 (pdf,63kb)
Guideline on Clinical Trials in Small Populations

CPMP/EWP/2330/99 (pdf,51kb)
Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study
Adopted by the TGA with the following notation:"Sponsors are reminded that they should submit all available new safety data that are relevant to the intended treatment population."

Pharmacokinetics

The median of individual estimates of terminal elimination half-life for RTX among 97 patients in the RAVE Study treated with RTX was 23.4 days (range: 9.38-48.7 days). Median RTX clearance (CL) was 281 mL/day (range: 116-726 mL/day), and the drug's volume of distribution (Vd) in the central compartment was 4.40 L (range: 2.25-7.39 L). The inter-patient variability (and % standard error of estimates) for CL and Vd were moderate at 42.1% (13.8%) and 26.8% (18.9%), respectively. The PK parameters observed for RTX in patients with ANCA vasculitis are similar to those observed in adult patients with active RA.

The presence of HACA significantly increases RTX clearance, with a consequent reduction in half-life and overall exposure to the drug. Gender also has a moderate effect on clearance and volume of distribution, and volume of distribution is additionally impacted upon by the subject's body surface area. RTX demonstrates moderate inter-individual variability, the majority of which cannot be readily explained.

As noted by the clinical evaluator, it is biologically plausible that increased rates of HACA development may occur with repeat courses and/or extended dose intervals, which would then have significant implications for the PK characteristics of RTX. The clinical evaluator also noted that there was a limited rationale provided by the sponsor to justify the RTX dose selected for assessment in the pivotal clinical study.

Pharmacodynamics

More than 90% of patients treated with RTX demonstrated B-cell depletion by 2-4 weeks following commencement of therapy, and most patients (83.3%; 70/84) maintained this effect until at least 6 months of follow-up. The relationship between achieving B-cell depletion and efficacy outcomes in the first 6 months following induction therapy with RTX is limited.

By 12 months, the majority of patients (80.5%; 66/82) showed signs of B-cell repletion. With increasing rates of B-cell repletion 6 months after RTX induction, there appeared to be a trend towards disease related flares (both severe and limited) suggesting a loss of effect with time for RTX beyond 6-12 months.

Efficacy

Dose-finding studies

No dose-finding studies were carried out for the indications of GPA and MPA and the clinical evaluator makes the comment that the dosage regimen appears to have been extrapolated from that recommended in the treatment of lymphoma. The clinical

evaluator did draw attention to a number of case reports/series in a diverse range of auto-immune conditions where lower doses of RTX were found to be clinically effective.

The clinical evaluator pointed out that the use of a single induction course of RTX in the RAVE study yielded no information about repeat dosing (either scheduled maintenance or on demand for disease relapse).

Pivotal study: the RAVE Study

The pivotal study was the RAVE Study [Study ITN021A1], a Phase II/III, multi-centre, randomised, active-controlled, double-blind, double-dummy, parallel-group trial which enrolled adult subjects with severe ANCA associated vasculitis (GPA or MPA). The objective of the trial was to demonstrate that RTX was non-inferior to conventional therapy for the induction of remission and was superior to historical control. It was conducted from 21 Dec 2004 to 9 Jan 2009.

The RAVE Study had 2 treatment periods: a 6 month induction of remission phase followed by a 12 month maintenance of remission period (18 months in total). During the induction of remission phase, patients were randomised to either the experimental treatment group to receive IV RTX at a dose of 375 mg/m^2 of body surface area (BSA) once weekly for 4 weeks plus daily placebo tablets of CYC for 3-6 months. The control arm received placebo IV infusions plus daily oral CYC at a dose of 2 mg/kg (adjusted for renal insufficiency) for 3-6 months. Both treatment groups received the same CS regimen.

Patients who experienced severe disease flares or treatment failure between visit 5 (1 week after last IV infusion of either RTX or placebo) and visit 8 (6 month visit) were crossed over in a blinded manner to the opposite treatment arm. Patients in either group who achieved remission (defined as BVAS/WG score of 0) before 6 months were switched from CYC/CYC placebo to AZA/AZA placebo tablets.

During the maintenance of remission phase (months 6-18), patients in the control group discontinued CYC and had their treatment switched to oral AZA. Patients in the experimental (RTX) group discontinued their placebo CYC tablets and received daily oral AZA placebo medicine. The AZA or matching placebo tablets were to continue to 18 months in both treatment groups.

The main efficacy variables were:

- BVAS/WG score: complete remission with score 0 or partial remission with score 2 or less
- Prednisone taper: ability to cease CS completely without a disease flare
- Severe or limited disease flares: defined according to changes in the BVAS/WG score and the new occurrence of major or minor items as defined in the instrument

The primary efficacy endpoint of the RAVE Study was the percentage of patients in each treatment group who achieved complete remission at month 6, defined as a BVAS/WG score of 0 and successful completion of CS taper; that is, receiving no CS at month 6.

There were a number of other efficacy outcomes, secondary and tertiary. The principal secondary efficacy endpoint was the superiority of RTX compared to CYC as determined by the percentage of subjects in each treatment group who had a BVAS/WG score of 0 and successful tapering of CS treatment by month 6.

The RAVE Study aimed to recruit 200 patients who were to be randomised 1:1 to the experimental [RTX] or control [conventional therapy] arms, stratified by type of ANCA (whether anti-PR3 positive or anti-MPO positive) as well as by study centre. Because of the overlapping of clinical features, the randomisation was not further stratified by the clinical type of ANCA associated vasculitis, that is, whether GPA or MPA. To ensure that the proportions of GPA and MPA patients were similar to those in a typical ANCA associated

vasculitis population, the maximum percentage of MPA patients which could be recruited into the study was set at 50% of all subjects.

The efficacy analyses in the RAVE Study were conducted on the intent to treat (ITT) population, defined as all randomised subjects who received any study medication, with sensitivity analyses to be performed on the per protocol (PP) population.

A sample size of 100 patients per treatment group was estimated to yield 83% power to conclude non-inferiority. The assumptions underlying the sample size calculations, as described in the clinical evaluation report (see Attachment 2 of this AusPAR), appear reasonable. If the lower limit of the two-sided 95.1% confidence interval (CI) for the difference in the rate of the primary endpoint between RTX and CYC/AZA was above -20%, then it could be concluded that RTX was non-inferior to CYC/AZA.

A total of 198 patients were randomised into the RAVE Study with 99 subjects assigned to each treatment group. A summary of patient disposition at 6 months is shown below.

Table 5. Patient disposition at 6 months

	Rituximab N=99 n (%)	Cyclophosphamide N=98 n (%)
Randomized and treated[a]	99 (100)	98 (100)
Completed 6 months	93 (93.9)	91 (92.9)
Without crossover or BMJ	82 (82.8)	79 (80.6)
Crossed over without BMJ by 6 months	5	7
BMJ by 6 months, no crossover	6	5
Discontinued by 6 months	6 (6.1)	7 (7.1)
Without crossover or BMJ	3	5
Crossed over without BMJ by 6 months	1	0
BMJ by 6 months, no crossover	2	2
Primary reason for discontinuation by 6 months		
Voluntary withdrawal	2	5
Death	1	2
Adverse event[b]	2	0
Other	1	0

a, b, [Information redacted]

In total, 123 patients completed 18 months of treatment follow-up, including 61.6% (61/99) of subjects in the RTX group and 63.3% (62/98) of patients in the CYC arm.

Both treatment groups in the RAVE Study had similar demographic characteristics at screening in terms of age, gender and ethnicity. Subjects in the RTX group were slightly older with a mean age of 54.0 years compared with 51.5 years for the CYC arm (range 15-92 years). In both groups, about half of all subjects were male, and more than 93% had Caucasian ethnicity. The majority of patients (74.6%, 147/197) had a diagnosis of GPA, 24.4% (48/197) had a diagnosis of MPA and 2 subjects had an indeterminate or unknown type of ANCA associated vasculitis.

Baseline disease characteristics were generally balanced between the 2 treatment arms, however estimated creatinine clearance (by Cockcroft-Gault formula) was an exception to this. Mean (standard deviation (SD)) creatinine clearance was 76.5 (46.3) mL/min for the RTX group and 91.4 (49.2) mL/min for the CYC/AZA group. In each arm, approximately two-thirds of patients were positive for cytoplasmic-ANCA by immunofluorescence, and the other one-third were positive for perinuclear-ANCA. Similarly, in each arm, approximately two-thirds of patients were positive for PR3-specific antibodies, and one-third were positive for MPO-specific antibodies.

Of the 98 patients randomized to receive CYC, 97 took at least one active dose. Most patients (191/197, 97.0%) received at least 75% of the total amount of RTX or RTX placebo infusions.

Results for the primary efficacy outcome in the pivotal study

At 6 months, 64.3% (63/98; 95.1% CI 54.76, 73.81) of patients in the RTX group achieved complete remission compared to 54.7% (52/95; 95.1% CI 44.68, 64.79) of patients in the CYC group. The treatment difference in the rate of complete remission was 9.5, with a lower limit of the 2-sided 95.1% CI being -4.3 (upper limit 23.4), which was greater (that is, less negative or to the right of on the number line) than -20. Therefore, the protocol-specified non-inferiority margin was achieved and RTX therapy demonstrated non-inferiority to CYC in the induction of complete remission for ANCA associated vasculitis.

A higher proportion of patients in the RTX group were of older age (>65 years) compared with the control group (36.4% [36/99] versus 19.4% [19/98]), and the complete remission rate appeared somewhat lower in both treatment arms for patients aged >65 years (55.6% [20/36] for RTX and 42.1% [8/19] for CYC) compared to those <65 years (68.3% [43/63] for RTX and 55.7% [44/79] for CYC). However, the difference in the rate of complete remission between the 2 treatment groups was of similar size (12.6-13.5%) across the comparable age range. The rates of complete remission rate and treatment difference were similar for males and females.

Table 6 below displays the rates of complete remission at 6 months by baseline disease characteristics.

Table 6. RAVE Study: Complete Remission at 6 months according to baseline disease subgroup characteristic (ITT Population)

	Rituximab n = 99	CYC n = 98	Absolute Difference 95.1% CI	p-value [a]
Disease status				
New	29/48 (60.4%)	31/48 (64.6%)	−4.2% −23.6, 15.3	0.673
Relapsing	34/51 (66.7%)	21/50 (42.0%)	24.7% 5.8, 43.6	0.013
Renal Involvement				
≥ 1 major renal item on BVAS/WG	31/51 (60.8%)	32/51 (62.7%)	−2.0% −20.9, 17.0	0.839
No major renal item on BVAS/WG	32/48 (66.7%)	20/47 (42.6%)	24.1% 4.6, 43.6	0.018
Creatinine clearance, mL/min				
Cr Cl < 60	25/45 (55.6%)	18/28 (64.3%)	−8.7% −31.8, 14.3	0.461
Cr Cl ≥ 60	38/54 (70.4%)	34/70 (48.6%)	21.8% 4.8, 38.8	0.015
Serum creatinine, mg/dL				
Creatinine ≤ 1.2 [b]	36/52 (69.2%)	21/53 (39.6%)	29.6% 11.3, 47.9	0.002
Creatinine > 1.2 [b]	27/47 (57.4%)	31/45 (68.9%)	−11.4% −31.1, 8.2	0.256
Alveolar hemorrhage				
With alv hem	16/27 (59.3%)	11/23 (47.8%)	11.4% −16.3, 39.1	0.419
Without alv hem	47/72 (65.3%)	41/75 (54.7%)	10.6% −5.2, 26.4	0.190
ANCA Type				
MPO+	20/33 (60.6%)	21/33 (63.6%)	−3.0% −26.5, 20.5	0.800
PR3+	43/66 (65.2%)	31/65 (47.7%)	17.5% 0.7, 34.3	0.044
AAV Type				
MPA	16/24 (66.7%)	15/23 (62.5%)	4.2% −23.0, 31.3	0.763
WG	46/73 (63.0%)	37/74 (50%)	13.0% −2.9, 29.0	0.112

In relation to baseline disease status, a significantly higher proportion of patients with relapsing disease at baseline in the RTX group met the primary endpoint (66.7%, 34/51) compared with those in the CYC group (42%, 21/50; p=0.013). However, the rates of complete remission were similar between the 2 groups in patients with newly diagnosed disease at baseline (60.4% [29/48] for RTX versus 64.6% [31/48] for CYC).

Also from Table 6 above, it appears that in the RTX treatment group, patients with better renal function at baseline (as defined by creatinine level <1.2 mg/dL, or creatinine

clearance >60 ml/min, or no major renal item on the baseline BVAS/WG score) had significantly higher response rates at 6 months compared to those with renal disease or impairment (RTX remission rates were 66.7% [32/48] for no major renal item and 60.8% [31/51] for renal disease). This is compared with the respective rates of 62.7% [32/51] for renal disease and 42.6% [20/47] for no renal disease in those who received CYC.

Results for other efficacy outcomes in the pivotal study

The main secondary efficacy objective for RAVE Study was to assess the superiority of RTX compared to CYC/AZA in terms of the percentage of patients who achieved complete remission at 6 months. Although the proportion of patients in the RTX group who achieved complete remission was numerically higher than in the CYC group (64.3% versus 54.7%), the 9.5% treatment difference (95.1% CI -4.3, 23.4) was not statistically significant (p=0.177). However, because the lower limit of the 95.1% CI for the rate of complete remission in the RTX group exceeded 50%, this finding confirmed that RTX is superior to historical placebo.

In the first 6 months of the RAVE Study, no significant difference in severe or limited flares was observed between the 2 treatment arms (see Table 7, below).

Table 7. Severe and limited flares during the first 6 months (ITT population)

	Rituximab N=99	Cyclophosphamide N=98	p-value[a]
Severe flares			
Total number of severe flares	6	10	
Patients with ≥1 severe flare	5 (5.1%)	10 (10.2%)	
Sum of patient-months	533.4	531.8	
Rate of severe flares	0.011	0.019	0.293
Limited flares			
Total number of limited flares	14	14	
Patients with ≥1 limited flare	12 (12.1%)	14 (14.3%)	
Sum of patient-months	533.4	531.8	
Rate of limited flares	0.026	0.026	0.980

ITT=Intent-to-Treat
Note: Flare assessments for patients during crossover were excluded from this analysis.
[a] P-value for the treatment effect was derived from the Poisson regression model and adjusted for clinical study center and the type of anti-neutrophil cytoplasmic antibody. The natural logarithm of patient-months was used as an offset in this model.

The median cumulative dose of prednisone from baseline to 6 months was slightly lower in the RTX group (3310 mg) compared with the CYC group (3450 mg), but this was not statistically significant (p=0.055).

The proportion of patients who became negative for ANCA was higher in the RTX group (44.3%, 39/88) compared with the CYC group (29.5%, 23/78; p=0.050). Patients who were PR3+ and treated with RTX had the highest likelihood of becoming seronegative by 6 months (47.5%, 29/61 for RTX versus 25.0%, 14/56 for CYC; p=0.012). However, the ability for treatment to induce seronegative results in MPO+ patients was similar between the 2 treatment groups (39.3%, 11/28 for RTX versus 40.9%, 9/22 for CYC; p=0.907).

Regarding the change from baseline in markers of inflammation, erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) levels decreased in both groups between baseline and 6 months with a larger improvement in ESR seen in those administered RTX.

As noted by the evaluator regarding the maintenance of remission beyond 6 months, the efficacy results from the RAVE Study indicate that RTX is non-inferior to CYC in achieving remission when used as an induction therapy, but the increased rates of disease flare (severe and limited) beyond 6-12 months of follow-up (see Table 8 below) reinforce the

requirement for maintenance therapy (AZA and/or low dose CS) in most patients for at least a period of 18 months.

Table 8. RAVE Study: Summary of key efficacy endpoints at 6, 12 and 18 months

Timepoint	Rituximab (n=99)	Cyclophosphamide (n=98)	Difference (Two-sided 95% CI)
Complete Remission			
6 mos	63.6%	53.1%	10.6% (-3.2%, 24.3%)
12 mos	47.5%	38.8%	8.7% (-5.1%,22.5%)
18 mos	39.4%	32.7%	6.7% (-6.6%, 20.1%)
BVAS of 0 on prednisone dose of <10mg/kg/day			
6 mos	70.7%	61.2%	9.5% (-3.7%, 22.65%)
12 mos	59.6%	61.2%	-1.6% (-15.3%, 12.0%)
18 mos	54.5%	53.1%	1.5% (-12.4%, 15.4%)
BVAS of 0 irrespective of prednisone dose			
6 mos	78.8%	63.3%	15.5% (3.0%, 28.0%)*
12 mos	66.7%	63.3%	3.4% (-9.9%, 16.7%)
18 mos	56.6%	55.1%	1.5% (-12.4%, 15.33%)
Severe flares (rate per patient-month [cumulative no. of flares])			
6 mos	0.009 (5)	0.019 (10)	
12 mos	0.014 (14)	0.020 (19)	NA
18 mos	0.016 (22)	0.017 (23)	
Limited flares (rate per patient-month [cumulative no. of flares])			
6 mos	0.026 (14)	0.026 (14)	
12 mos	0.029 (29)	0.024 (23)	NA
18 mos	0.028 (38)	0.023 (30)	

Note: remission and partial remission rates based on worst case analysis
Flares occurring after switch of therapy were excluded from analysis.
*p< 0.05

Supportive study: the RITUXVAS Study

This was Phase II, open-label randomised trial of 44 patients from 8 centres in Europe (Britain, Germany, Sweden, Netherlands, Switzerland and Czech Republic) and Australia. The trial enrolled patients between June 2006 and June 2007. Patients were to be randomised 3:1 to receive RTX + concurrent low dose IV CYC, or IV CYC followed by AZA (control group).

The main trial design differences between the RITUXVAS and RAVE studies were: recency of diagnosis (newly diagnosed versus a mixture of new and relapsing disease, respectively), renal involvement (an inclusion criterion in RITUXVAS versus an exclusion if significantly impaired in RAVE), concomitant treatment with CYC (IV low dose CYC was used concurrently with RTX induction in RITUXVAS versus no concurrent CYC in the RTX arm in RAVE), and route of administration of CYC (IV CYC was exclusively used in RITUXVAS versus oral CYC as the comparator in RAVE).

After randomisation, both treatment groups were given 1000 mg of IV methylprednisolone followed by an identical oral CS tapering regimen (starting at 1 mg/kg/day [maximum starting dose of 60 mg/day] and then reduced to 5 mg/day by 6 months). In the experimental arm, patients were to receive RTX 375 mg/m^2 weekly for 4 weeks plus IV CYC at a dose of 15 mg/kg with their 1st and 3rd RTX infusions. In the control group, patients were administered IV CYC 15 mg/kg fortnightly for the initial 3 doses, and the every 2-3 weeks for 3-6 months until remission was achieved (BVAS of 0 for 2 consecutive months). In this group CYC induction therapy could be followed by AZA (up to 2 mg/kg/day) maintenance treatment. The RTX arm did not receive any scheduled maintenance treatment apart from tapering oral CS up until 6 months. However, patients in either group were allowed to receive further RTX or CYC for disease relapse at the discretion of the investigator.

The main efficacy variables were:

- BVAS score (and not the BVAS/WG, which has been specifically modified for GPA to remove some redundant evaluation items). The score range is 0-63.
- Vasculitis Damage Index (VDI), which measures vasculitis damage across multiple organs with 1 point assigned per item, and a maximum score of 64.
- Sustained Remission, defined as the absence of disease activity for 6 consecutive months.
- Remission, defined as the absence of clinical disease activity (BVAS 0) for at least 2 consecutive months.

There were a number of other efficacy outcomes including for example median time to remission, median change in BVAS score over the first 3 months, median change in GFR over 12 months, and prednisolone dose requirements.

The primary efficacy outcome was the percentage of patients achieving sustained remission at 12 months. As opposed to RAVE, the RITUXVAS study did not require patients to cease CS altogether. Analyses were performed on an ITT basis and included all 44 patients who were randomised into the study. Proportions were compared between the 2 treatment groups using chi-square test. Time-to-event analyses were performed using a log-rank test.

A total of 44 patients were randomised 3:1 (33 for RTX, and for 11 control treatment) into the RITUXVAS Study. No patients who were alive were lost to follow-up over 12 month study period, but 6 patients (18%) in the RTX + low dose CYC group and 1 patient (9%) in the CYC group had died prior to 12 months. Another patient in the CYC group died at 19 months.

In this study patients had new-onset of ANCA associated vasculitis with renal involvement. Subjects had a median age of 67 years (range: 20-85) and 52% (23/44) were male. Disease activity was high with the median BVAS score being 19 for the RTX group (range: 9-42), and 18 for the CYC arm (range: 12-23). At study entry, renal function was markedly impaired in both groups with the median GFR in mL/min/1.73 m^2 being 20 for the RTX group (range: 0-74) and 12 for the CYC arm (range: 0-48).

Primary efficacy outcome (RITUXVAS supportive study)

Sustained remission was achieved in 25 of 33 patients (76%) in the RTX + low dose CYC group and in 9 out of 11 patients (82%) in the CYC/AZA group. The absolute difference in sustained remission with RTX compared with CYC was -6% (95% CI: -33%, 21%), which is not statistically significant. Among patients who reached 12 months of follow-up, 93% (25/27) of patients in the RTX + low-dose CYC group, and 90% (9/10) of patients in the CYC group achieved sustained remission.

Other efficacy outcomes (RITUXVAS supportive study)

The median time to remission was 90 days (IQR, 79-112 days) in the RTX + low dose CYC group, and 94 days (IQR, 91-100 days) in the CYC group. Overall, remission occurred in 30 out of 33 patients (91%) in the RTX + low dose CYC group, and 10 of 11 patients (91%) in the CYC group.

The median BVAS score reduced from 19 (IQR, 14-24) at entry to 0 (IQR, 0-1.5) at 3 months in the RTX + low-dose CYC group, and 18 (IQR, 12-25) at entry to 0 (IQR, 0-0) at 3 months in the CYC group.

For the RTX + low dose CYC group, the median estimated GFR increased from 20 (IQR, 5-44) at baseline to 39 (IQR, 20-45) at 12 months. In the CYC group, the median GFR increased from 12 (IQR, 9-33) at entry to 27 (IQR, 12-47) at 12 months.

Prednisolone doses were reduced in both groups according to the study protocol, with 96% of patients from the RTX + low dose CYC group and 89% from the CYC group receiving prednisolone 5mg/day by 9 months.

Published Investigator Initiated Studies

A total of 162 patients with treatment refractory ANCA associated vasculitis participated in the 12 published investigator initiated studies, most (n=121) of whom received the same dose of RTX (375 mg/m^2 weekly for 4 weeks) used in the RAVE Study, as well as concurrent CS. All the studies collected data in an unblinded manner. Cumulatively, it was reported that 93% (151/162) of patients achieved either a complete or partial remission at 6-12 months of follow-up.

The Holle et al Study (published October 2011 and included by clinical evaluator): This publication reported on a retrospective study, using a standardised data collection methodology, for all patients who received RTX according to a standardized regimen for refractory GPA between 2002 and 2010 at a single tertiary referral centre in Germany. Included were 59 patients who received 75 cycles of RTX, and they were evaluated using the BVAS, Disease Extent Index, serum inflammatory markers (ESR and CRP), prednisolone dose requirements and clinical assessments. Patients in this cohort were predominately male (59%, 35/59) with a median age of 54 years (range: 22-76 years) and median disease duration of 37 months (range: 3-211 months). Most had received prior CYC (78.3%, 47/59) at a median cumulative dose of 27.75 g[5], indicating extensive prior therapy.

Complete remission was achieved in 7 (9.3%) patients. A response was documented in 61.3% of patients (52% [39/59] showed objective improvement, and 9.3% [7/59] had unchanged disease activity), and refractory disease was observed in 26.7% (20/59). Granulomatous disease manifestations such as orbital masses and meningitis were far less likely to respond than vasculitis. For example, complete remission or improvement was only recorded in 44.4% (12/27) of patients with orbital granulomas compared with 88.5% (23/26) of patients with renal disease. Furthermore, almost half of the patients (44.4%, 16/36) relapsed following RTX induction after a median period of 13.5 months (range: 3-54 months).

Safety

The overall clinical safety data (common close out (CCO) date for RAVE Study was 27 January 2010, and the cut-off date for the Global Safety Database was 31 August 2011) consists of a patient exposure of 374 patients in 15 studies, of who 266 received RTX. Most of the RTX treated subjects only received a single course of RTX therapy, at the sponsor's requested dose of 375 mg/m^2 weekly for 4 weeks. In the current submission, fewer than 40 subjects in total have been reported to have been exposed to a repeat course of RTX.

At 18 months of follow-up, the pivotal RAVE Study safety dataset provided a total of 139.6 patient-years of observation for RTX, and 134.7 patient-years of observation for CYC/AZA. For the analysis through to the CCO date, there were 299.2 patient-years of follow-up in the RTX group, and 274.7 in the CYC group. For sensitivity analyses in which data were summarised until the point of treatment switch, patient-years of follow-up were 168.4 for the RTX group and 136.1 for the CYC group.

As noted by the clinical evaluator and strongly endorsed by the Delegate, the current safety dataset provides sufficient information about the short-term risk with RTX in this population, that is, risks such as haematological toxicity, infections, infusion reactions, and

[5] Sponsor clarification: All patients had received CYC previously. Directly before treatment, 78.3% of patients (47/59) were receiving treatment with CYC at a median cumulative dose of 27.75 g.

discontinuations due to AEs. However, the extent of long-term follow-up is not adequate to assess for some potential AEs of concern that may have a long latency between drug exposure and AE occurrence, particularly malignancy, some opportunistic infections (such as PML) and cardiovascular safety. The study populations had baseline characteristics, disease activity and concomitant medications indicative of the intended target population for the claimed indication.

Key safety conclusions as noted in the clinical evaluation report

At 6 and 18 months, the overall incidence and rates per patient-year of exposure of any AE, AEs of pre-specified interest, grade 3 or higher AEs, and serious infections were similar in the RTX and CYC/AZA treatment groups.

However, infections (of any severity) were numerically greater and occurred at higher rate in patients who received RTX compared with control treatment (CYC/AZA) for both the 6-month (61.6% for RTX versus 46.9% for CYC/AZA) and 18-month analysis (79.8% for RTX versus 70.4% for CYC/AZA) time points.

The most frequent type of infectious AE in both treatment groups involved the respiratory tract (for example, there were 34 respiratory tract AEs in 22 RTX patients, and 28 corresponding AEs in 22 CYC subjects, at 6 months of follow-up).

Various types of herpes (11% for RTX versus 3% for CYC) and fungal infections (15% for RTX versus 11% for CYC) were also more common at 6 months in the RTX versus CYC treatment group.

The most common individual types of AEs (occurring in >10% of patients in either treatment group) showing a differential treatment related occurrence (>5% differential incidence) were diarrhoea, peripheral oedema, urinary tract infection and hypertension for RTX; and leucopenia, increased serum transaminases, and alopecia for CYC.

Permanent discontinuations of study medication as a result of AEs were more frequent in the CYC group (13.3% at 6 months) than the RTX arm (6.1% at 6 months).

At 6 and 18 months of follow-up, the incidences of overall SAEs were similar in the 2 treatment groups (33-34% at 6 months) with the most frequent type of SAE being infection (overall, 10.7% at 6 months; and 15.2% at 18 months).

The RAVE Study also clearly identified subsets of patients at the highest risk of AEs from RTX (or any other treatment strategy). Older patients (aged > 65 years) or those with significant renal impairment are the most vulnerable to a broad spectrum of AEs, particularly infections.

Older patients (>65 years) in both treatment groups had a higher incidence of severe (at least grade 3) and serious AEs compared to younger patients. All 4 deaths (2 in each treatment group) in the RAVE Study occurred in older patients. More hospitalisations due to either disease or study medication occurred in patients > 65 years of age, particularly in those who received RTX. Cardiac events also occurred more frequently in older patients who were given RTX induction therapy.

Subjects with impaired renal function at baseline had an increased risk of many AE types, including all infections (especially pneumonia and urinary tract infections), serious infections, death, hospitalisation, and anaemia. This outcome was regardless of treatment strategy (RTX or CYC induction therapy). Interestingly, all 4 (serious) cases of pulmonary embolism occurred in patients with higher creatinine clearance at baseline (2 in each treatment group).

In the supportive studies, a total of 254 subjects received treatment with RTX (for most subjects a single fixed induction course of 375 mg/m^2 x 4 infusions), and treatment follow-up was limited to 6-12 months. It is unclear for most of these studies how systematic the reporting of safety outcomes was in order to detect any potential safety concerns, but

SAEs appeared to be recorded. In the RITUXVAS Study, 48% (16/33) patients who received RTX experienced 35 SAEs. Similarly, the largest of the studies identified by literature search (the Jones *et al* Study) reported 45 SAEs in 25 subjects (38% of 65 affected) with 129 patient-years of follow-up. The study by Holle *et al* reported 24 SAEs in 59 individuals.

The consistent, key safety finding from all of these supportive studies is that infections were the most common type of SAE, and that the respiratory tract was the most common site of those infections.

Death has been reported in at least 15 subjects with ANCA associated vasculitis exposed to RTX (2 in the RAVE Study, 6 in RITUXVAS, 5 in the published investigator initiated studies plus a further 2 deaths were reported in the Holle *et al* trial). Five deaths (and 2 unknown) have resulted from infections. Disease progression despite treatment appears to explain at least 5 of the other deaths and 2 RTX treated patients from cardiovascular disease. However, the mortality rates and types of deaths observed in the RAVE, RITUXVAS and other studies is consistent with those expected in the target population of ANCA associated vasculitis.

A total of 6 malignancies in 5 RTX treated patients in the RAVE Study, and 4 patients treated with RTX + low dose CYC in the RITUXVAS trial developed cancers. No specific type of malignancy was observed. This result is within expectations for the target population.

Delegate's requests for information from the sponsor

In the following assessment, the Delegate raised several matters that the sponsor was requested to address in the sponsor's response to the Delegate's overview. These matters, below, are presented in bolded text.

A total of 8 deaths occurred in the RITUXVAS Study: 6 (18% of 33) occurring in the RTX group prior to 12 months and 2 (18% of 11) in the CYC group. Elsewhere in the CER, the number for the CYC group is reported as 1 patient (9%). **The sponsor is requested to clarify this discrepancy in their response to this overview**. The death rate in the RITUXVAS Study appears to be much higher than in the RAVE Study. There appears to be limited data available reporting on these deaths. **The sponsor is requested to provide as detailed a summation and clarification of these deaths,** particularly in relation to the deaths in the RAVE study and to what is known about deaths in the entire global safety database for rituximab, that is, for all indications. Is the higher rate of deaths in the RITUXVAS Study attributable to the fact that all patients in RITUXVAS had renal involvement? Are there any other factors involved?

RTX is associated with an increased risk of opportunistic infection, including pneumocystis pneumonia and PML (although no confirmed cases have been reported thus far in patients treated with GPA or MPA), as well as significant viral reactivations (individual reports of hepatitis B, CMV and fulminant adenovirus infection have been recorded in the ANCA vasculitis population).

The sponsor is asked to confirm that there have been no cases of PML reported, firstly in any patient treated with rituximab for either GPA or MPA and secondly in any patient treated with rituximab for any form of ANCA associated vasculitis, that is also including patients with Churg-Strauss Syndrome. The report is to have considered all data up to the latest possible cut-off date prior to the required submission of the pre-ACPM response on 12 Feb 2013.

The RAVE Study specifically examined the rate of hospitalisations due to either disease activity or study medication. More patients in the RTX group (10 of 99) were hospitalised because of active disease or study drug problems by 6 months compared to the CYC group

(4 of 98 subjects). The reasons for hospitalisation in both the RTX and CYC groups were typical for this population and included respiratory tract infections in 7 patients (pneumonia in 5 patients, upper respiratory tract infection in 1 patient, and bronchitis in 1 patient) as well as single cases of each of Adult Respiratory Distress Syndrome (ARDS), pulmonary haemorrhage, pulmonary embolism, renal failure, osteomyelitis, and a hypersensitivity reaction. Several of these hospitalisations appeared related to active vasculitis, or concomitant therapies such as CS. Two of the patients with pneumonia also had significant leucopenia and/or neutropenia. The data at 18 months and through to the CCO date was consistent with outcome observed at 6 months in that more patients were hospitalised for reasons related to disease activity or study drug (per the investigator's assessment) in the RTX group.

The type of AEs consistent with a disease flare in the RTX group in the RAVE Study included 3 patients with GPA who developed laryngeal stenosis, and 1 patient with GPA who experienced pulmonary haemorrhage. Events such as laryngeal stenosis and pulmonary haemorrhage were associated with hospitalisation. Two cases of laryngeal stenosis in the RTX group resulted in discontinuation from the RAVE Study.

The sponsor is requested to provide a detailed summary of all events of laryngo and/or tracheal and/or bronchial stenosis within the dossier.

By 6 months in the RAVE Study, 3 patients (2 in the RTX group and 1 in the CYC group) had developed grade 2 haemorrhagic cystitis.

In the RAVE Study, the overall incidence of any cardiac AE at 18 months was higher in the RTX group (18.2%; 18/99) than in the CYC arm (12.2%; 12/98). The difference was less pronounced at 6 months of follow-up but evident (12.1% in the RTX group versus 8.2% in the CYC group). The imbalance at 18 months was mainly attributable to grade 1 or 2 tachycardia and atrial fibrillation AEs. The incidence of cardiac SAEs was similar between the RTX and CYC groups (2.0%, or 2 cases each) at 18 months. Up to the CCO date, 1 serious cardiac SAE (myocardial infarction) was reported in a patient in the CYC group.

With respect to vascular AEs, at 18 months of follow-up in the RAVE Study, the overall incidence of venous thromboembolic events (a pre-defined AE of special interest) remained higher in patients treated with CYC (9.2% [9/98]) compared with 5.1% (5/99) in the RTX group. The AEs included 3 cases of deep vein thrombosis (DVT) and 2 of pulmonary embolism (PE) in the RTX group, and 8 DVTs and 2 cases of PE in the CYC group. Most of these events were rated as serious (3/5 in the RTX group, and 10/10 in the CYC arm).

A total of 6 malignancies in 5 patients treated with RTX, and 2 cancers in 2 patients treated with CYC were reported in the RAVE Study from randomisation until CCO. Two of the cases in the RTX group had received significant prior CYC therapy. There was no particular pattern in the type of malignancies observed. No melanoma cases were reported in the RAVE Study but 2 patients treated with CYC developed squamous cell skin cancers. A further 5 patients (3 treated with RTX and 2 given CYC/AZA) experienced non-serious skin cancers.

The RAVE Study demonstrated a higher frequency of leucopenia in the CYC versus RTX treatment groups at both the 6 (17.3% for CYC versus 5% for RTX) and 18-month time points (20.4% for CYC/AZA versus 7.1% for RTX). However, in both treatment groups no clear association between the occurrence of leucopenia and significant infections emerged. Thrombocytopenia of at least grade 2 severity by 18 months of follow-up was uncommon, but recorded in a higher number of RTX treated individuals (n=4; 2 with concurrent bleeding) compared with CYC/AZA managed subjects (n=1).

Infusion related reactions occurred in 11.2-12.1% of subjects in the RAVE Study, with a similar proportion of reported AEs in each of the treatment groups (RTX versus RTX

placebo infusions). RTX treated patients recorded a slightly different pattern of IRRs with features consistent with cytokine release syndrome being more common in the RTX group (5 patients in the RTX group versus 2 in the CYC arm). Only 1 subject in the RTX arm had to cease treatment due to an IRR. In the supportive studies, a small number of subjects (n=5) recorded significant IRRs.

Human Anti-Chimeric Antibodies (HACA) were only assessed in the RAVE Study, and developed in 28 subjects (22.6% of 124) as of the CCO date. The clinical relevance of positive HACA remains unclear with no discernible link to the risk of infection or acute infusion reactions. However, the presence does produce changes in PK behaviour with HACA positivity being clearly associated with increased clearance of RTX and reduced exposure to the drug.

In summary, the safety data indicates that RTX has an overall comparable safety profile to the current standard of care (CYC and/or AZA) in patients with severe systemic manifestations of GPA and MPA. There are some significant safety concerns including infection (particularly, involving the respiratory tract), hospitalizations for disease activity or medication side-effects, leucopenia, and thrombocytopenia. The Delegate shares the concerns of the clinical evaluator about the limited overall exposure to RTX for the target population, and that there was no significant safety information presented for repeat dose exposure. While the requested indication in this application is for "induction of remission", the Delegate is concerned that practitioners, on the basis of the approval of this application, will proceed to place patients on medium to long-term RTX.

The Delegate requests that the sponsor give very serious consideration as to how the wording of the PI may be amended/clarified/strengthened to reinforce the fact that the indication is ONLY for induction of remission. Such amendments could include extra wording in the indications, a precautionary statement, clarification in the *Clinical Trials* and/or *Dosage and Administration* sections. Both the sponsor and the ACPM are asked to comment on this issue.

Significant pharmacovigilance would be required if approval is granted for severely active granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). This would include vigilance for opportunistic infections, malignancy, all cause death, and cardiovascular AEs.

The sponsor is requested to provide a report in it pre-ACPM response detailing the precise pharmacovigilance activities it intends to put into place should this application be approved. Has the sponsor given consideration to the setting up of any patient registries, whether for this indication (GPA and MPA) or for any other indications?

The Delegate acknowledges the fact that the sponsor has been providing (and continues to provide) regular up-dates to the TGA regarding cases of PML and that a major review of the issue was undertaken by OPR late in 2012. However, given the importance and seriousness of this condition and despite the fact that there is already in the PI a boxed warning concerning PML, **the Delegate requests the sponsor to provide the most up-to-date summary of the numbers of confirmed cases of PML which have occurred in patients treated with rituximab** for all indications, whether approved in Australia or not. The sponsor is also asked to detail any cases which have occurred in Australia.

First round risk-benefit balance and list of questions

The clinical evaluator was of the opinion that the benefit-risk balance of RTX, given the proposed usage (induction of remission) in the target population (severely active systemic forms of GPA and MPA), is favourable. The clinical evaluator also expressed the view that the efficacy and safety of re-treatment with RTX has not been adequately evaluated to determine its role in this scenario. The natural history of ANCA associated vasculitis is that

a significant proportion of patients will relapse and require additional treatment in the future (2-7 years after diagnosis).

The clinical evaluator asked a number of questions of the sponsor (see Section 11 in Attachment 2 of this AusPAR). The Delegate's assessment of the issues raised in the questions (see *List of questions and Second round evaluation of clinical data submitted in response to questions*, above) is as follows:

There was agreement between the sponsor and the clinical evaluator that the assessment of alternative dose regimens for RTX requires additional controlled prospective trials. It would appear that the sponsor has acknowledged that in some centres around the world and in some published case series, beneficial efficacy outcomes have been achieved with RTX using lower dose regimens. **The sponsor is to clarify exactly the implications of this acknowledgement for the proposed dosage regimens in this submission**. Does the sponsor intend to carry out any studies with lower dose regimens?

In answer to the question about disease relapse, the sponsor has acknowledged that a significant proportion of patients with GPA and MPA experience disease relapse (up to half within 2 years) and that there is interest in evaluating the utility of maintenance RTX therapy for these patients. There was some brief discussion about two investigator-led studies in this field, namely the MAINRITSAN and RITAZAREM studies. **The sponsor is asked to clarify whether it has any intention of carrying out any specific studies involving maintenance RTX therapy for GPA and MPA**. The Delegate is minded to impose specific conditions of registration, the effect of which will be for the sponsor to provide to the TGA, as soon as available, the full published reports of the MAINRITSAN and RITAZAREM studies together with commentary from the sponsor as to the relevance of the findings of those studies.

From the clinical evaluator's comments about Question 3[6], it is unclear to the delegate whether the sponsor does have a plan to examine the possibility that increased rates of HACA may occur with repeat courses of RTX and/or extended dose intervals. **Does the sponsor have any plan to examine this issue?**

There is agreement, in relation to the answer to Question 4, that changes in CD19+ B-cells constitute an exploratory PD response biomarker at this stage.

With regard to Question 5, the sponsor has indicated that investigation into genetic-related differences in PD response to RTX is planned by the Immune Tolerance Network but that this work has not yet commenced. **The Delegate requests the sponsor to give a brief description of the latter network and its relationship, if any, with the sponsor**. Does the sponsor have any idea as to when this work will commence and therefore will be available?

With regard to Question 6, the sponsor replied that it is aware that several investigator-initiated studies have been performed in patients with autoimmune conditions (such as SLE and Sjogren's syndrome) using various RTX dosing regimens. The sponsor concurs that peripheral B-cells are depleted at relatively low doses of RTX, but only a minority of the whole body B-cell population resides in the peripheral blood. Furthermore, the sponsor considers peripheral blood B-cell depletion to be an unreliable PD marker correlating with clinical efficacy. As outlined in the section on *Relationship between pharmacodynamic effects and efficacy* of the CER (see Attachment 2 of this AusPAR) there is a limited relationship between B-cell depletion and efficacy outcomes in the first 6 months following induction therapy with RTX (RAVE Study). However, the data beyond 6 months suggests a different relationship outcome, in that many RTX treated patients had a

[6] *it is biologically plausible that increased rates of HACA development may occur with repeat courses of RTX and/or extended dose intervals, which may then have significant implications for the PK characteristics of RTX. Could the sponsor please comment if there is a plan to examine this issue?*

significant return of CD19+ B-cell counts between 6 and 12 months. Peripheral B-cell repletion did not appear to impact upon the rate of complete remission over time (up to 18 months), but showed a signal towards recurrence of ANCA disease. The number of disease flares between 6 and 18 months were 17 severe and 24 limited flares for the RTX group compared with 13 severe and 16 limited for the CYC/AZA arm. This result suggests the loss of RTX treatment effect beyond 6-12 months, which may be associated with B-cell recovery.

With regard to Question 7 concerning the relationship between dose and clinical outcomes, the sponsor included an additional analysis whereby the rates of remission outcomes (complete remission; and remission according to BVAS/WG score=0) at 6 months were assessed according to $AUC_{0\text{-}inf}$ quartiles (n=24 for each quartile). There was no evidence of any clear relationship just as there was no evidence of any clear relationship in the original submission between RTX $AUC_{0\text{-}inf}$ at or above the median value and complete remission at 6 months.

With regard to Question 8, the sponsor has replied that, despite a variety of opinions in the published literature, the sponsor is still of the view that the clinical trial evidence supports the use of RTX for both granulomatous and vasculitic manifestations of the disease. The Delegate would agree with the clinical evaluator that the issue is not entirely clear and needs to be kept under close observation.

With regard to Question 9, the sponsor stated that it had received no additional information on a case of suspected (but unconfirmed) PML in the Global Safety Database. As stated above, **the sponsor is asked to provide an up-to-date report on PML**.

Clinical evaluator's recommendation

The clinical evaluator has recommended that the extension of indications, as sought by the sponsor, should be approved.

Risk management plan

The Delegate noted that the sponsor has adequately addressed all OPR recommendations and the RMP evaluator has recommended 2 specific conditions of registration, namely the implementation of the appropriate PMP with the appropriate ASA and a condition relating to the provision of post-marketing reports.

Risk-benefit analysis

Delegate considerations

Risks

- Associated with the use of RTX in the treatment of patients with granulomatous polyangiitis and microscopic polyangiitis, there was a moderately high incidence of SAEs, death and hospitalizations, particularly for those of older age (>65 years) and with significant renal impairment, particularly when compared with patients ≤ 65 years and with patients without significant renal impairment.
- There is a lack of clarity with regard to the efficacy of rituximab in the treatment of granulomatous disease manifestations of GPA such as orbital masses, meningitis and tracheo-bronchial stenosis compared with what may be termed purely vasculitic manifestations. Such granulomatous disease manifestations may be less responsive to treatment with rituximab.

- Associated with rituximab therapy there is a significant risk of infections, including a variety of opportunistic infections, such as PML and PJP.
- The optimal dose and scheduling for rituximab infusions have not been adequately defined, nor has the role of concomitant or maintenance immunosuppression been delineated.
- As pointed out by the clinical evaluator, the design of the RAVE Study (that is, by using a single induction course of rituximab) provides no information about repeat dosing (either scheduled maintenance, or on-demand for disease relapse) of rituximab in patients with ANCA associated vasculitis. The Delegate would agree that this is a major deficiency in the current knowledge regarding the utility of rituximab treatment for patients with vasculitis, and requires further on-going studies or analysis by the sponsor.
- Sufficient numbers of treated patients with long-term (multi-year) follow-up have not been achieved. The delegate strongly agrees with the clinical evaluator that this may be important for issues such as malignancy development and cardiovascular disease.

Benefits

- At 6 months, 64.3% (63/98; 95.1% CI 54.76, 73.81) of patients in the RTX group achieved complete remission compared to 54.7% (52/95; 95.1% CI 44.68, 64.79) of patients in the CYC group. The treatment difference in the rate of complete remission was 9.5, with a lower limit of the 2-sided 95.1% CI being -4.3 (upper limit 23.4), which was greater than -20. Therefore, the protocol-specified non-inferiority margin was achieved and RTX therapy demonstrated non-inferiority to CYC in the induction of complete remission for ANCA associated vasculitis.
- The main secondary efficacy objective for RAVE Study was to assess the superiority of RTX compared to CYC/AZA in terms of the percentage of patients who achieved complete remission at 6 months. Although the proportion of patients in the RTX group who achieved complete remission was numerically higher than in the CYC group (64.3% versus 54.7%), the 9.5% treatment difference (95.1% CI -4.3, 23.4) was not statistically significant (p=0.177). However, because the lower limit of the 95.1% CI for the rate of complete remission in the RTX group exceeded 50%, this finding confirms that RTX is superior to historical placebo. **The sponsor is asked to define precisely what is understood, in this context, by the term historical placebo**.
- The Delegate agrees with both the sponsor and the clinical evaluator that RTX offers an alternative treatment strategy for life-threatening diseases (GPA and MPA) which currently have limited treatment options and a significant unmet therapeutic need.

Benefit-risk balance

The benefit-risk balance of rituximab, given the proposed usage (induction of remission) in the target population (severely active systemic forms of GPA and MPA), is favourable. The delegate agrees with the clinical evaluator that the efficacy and safety of re-treatment with rituximab have not been determined. This is of great importance given that the natural history of ANCA associated vasculitis is that a significant proportion of patients will relapse and require additional treatment in the future.

Proposed Action

The Delegate proposed to approve this submission by Roche Products Pty Limited to register MabThera injection concentrated vials (containing rituximab 100 mg/10 mL and 500 mg/50 mL) based on the safety and efficacy of the product having been satisfactorily established for the indication below, for the reasons stated above in the risk / benefit discussion, above.

"MABTHERA in combination with glucocorticoids is indicated for the induction of remission in patients with severely active Granulomatosis with Polyangiitis (GPA also known as Wegener's granulomatosis) and Microscopic Polyangiitis (MPA)"

This approval will be contingent upon the provision, by the sponsor, of satisfactory answers to all questions asked of the sponsor in this Overview and also upon amendment of the PI document[7] to the satisfaction of the TGA.

The Delegate intends to impose the following specific conditions of registration:

1. The implementation of Risk Management Plans as follows:

   The Core Risk Management Plan Version: 2.0, dated 16 March 2012, with an Australian Specific Annex (ASA) identified as Version: 1.0, dated 12 April 2012, to be revised as specified in the sponsor's correspondence dated 2 November 2012 with any future up-dates as may be agreed with the Office of Product Review.

2. Post marketing reports are to be provided in line with the current published list of European Union (EU) reference dates and frequency of submission of periodic safety update reports (PSURs) until the period covered by such reports is not less than three years from the date of this approval letter. The reports are to meet the requirements in accordance with ICH E2C (R2) guideline on Periodic Benefit-Risk Evaluation Reports and Module VII of the EMA Guideline on Good Pharmacovigilance (GPV) Practices relating to PSURs. Submission of the report must be within the 70 days of the data lock point for PSURs covering intervals up to and including 12 months and within 90 days of the data lock point for PSURs covering intervals in excess of 12 months. The submission may be made up of periodic Safety Update Reports each covering six months.

3. A condition of registration the effect of which will be for the sponsor to provide to the TGA, as soon as available, the full published reports of the MAINRITSAN and RITAZAREM studies together with commentary from the sponsor as to the relevance of the findings of those studies.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM, and requested advice and comment specifically with regards to the following issues:

a) The Delegate has requested that the sponsor give very serious consideration as to how the wording of the PI may be amended/clarified/strengthened to reinforce the fact that the indication is ONLY for induction of remission. The Delegate also requests the ACPM for advice on how this may be best achieved, not only in the wording of the Indications but elsewhere in the PI if thought appropriate.

b) Is the ACPM of the opinion that sufficiently detailed information exists in the proposed PI to highlight, clarify and explain the risks identified (see under *Risks*, above)? Again the Delegate requests ACPM to provide advice on how this may be best achieved.

c) Does the ACPM agree that it would be useful to include in the PI the Table showing complete remission at 6 months (see Table 6, above) according to baseline disease sub-group?

[7] Details of discussion and revisions to the PI and CMI are beyond the scope of the AusPAR.

Response from Sponsor

Comment on the Delegate's Proposed Action:

The Sponsor concurs with the Delegate's recommendation to approve MabThera (rituximab) 100 mg/10 mL and 500 mg/50 mL injection vials for the following indication:

> *"MABTHERA in combination with glucocorticoids is indicated for the induction of remission in patients with severely active Granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) and Microscopic polyangiitis (MPA)."*

Comments in response to the Delegate's specific requests

Clarification and summary of the deaths observed in the RITUXVAS study Deaths: RITUXVAS versus RAVE.

A total of 197 patients were enrolled in RAVE study (99 in the rituximab (RTX) group and 98 in the control group). The median age at study entry was 52 years. The treatment groups were balanced with respect to GPA versus MPA, disease activity and organ involvement (Table 9). Patients with advanced renal dysfunction (serum creatinine level, >4.0 mg/dL [354 µmol/L]) or who received treatment with plasma exchange within the 3 months preceding the screening visit were excluded from the study. Creatinine clearance (CrCl, measured in RAVE) an estimate of GFR (measured in RITUXVAS) was substantially higher in RAVE (Table 9).

Table 9. Key baseline demographic and clinical characteristics of the patients and deaths in the two studies RAVE and RITUXVAS

Baseline	**RAVE**			**RITUXVAS****		
Treatment Arm	**RTX**	**CYC**	**Both**	**RTX + CYC +**	**CYC+ steroids**	**Both**
Number of patients				33	11	44
Age (yrs) median Interquartile range	55 44-68	52 44-60	52 44-66	68 56-75	67 58-76	68
N (%) Male N (%) Female	47 (48%) 52 (52%)	53 (54%) 45 (46%)	100 (51%) 97 (49%)	17 (52%) 16 (48%)	6 (55%) 5 (45%)	23 (52%) 21 (48%)
Diagnosis N (%): GPA(WG) MPA Indeterminate / Missing Renal-limited vasculitis	73 (74%) 24 (24%) 2 (2%)	74 (75%) 24 (25%)	147 (75%) 48 (24%) 2 (1%)	18 (55%) 12 (36%) 3 (9%)	4(36%) 4 (36%) 3 (27%)	22 (50%)
GFR (mL/min/1.73m^2) median Interquartile range				20 5-44	12 9-33	

Baseline	RAVE			RITUXVAS**		
Treatment Arm	RTX	CYC	Both	RTX + CYC +	CYC+ steroids	Both
Creatinine clearance mL/min Median Interquartile range	68 42-99	88 50-121	75 46-110			
BVAS (RITUXVAS) BVAS/WG (RAVE) median Interquartile range	8 6-10	7 5-10	8 6-10	19 14-24	18 12-25	
Dialysis required N (%)	0	0		8* (24%)	1* (9%)	8
Use of plasma exchange N(%)	0	0		8 (24%)	3 (27%)	
Deaths	2	2		6	3***	9

* The glomerular filtration rate was 0 ml per minute among patients who underwent dialysis.

** Jones RB et al Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis. N Engl J Med 2010, 363:211-20

*** Jones RB et al Verbal presentation of abstract 2010a

Three deaths occurred during the first 6 months of treatment. Two patients in the CYC arm died of infections. One patient in the RTX arm died of multi-organ failure. One more death occurred in the RTX arm subsequently by the two year follow-up (Table 10).

Table 10. Summary of deaths in RAVE

Group	Related-ness	Age (yrs)	Creatinine at Entry	Died months from entry	Cause
RTX	unrelated	65	157 µmol/L no dialysis	2	Multi-organ failure; considered associated with the patient's underlying disease by the investigator
RTX	unrelated	78		16	Respiratory failure; investigator considers alveolar haemorrhage due to disease flare being life threatening, fatal, and unrelated to study medication, but rather related to a lack of efficacy.
CYC	Possibly	68	no dialysis	4	Pneumonia (multi-organ system failure with sepsis, due to

					Pseudomonas bacteremia and pneumonia); Investigator considered etiology to be multifactorial, possibly due to recent discontinuation of erythropoietin and/or bone marrow suppression from CYC or Bactrim.
CYC	Possibly	80	no dialysis	within 6	Septic shock (preceded by serious adverse events of Pneumocystis jiroveci pneumonia and myocardial infarction).

A total of 44 patients were enrolled in RITUXVAS study (33 in the RTX group and 11 in the control group). The median age at study entry was 68 years. Unlike RAVE, the use of plasma exchange at enrolment was allowed and was balanced between the groups (Table 9). However, the patients in the RTX arm in RITUXVAS had more renal dysfunction at baseline. 6 patients in the RTX group (1 at 0 month, 3 at 2 months 1 at 3 months, 1 at 10 months) and 1 patient in the control group had died by 12 months. An additional patient in the control group died at 19 months (Table 11).

Table 11. Summary of deaths in RITUXVAS

Group	Related-ness	Age (yrs)	Creatinine at Entry	Died months from entry	Cause
RTX	possibly	77	4.92 mg/dL (433 µmol/L) no dialysis	<1	Unstable angina, pulmonary oedema, congestive cardiac failure.
RTX	possibly	76	3.53mg/dL (311 µmol/L) dialysis x 1	2.5	ARDS query cause.
RTX	possibly	64	2.32mg/dL (204 µmol/L) no dialysis	3.5	Withdrawal of ESRD therapy.
RTX	unlikely	72	1.95mg/dL (172 µmol/L) no dialysis	2	Stroke, secondary pneumonia.
RTX	possibly	85	1.7 mg/dL (150 µmol/L) no dialysis	3	Multifactorial. Renal failure, C- diff infection, failure to thrive, withdrawal of therapy.
RTX	possibly	80	537 µmol/L dialysis for 3 months	10	Hypogammaglobulinaemia, diarrhoea, pneumonia, renal failure, cardiac ischaemia multiorgan failure
CYC	unlikely	82	8.51mg/dL (749 µmol/L) dialysis x 1	2 days	Sudden death, had received one dose of IV cyclophosphamide and 1g IV methylprednisolone.
CYC	unlikely	76	367 µmol/L no dialysis	19	Diverticulitis, colectomy, C- diff infection, failure to thrive

Group	Related-ness	Age (yrs)	Creatinine at Entry	Died months from entry	Cause
CYC***	unlikely	71	489 µmol/L no dialysis	20	Cardiac ischemia, renal failure, tracheal stenosis post trachyostomy

Sources: Jones RB *et al* Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis. *N Engl J Med* 2010; 363:211-20; *** Jones RB *et al.* Verbal presentation of abstract 2010a

[Note: the table above has been amended from the original to remove patient details.]

Since the peak age at diagnosis of ANCA associated vasculitis is 65–74 years[8], unlike previous studies that excluded older patients, RITUXVAS included elderly patients (typically with severe renal dysfunction) with no upper age limit, in order to provide a more accurate reflection of the population of patients with severe disease. The patient population overall was thus older and had more severe renal disease in RITUXVAS than the patients enrolled in the RAVE trial. These baseline demographic and clinical characteristics would likely explain observed higher mortality in RITUXVAS given that older age (> 65) and a lower GFR (dialysis dependency at diagnosis) are strong predictors of death among patients with ANCA associated vasculitis[9 ,10] with rapidly progressive glomerulonephritis being most common in elderly patients. Importantly, mortality observed in the 2 treatment groups (study drug and control arms) was almost the same in both RITUXVAS and RAVE. High mortality in RITUXVAS is consistent with the 18% rate of death reported in a large cohort study involving patients with ANCA associated renal vasculitis[2] as well as the rates of death in other trials involving patients with ANCA associated renal vasculitis.[11, 12, 13] In the RITUXVAS trial, 50% of deaths were attributed to infection, and the majority of deaths occurred early in treatment (before 3 months). Up to 6 weeks from trial entry, the 2 groups received the same glucocorticoid and CYC regimens; two initial CYC pulses were given with the RTX regimen because of the inclusion of patients with rapidly progressive glomerulonephritis and the lack of experience with RTX as primary therapy in such patients. Safety data involving the use of combination of RTX + CYC + steroids (also used in RITUXVAS) in the patients with rheumatoid arthritis (RA) or refractory SLE do not implicate this combination as an explanation for observed higher mortality in RITUXVAS as it did not do so in other autoimmune indications.

In conclusion, an older patient population with more severe renal disease in RITUXVAS compared to the patients enrolled in the RAVE trial likely accounted for observed higher mortality. This finding is consistent with previous studies involving patients with ANCA associated renal vasculitis.

[8] Watts RA, Mooney J, Skinner J, Scott DG, Macgregor AJ. The contrasting epidemiology of granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis. *Rheumatology (Oxford)* 2012, 51(5):926-31.
[9] Booth AD, Almond M, Burns A, *et al*. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. *Am J Kidney Dis* 2003;41:776-84.
[10] Slot MC, Tervaert JW, Franssen CF, Stegeman CA. Renal survival and prognostic factors in patients with PR3-ANCA associated vasculitis with renal involvement. *Kidney Int.* 2003, 63(2):670-7.
[11] de Groot K, Harper L, Jayne DRW, *et al.* Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med* 2009;150:670-80.
[12] Jayne D, Rasmussen N, Andrassy K, *et al*. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003;349:36-44.
[13] Jayne DR, Gaskin G, Rasmussen N, *et al*. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol* 2007;18:2180-8.

Clarification of PML cases in patients treated with rituximab for GPA, MPA and Churg-Strauss Syndrome

Up to the cut-off date of 17 January 2013 one case of unconfirmed PML has been reported in a patient with Wegener's granulomatosis. A copy of the case narrative was provided. Up to the same cut-off date no cases of PML have been reported in either MPA or Churg-Strauss Syndrome.

Summary of all events of laryngo and/or tracheal and/or bronchial stenosis

Subglottic inflammation and endobronchial involvement are considered manifestations of granulomatous diseases typically associated with GPA. Tracheal or bronchial stenosis is a physiologic term associated with narrowing, which can be associated with either inflammation or damage. Tabulated information was provided listing events associated with these conditions. The information reports on patients in both treatment groups that did not have these features at baseline yet developed them during follow-up in RAVE in the safety population: 7 patients developed these events in the CYC group, and 3 patients developed these manifestations in the RTX group. The occurrence of these events in patients that entered RAVE with baseline involvement of these events was also described. All patients shown had a baseline diagnosis of GPA, which is consistent with expectations. 7/13 patients in the CYC group also had an event post baseline, and 6/10 patients in the RTX group also had an event post-baseline. The details of the individual cases were also provided.

Amendments to the PI to reinforce that the indication is only for the induction of remission

The sponsor proposes additional text for the *Precautions*, *Adverse Effects* and *Clinical Trials* sections of the PI to address this issue. Details of these revisions are beyond the scope of this AusPAR.

Pharmacovigilance activities and patient registries for the proposed indication

The pharmacovigilance (PV) activities for the proposed GPA/MPA indication are listed below. They are either already included in the RMP or will be added to the RMP.

i. The sponsor is currently conducting a multi-centre (US-based), prospective, observational study designed to follow 100 RTX-treated patients with GPA or MPA for a maximum of 4 years (Study WA27893). An interim analysis will be performed when all patients are enrolled and approximately 50% of the estimated total patient-year exposure data (327 patient years) have been collected. WA27893 is already included in the RMP as a GPA/MPA PV activity for the following safety concerns: acute infusion-related reactions; infections; *de novo* hepatitis B and hepatitis B reactivation; opportunistic infections; malignant events; impact on cardiovascular disease; gastrointestinal (GI) perforation.

ii. Study ML22990 (GRAID II). The GRAID (German Register in Autoimmune Diseases) registry is already included in the RMP as a PV activity for the safety concerns: *de novo* hepatitis B and hepatitis B reactivation; opportunistic infections; malignant events; impact on cardiovascular disease; GI perforation. ML22990 is a retrospective study describing the use of biologics in autoimmune diseases, including use in vasculitis.

iii. Roche is planning to contact principal investigators from three national patient registries in the EU to investigate the possibility of obtaining standardised biannual (or annual) AE reports from cohorts of RTX-treated and RTX-naïve ANCA associated vasculitis patients. The national patient registries are the National Czech Registry of

ANCA associated vasculitis patients[14] and 2 Spanish patient registries that recruit biologic-treated, non−RA patients (BIOGEAS and BIOBADASER studies[15, 16]). The principal investigators from each registry will be contacted during Quarter (Q)1 2013 and Roche will initiate the generation of AE reports from ANCA associated vasculitis patient cohorts by end Q3 2013 for inclusion in subsequent Periodic Benefit−Risk Evaluation Reports (PBRERs). An investigation with the European Vasculitis Study Group (EUVAS) did not identify any additional relevant registries. The sponsor will continue to monitor EUVAS activities in case any relevant data sources may be identified in the future.

iv. The sponsor plans to utilise a standard AE reporting template (the "Manchester AE Reporting Template") to provide a standardised data reporting methodology across the above ANCA associated vasculitis patient registries. The Manchester template enables the generation of standardised semi-annual (or annual) reports from patient registries that include patient counts, baseline demographics and disease severity, treatment regimens, and incidences of specific AEs. The Manchester template will be used to generate biannual reports on AE rates in RTX-treated and RTX-naive ANCA associated vasculitis patients. Data will be requested for grouped and individual AEs listed in the RMP. The precise content of individual reports will be dependent on the data collection and reporting in each registry and will be discussed with the principal investigators prior to report generation.

v. For the specific risk of infections an additional planned PV activity is monitoring and evaluation of published data from any on-going studies where a 2 x 1000 mg fixed dose of RTX is used in the induction treatment of GPA/MPA (see response to the *Implications of the Sponsor's acknowledgement of the need for further evaluation of alternative dose regimens of rituximab in ANCA associated vasculitis and does the Sponsor intend to carry out any studies with lower dose regimens*, below), as well as evaluation of data from the ongoing PEXIVAS trial (once available). The objective is to capture long-term safety data, especially from the PEXIVAS study, to further evaluate dose regimen of RTX in relation to the frequency, seriousness and severity of infections. PEXIVAS is an academia-sponsored trial investigating plasma exchange and glucocorticoids for the treatment of ANCA associated vasculitis. The study began in 2010 and is planned for completion in 2016 with an estimated enrolment of up to 500 patients. During the study, a standard glucocorticoid dose regimen will be compared with a reduced glucocorticoid dose regimen. All patients will receive the same glucocorticoid dose for the first 2 weeks, after which the dose will decrease to follow either a standard regimen or a reduced regimen.

vi. Although relapses are a manifestation of the underlying GPA/MPA disease process rather than an adverse effect of treatment, the Sponsor plans to include 'Relapses' in the RMP as an additional important potential risk. The proposed PV activities for 'Relapses' will be the observation and evaluation of data from the on-going studies on maintenance therapy (MAINRITSAN and RITZAREM), with the aim of developing guidance for relapse-prevention treatment. Further information about the MAINRITSAN and RITZAREM studies is provided under the response to *Investigation of maintenance rituximab therapy for GPA and MPA,* below.

[14] Hruskova, Z, Jancova, R, Hanzal, V, *et al*. Clinical features and outcomes of cANCA-vs pANC Aassociated renal vasculitis [abstract]. 49th European Renal Association-European Dialysis and Transplant Association Congress, 2012 May 24−27.
[15] Ramos-Casals, M, García-Hernandez, FJ, de Ramo, J *et al* Off label use of rituximab in 196 patients with severe, refractory systemic autoimmune diseases. *Clin Exp Rheum* 2010;28:468−476.
[16] BIOBADASER 2012. https://biobadaser.ser.es/biobadaser/eng/index.htm

Up-to-date summary of PML cases

The table below reports the numbers and details of the unconfirmed and confirmed cases of PML which have occurred in approved and unapproved indications in Australia. The cut-off date is 17 January 2013.

Table 12. PML cases from Australia, cut-off date 17 January 2013

Indication	Confirmed	Unconfirmed	Total
rheumatoid arthritis	1		1
systemic lupus erythematosus		1	1
chronic lymphocytic leukaemia	1		1
chronic lymphocytic leukaemia		1	1
B-cell lymphoma	1		1
non-hodgkin's lymphoma		1	1
non-hodgkin's lymphoma	1		1
low grade lymphoma		1	1
follicular lymphoma		1	1
waldenstrom's macroglobulinaemia	1		1
lymphoma		1	1
lymphoma		1	1
lymphoma		1	1
lymphoma		1	1
drug use for unknown indication		1	1
Totals	5	10	15

An copy of the most recent PML Drug Safety Report (DSR) #1053546 (cut-off date 17 November 2012) was provided The DSR is a comprehensive review of the current available information for PML.

Implications of the sponsor's acknowledgement of the need for further evaluation of alternative dose regimens of rituximab in ANCA associated vasculitis and does the sponsor intend to carry out any studies with lower dose regimens

The dosing schedule used in the RAVE study was selected by the experienced key opinion leaders and investigators specialising in the treatment of this rare condition, in consultation with the National Institute of Allergy and Infectious Diseases (NIAID) and Roche (Genentech). The dosing recommendations were based on investigators' knowledge and initial experiences published by Keogh *et al* (2005).[17] Consideration in dose selection was given to concerns related to the severity of GPA/MPA, and the relapsing nature of these rare diseases. In addition, the proposed dosing regimen has also been used off-label in routine clinical practice for ANCA associated vasculitis and other indications.

Using a lower dosing regimen allowing exposure to lower RTX concentration would be unproven in a condition which requires aggressive treatment with immunosuppressive therapies. For example, some studies that suggested that RTX is less effective in patients in whom granulomatous manifestations predominated[18] were later on considered using a lower RTX dosing regimen.[19] Although some literature information may suggest the possibility of lower dose, on the basis of available data it remains a challenge to postulate whether lower RTX dose regimens would be non-inferior to the current standard of care in the absence of controlled prospective clinical trials. RAVE trial involving 197 patients took approximately 5 years to enrol and complete. Patients enrolled in RAVE could potentially have life threatening renal or pulmonary involvement, and evaluation of doses that might not enable adequate B cell depletion was a point of concern. So while the sponsor agrees that alternative dose regimens for RTX require additional controlled prospective trials, undertaking additional studies was not considered practical in this rare disease.

The data from two investigator-sponsored studies[20, 21], where the 2 x 1000 mg fixed dose of RTX is applied in the induction treatment of GPA/MPA was reviewed to assess a potential difference for the specific risk of infections with the use of different doses of RTX. On the basis of the data reported in these studies the sponsor does not consider that additional measures are required for the evaluation of infections. The sponsor will continue to review academia and investigator-sponsored study results with different doses of RTX through our signal detection activities, which includes literature review. Additionally the current PI contains detailed information about infections and their management. Since the results of the RAVE trial have been reported, no further dose ranging studies have been performed and none are planned by Roche for the induction of remission for patients with GPA or MPA.

Investigation of maintenance rituximab therapy for GPA and MPA

Roche is not planning to carry out any specific studies involving maintenance RTX therapy for GPA/MPA. However the sponsor will observe and evaluate data from the on-going maintenance therapy studies MAINRITSAN and RITZAREM, and these studies will form the basis of the PV activities for the new important potential 'Relapses' risk which is to be

[17] Keogh KA, Wylam ME, Stone JH, *et al*. Induction of remission by B lymphocyte depletion in eleven patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2005;52:262–268.
[18] Aries PM, Hellmich B, Voswinkel J, *et al*. Lack of efficacy of rituximab in Wegener's granulomatosis with refractory granulomatous manifestations. *Ann Rheum Dis* 2006; 65:853–858.
[19] Cartin-Ceba R, Fervenza FC, Specks U. Treatment of antineutrophil cytoplasmic antibody associated vasculitis with rituximab. *Curr Opin Rheumatol* 2012a; 24:15-23.
[20] Jones RB, Ferraro AJ, Chaudry AN, Brogan P, Salama AD, Smith KGC, Savage CSO, Jayne DRW. A Multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2009; 60:2156-2168.
[21] Smith RM, Jones RB, Guerry MJ, Laurino s, Catapano F,Chaudhry A, Smith KGC, Jayne DRW. Rituximab for remission maintenance in relapsing ANCA-associated vasculitis. *Arthritis Rheum* 2012;64(11):3760-3769.

added to the MabThera RMP. MAINRITSAN and RITZAREM are randomised, controlled studies of RTX versus AZA. They will provide important data to inform if scheduled retreatment with RTX in maintenance therapy is as effective or safe as AZA once remission has been achieved. Both studies include PK analyses. Recently published data from MAINRITSAN I demonstrate that retreatment with RTX is effective at treating relapses. The results demonstrated that retreatment with 500 mg of RTX every 6 months was superior to AZA in the maintenance of remission. The infection frequencies were comparable across both groups.[22] The next stage, MAINRITSAN II, will compare two treatment arms. In Arm A, RTX infusion will be performed on Days 1 and 15, and at Months 6, 12, and 18 (that is, a total of five infusions) with a fixed dose of 500 mg. In Arm B, RTX infusion will be performed on Day 1, and ANCA status and CD19+ lymphocyte counts will be monitored every 3 months. Patients in Arm B will receive new 500 mg RTX infusions if CD19+ counts are >0 cells/mm^3, if ANCA status becomes positive, or if the ANCA titre rises significantly. All patients in Arm A and Arm B will receive CS, starting from induction with prednisone (or equivalent) at a dose of 1 mg/kg/day with gradual tapering according to a regimen adjusted to body weight over a mean period of 18 months from diagnosis.

RITAZAREM protocol development is currently underway. This study will compare retreatment with 1000 mg RTX every 4 months with 2 mg/kg AZA daily for 24 months after the induction of remission (remission induced with 375 mg/m^2 RTX once weekly for 4 weeks). The study will include evaluation of anti-drug antibody development. RITAZAREM will enrol 160 patients with GPA or MPA and treated with either RTX or CYC <http://prsinfo.clinicaltrials.gov/ct2/show/NCT01697267>.

Roche concurs with the Delegate's proposed *Condition of Registration* to provide to the TGA as soon as available the full published reports for the MAINRITSAN and RITAZAREM studies together with commentary as to the relevance of the findings.

Investigation of HACA rates with repeat rituximab courses and/or extended dose intervals

Information available from limited studies in ANCA associated vasculitis[23, 24, 25], in addition to RAVE, suggest that while HACA development can occur over time in patients with ANCA associated vasculitis following the receipt of RTX, these HACA do not have clinical relevance. Importantly, this conclusion is consistent with that drawn from the assessment of safety and efficacy of RTX re-treatment in HACA-positive patients with RA. The findings of this assessment are as follows: In RA clinical trials, as of September 2011, 3,595 patients had received ≤19 courses of RTX over the 10 year observation period with 14,008 patient-years. Approximately 10% of patients with RA tested positive for HACA. The development of HACA following RTX exposure did not appear to affect the subsequent safety profile of HACA positive patients in terms of incidence, severity or type of AE, SAE or IRR experienced. HACA did not impact efficacy with the majority of HACA positive patients maintaining or improving American College of Rheumatology (ACR) response after HACA development (Roche data on file). Since there is no reason to consider that HACA development will be different in patients with different autoimmune indications, no

[22] Guillevin L, Pagnoux C, Karras A, *et al*. Rituximab versus azathioprine for maintenance in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis. Accepted abstract for ACR annual meeting, 9–14 November 2012; Washington DC.
[23] Smith RM, Jones RB, Guerry MJ, Laurino S, Catapano F, Chaudhry A, Smith KGC, Jayne DRW. Rituximab for remission maintenance in relapsing ANCA-associated vasculitis. *Arthritis Rheum* 2012;64(11):3760-3769.
[24] Keogh KA *et al*. Rituximab for refractory Wegener's granulomatosis: report of a prospective, open label pilot trial. *Am J Respir Crit Care Med* 2006; 173(2): 180-7.
[25] Cartin-Ceba R, Golbin JM, Keogh KA, Peikert T, Sanchez-Menendez M, Ytterberg SR, Fervenza FC, Specks U. Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener's): A single-center ten-year experience. *Arthritis & Rheumatism* 2012; 64: (In Press).

further studies are planned by Roche to investigate HACA following repeat courses of RTX and/or extended dose intervals, in patients with GPA or MPA.

Description of the Immune Tolerance Network [ITN] and work to be undertaken by ITN

The ITN is an international clinical research consortium sponsored by NIAID, part of the National Institutes of Health, with the objective to accelerate the clinical development of immune tolerance therapies through its hybrid academic/industry model. This interactive process capitalises on ITN's wide-ranging, multidisciplinary expertise, provided by an advisory board of highly respected faculties from global institutions helping investigators develop high quality research studies. The ITN actively investigates the mechanisms of tolerance induction and maintenance, integrating hypothesis-driven, mechanism-based research into all its clinical trials, also seeking to define new biomarkers of tolerance in human disease. An investigation into genetic-related differences including Fc-gamma receptor alleles and ribonucleic acid (RNA) profiling in PD response to RTX has been planned by the Mechanistics Group at the ITN however, the studies have only been outlined in broad terms; it is not yet clear if/when they will commence. The RAVE study was carried out by ITN and was partially funded by Roche.

Definition of historical placebo in the context of assessment of rituximab superiority in the RAVE study

The primary objective for RAVE was to demonstrate the non-inferiority of RTX compared with CYC/AZA and the superiority of RTX compared with historical placebo control, with respect to complete remission (CR) at 6 months. Explanation regarding the historical placebo control can be found in the Summary of Clinical Efficacy (in the submission dossier). In order to conclude that RTX was efficacious in RAVE, superiority to the expected CR rates for untreated patients, in addition to noninferiority to the active control at the pre-specified non-inferiority margin, would have to be demonstrated. In the absence of current data on CR rates in untreated patients at 6 months, RTX outcomes were to be compared with the survival rate generated from the Walton article[26] describing a cohort of 56 largely untreated patients with WG (GPA). Under a "best-case scenario" for untreated patients, assuming that all patients who survived would have achieved the definition of CR at 6 months, a maximum of 38% of the untreated patients (95% CI: 24.9%, 51.5%) would have met this endpoint. As the percentage of patients in CR can be no greater than the percentage of survivors, the actual number of untreated patients in CR was likely much lower than 38%. Based on the upper limit of this 95% CI, to conclude efficacy for RTX in RAVE, the lower limit of the 95% CI of the CR rate at 6 months in the RTX group was required to be >50%.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of quality, efficacy and safety agreed with the delegate and considered these products to have an overall positive benefit–risk profile for the proposed indication**;**

> *MABTHERA in combination with glucocorticoids is indicated for the induction of remission in patients with severely active Granulomatosis with Polyangiitis (GPA also known as Wegener's granulomatosis) and Microscopic Polyangiitis (MPA)*

[26] Walton EW. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). Br Med J 1958;2(5091):265-70.

The ACPM noted there were no studies submitted exploring optimal dose or use in maintenance therapy and very limited data provided on retreatment.

The ACPM advised that the pharmacovigilance measures to identify opportunistic infections, malignancy, cardiovascular adverse events and death as proposed by the sponsor are not considered sufficient. Only the European survey appears appropriate but its coverage, being limited to 2 countries, is inadequate. More extensive surveillance is necessary. There are many patient registries, including those run in Australia, which could be used.

The ACPM further advised that the age distribution, the frequency and severity of renal disease are quite different to the RA population identified in other indications for these products. The use of other immunosuppressive therapies is also quite different in these populations and these should be discussed clearly, using separate headings in the PI.

Proposed PI/CMI amendments:

The ACPM agreed with the Delegate to the proposed amendments to the PI and Consumer Medicine Information (CMI). The ACPM advised that the PI is often not clear as to which indication the information on any one page pertains to. A header or footer should be used to make the distinction clear.[27]

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised that an extensive review and amendment of the PI to the satisfaction of the TGA is required.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of MabThera (rituximab) 100 mg/10 mL and 500 mg/50 mL injection concentrate vials for:

> *MABTHERA in combination with glucocorticoids is indicated for the induction of remission in patients with severely active Granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) and Microscopic polyangiitis (MPA). The efficacy and safety of retreatment with MABTHERA have not been established.*

[27] Details of the ACPM advice on specific amendments to the PI and CMI are beyond the scope of the AusPAR.

The **full indications** are now:

Non-Hodgkin's lymphoma

MABTHERA is indicated for treatment of patients with:

- *CD20 positive, previously untreated, Stage III/IV follicular, B-cell non-Hodgkin's lymphoma*
- *CD20 positive, relapsed or refractory low grade or follicular, B-cell non-Hodgkin's lymphoma*
- *CD20 positive, diffuse large B-cell non-Hodgkin's lymphoma, in combination with chemotherapy.*

Chronic lymphocytic leukaemia

MABTHERA is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia (CLL) in combination with chemotherapy

Rheumatoid arthritis

MABTHERA (rituximab) in combination with methotrexate is indicated for the treatment of adult patients with severe, active rheumatoid arthritis who have had an inadequate response or intolerance to at least one tumour necrosis factor (TNF) inhibitor therapy.

MABTHERA has been shown to reduce the rate of progression of joint damage as measured by x-ray when given in combination with methotrexate.

Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA)

MABTHERA in combination with glucocorticoids is indicated for the induction of remission in patients with severely active Granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) and Microscopic polyangiitis (MPA). The efficacy and safety of retreatment with MABTHERA have not been established.

Specific conditions applying to these therapeutic goods

- The sponsor is required to implement the Risk Management Plan as follows: The Core Risk Management Plan Version: 2.0, dated 16 March 2012, with an Australian Specific Annex (ASA) identified as Version: 1.0, dated 12 April 2012, to be revised as specified in your correspondence dated 2 November 2012 with any future up-dates as may be agreed with the Office of Product Review.
- The sponsor is required to provide to the TGA, as soon as available, the full published reports of the MAINRITSAN and RITAZAREM studies together with commentary from the sponsor as to the relevance of the findings of those studies.

References

Aries PM, Hellmich B, Voswinkel J, *et al*. Lack of efficacy of rituximab in Wegener's granulomatosis with refractory granulomatous manifestations. *Ann Rheum Dis* 2006; 65: 853-858.

Barcellini W, Zaja F, Zaninoni A, *et al*. Low-dose rituximab in adult patients with idiopathic autoimmune haemolytic anaemia: clinical efficacy and biologic studies. *Blood* 2012; 119: 3691-3697.

Blum S, Gillis D, Brown H, *et al*. Use and monitoring of low dose rituximab in myasthenia gravis. J Neurol Neurosurg *Psychiatry* 2011; 82: 659-663.

Cartin-Ceba R, Golbin JM, Keogh KA, *et al*. Rituximab for remission induction and maintenance in refractory granulomatous with polyangiitis (Wegener's) : a single-center, ten-year experience. *Arthritis Rheum* 2012; 64: 000-000 (in ePress).

de Groot K, Harper L, Jayne DR, *et al*. Pulse versus oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med* 2009; 150: 670-680.

Hogan SL, Falk RJ, Chin H, *et al*. Predictors of relapse and treatment resistance in antineutrophil cytoplasmic autoantibody-associated small vessel vasculitis. *Ann Intern Med* 2005; 143: 621-631.

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. *Ann Rheum Dis* 2012;71:327-333 (published online October 21, 2011; doi: 10.1136/ard.2011.153601).

Horvath B, Huizinga J, Pas HH, *et al*. Low-dose rituximab is effective in pemphigus. *Br J Dermatol* 2012; 166: 405-412.

Jayne D, Rasmussen N, Andrassy K, *et al*. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Eng J Med* 2003; 349: 36-44.

Jones RB, Ferraro AJ, Chaudry AN, *et al*. A multicentre survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2009; 60: 2156-2168.

Jones RB, Cohen Tevaert JW, Hauser T, *et al*. Randomised trial of rituximab versus cyclophosphamide in ANCA associated renal vasculitis "RITUXVAS". *N Eng J Med* 2010; 363: 211-220.

Mukhtyar C, Lee R, Brown D, *et al*. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). *Ann Rheum Dis* 2009; 68: 1827-1832.

Pagnoux C, Hogan SL, Chin H, *et al*. Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated small vessel vasculitis: comparison of two independent cohorts. *Arthritis Rheum* 2008; 58: 2908-2918.

Ruyssen-Witrand A, Rouanet S, Combe B, *et al*. Fc gamma receptor type IIIA polymorphism influences treatment outcomes in patients with rheumatoid arthritis treated with rituximab. *Ann Rheum Dis*; published online February 25, 2012 (doi:10.1136/ard.2011.200337).

Seror R, Pagnoux C, Ruivard M, *et al*. Treatment strategies and outcome of induction-refractory Wegener's granulomatosis or microscopic polyangiitis: analysis of 32 patients with first-line induction-refractory disease in the WEGENT trial. *Ann Rheum Dis* 2010; July 19 (Epub).

Stone J, Merkel, P., Spiera R *et al*. Rituximab versus cyclophosphamide for ANCA–associated vasculitis. [The RAVE study] *New Eng J Med* 2010;363: 221-232.

Stone JH, Merkel PA, Seo P, *et al*. Rituximab versus cyclophosphamide for induction of remission in ANCA-associated vasculitis: a randomised controlled trial (RAVE). *N Eng J Med* 2010; 363: 221-232.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au