Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Rituximab

Proprietary Product Name: MabThera

Sponsor: Roche Products Pty Ltd

August 2015

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 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 <https://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

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
ACR	American College of Rheumatology
AE	Adverse event
ALP	Alkaline phosphatase
ALT [SGPT]	Alanine aminotransferase
AST [SGOT]	Aspartate aminotransferase
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence interval
CRF	Case report form
CTCAE v4.0	Common Terminology Criteria for Adverse Events version 4.0
DBP	Diastolic blood pressure
DMARD	Disease-modifying antirheumatic drug
ECG	Electrocardiogram
eform	Electronic form (page)
ESF	Eligibility screening form
FDA	Food and Drug Administration
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
IRB	Institutional review board
IRR	Infusion-related reaction
IV	Intravenous

Abbreviation	Meaning
IxRS	Interactive voice and web response system
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NCI	National Cancer Institute
NSAID	Nonsteroidal anti-inflammatory drug
RA	Rheumatoid arthritis
RBC	Red blood cell
RF	Rheumatoid factor
RTX	Rituximab
SAE	Serious adverse event
SBP	Systolic blood pressure
SIRR	Serious infusion-related reaction
SIE	Serious infection event
SSR	SUSAR Report
SUSAR	Suspected unexpected serious adverse reaction
TNF	Tumor necrosis factor
ULN	Upper limit of normal
WBC	White blood cell

I. Introduction to product submission

Submission details

Type of submission:	New dosing schedule in rheumatoid arthritis (RA) (major variation)
Decision:	Approved
Date of decision:	5 March 2015
Active ingredient(s):	Rituximab
Product name(s):	MabThera
Sponsor's name and address:	Roche Products Pty Ltd PO Box 255 Dee Why NSW 2099
Dose form(s):	Solution for injection
Strength(s):	100 mg/10 mL and 500 mg/50 mL
Container(s):	Single use vials for
Pack size(s):	2x 10 mL and 1x50 mL
Approved therapeutic use:	***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.*
Route(s) of administration:	Intravenous infusion (IVI)
Dosage:	A course of MabThera consists of two 1000 mg infusions. The recommended dosage of MabThera is 1000 mg by IV infusion followed by a second 1000 mg IV infusion two weeks later. The course of MabThera is given concomitantly with the dose of MTX tolerated by the patient. The minimal effective dose is not yet known.
ARTG number (s):	AUST R 60318 and AUST R 60319

Product background

This AusPAR describes the application by the sponsor to register an alternative, faster (2 h) infusion schedule of MabThera (rituximab) for the rheumatoid arthritis (RA) indication.

The faster 2 h infusion schedule will not apply to any non RA indication. Note this update also does not apply to a separately registered subcutaneous (SC) formulation of rituximab which does not have RA indication.

The currently approved dosage regimen for MabThera in RA is as follows:

> ***First infusion of each course:*** *The recommended initial rate for infusion is 50 mg/h; after the first 30 minutes, it can be escalated in 50mg/h increments every 30 minutes, to a maximum of 400 mg/h.*
>
> ***Second infusion of each course:*** *Subsequent doses of MABTHERA can be infused at an initial rate of 100 mg/h, and increased by 100 mg/h increments at 30 minutes intervals, to a maximum of 400 mg/h.*

With this application, the sponsor seeks to change this to:

> ***First infusion:*** *The recommended initial rate for infusion is 50 mg/h; after the first 30 minutes, it can be escalated in 50mg/h increments every 30 minutes, to a maximum of 400 mg/h.*
>
> ***Subsequent infusions:*** *Subsequent doses of MABTHERA can be infused at an initial rate of 100mg/h, and increased by 100mg/h increments at 30 minutes intervals, to a maximum of 400mg/h.*
>
> ***Rheumatoid Arthritis only: Alternative Subsequent, Faster, Infusion Schedule****:*
>
> *In RA, with a dose of 1000mg MABTHERA, if there are no infusion related reactions or other reasons to slow or cease the infusion, the standard infusion schedules shown above result in an estimated duration of infusion of 4h 15 minutes for the first infusion and 3h 15 minutes for the subsequent infusions.*
>
> *If patients do not experience a serious infusion related reaction with their first or subsequent infusions administered over the standared infusion schedule, a more rapid infusion can be administered for second or subsequent infusions using a concentration of 4mg/mL in a 250mL volume. Initiate at a rate of 250mg/h for the first 30 minutes and then 600mg/h for the next 90 minutes. With this infusion schedule, the 1000mg/250mL infusion will generally be completed in 2 h. If the more rapid infusion is tolerated, this infusion schedule can be used when administering subsequent infusions.*
>
> *Patients who have clinically significant cardiovascular disease, including arrhythmias or previous serious infusion reactions to any prior biologic therapy or to rituximab, should not be administered the more rapid, 2 h, infusion.*

In addition to proposing an alternative 2 h infusion schedule in RA, the following changes to the dosing schedule are also inherent in this update:

1. The currently approved dosing schedule mandates a slow (4 h) infusion schedule for the first infusion of every course of rituximab. The second infusion in each course is then given as a 3 h infusion.
2. This submission is seeking to limit the 4 h infusion to only the first ever infusion in a patient. All subsequent infusions can be standard 3 h infusions. The new 2 h infusion schedule may be used in as an alternative to 3 h infusions in any infusion subsequent to the first infusion in a patient where a patient has not previously experienced any serious infusion related adverse reaction (SIRR).
3. Limitation of the 4 h schedule to first infusion only was not investigated but appears to have been a consequence of the proposal to adopt 3 h or 2 h alternative schedules for all subsequent doses.

The sponsor has not proposed any changes to the current indications for MabThera. For the currently approved indications in Australia for MabThera in RA see *Submission details* above and Attachment 1 PI. For non-rheumatoid arthritis indications please see the approved PI (Attachment 1). There are no changes proposed to the currently registered formulation.

Rituximab is a chimeric part-human part-mouse monoclonal antibody against human CD20, a cell surface antigen expressed on B-lymphocytes. Rituximab is a highly purified 1328-amino acid antibody with an approximate molecular weight of 145 kilo Daltons (kD). It is a glycosylated immunoglobulin (Ig) G1 kappa immunoglobulin containing murine light and heavy chain variable regions and human gamma 1 heavy-chain and kappa light-chain constant regions.

Rituximab binds specifically to the CD20 antigen[1] expressed on B cells; it does not bind to haematopoietic stem or CD20 negative precursor cells. Rituximab depletes peripheral B cells by several potential mechanisms, including complement-mediated lysis, antibody dependent cellular cytotoxicity (ADCC) mediated killing and apoptosis.

The application is supported by clinical data and a Risk Management Plan (RMP) only. The clinical data comprised one uncontrolled study using 2 h schedule (Study ML25641) for assessment of safety outcomes. No new efficacy data were included in the submission.

The following Guidance relates to the present application:

- CPMP/EWP/556/95 Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDs for Treatment of Rheumatoid Arthritis.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) in October 1998.

At the time the TGA considered this application, a similar application had been approved in the European Union (EU) and New Zealand. A provisional approval letter had been given by Swissmedic. At the time the TGA considered this application, a Complete Response Letter had been issued in the USA (see details in Table 1 below).

Table 1: International regulatory status

Country	Status
Canada	Not yet submitted
European Union/UK	Approved 23rd May 2014
New Zealand	Approved 16th May 2014
Switzerland	Provisional approval letter issued 18 December 2014 Approval due in May 2015, subject to labelling negotiations
USA	Complete Response Letter issued 28 July 2014. The Sponsor is currently evaluating this.

[1] The protein has no known natural ligand and its function is to enable optimal B cell immune response, specifically against T-independent antigens.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

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

Clinical Rationale

Currently a patient visit for the second or subsequent infusion in RA takes 4 to 5 h including the time for premedication and post infusion observation. With a faster infusion rate this time would be reduced to approximately 3 h, thereby reducing the burden of time per treatment.

The only infusion regimen studied throughout the RA development program was largely based on the protocol used to treat patients with Non-Hodgkin Lymphoma (NHL). Patients with RA do not have an expanded pool of B cells compared with B-cell NHL or chronic lymphocytic leukaemia (CLL) patients. This may partially explain why the rate of infusion-related reactions (IRRs) reported in patients with RA is lower than those with oncology indications in which a large pool of B cells are rapidly depleted with the first infusion.

The sponsor has identified five Investigator sponsored, published studies that explored accelerated administration regimens (Table 2). However, due to the limitations of the published studies (primarily the identification and definition of IRRs) the sponsor considers these data to be supportive only. Hence, the sponsor has initiated their own study to demonstrate the safety of an accelerated administration regimen in patients with RA. These studies are discussed in more detail under *Safety* in Attachment 2.

Table 2: Summary of Published Studies with Faster-Infusions of Rituximab in Patients with Rheumatoid Arthritis and Other Autoimmune Disorders

Study (Reference)	No. of Patients (Histology)	Treatment Regimen	Infusion Time	Premedication	Treatment Courses (No. of IRRs)
Larsen and Jacobsen 2013	54 patients with various autoimmune diseases (RA, Wegener's granulomatosis, systemic lupus erythematosus, primary Sjögren's syndrome)	RTX, 2 × 1000 mg separated by 2 weeks	First infusion of 195 minutes followed by a second infusion over 90 minutes	Oral prednisone, acetaminophen, antihistamine	5 (9.2%) had IRRs on first infusion; 2 (3.7%) had IRRs on second infusion; 3 (5.5%) had IRRs on both infusions
Schoeffel et al. 2008	42 patients with RA	RTX, 2 × 1000 mg separated by 2 weeks	First infusion administered per product label followed by a second infusion over an average of 67 minutes (range: 37 to 150 min)	Not specified	74 treatment courses; patients who experienced AEs during first course tolerated second course (details of IRRs not available)
Bukh et al. 2008	12 patients with RA; 1 subject with juvenile RA	RTX, 2 × 1000 mg separated by 2 weeks	First infusion 50 mL/hr [a], increased by 50 mL/hr every 30 minutes; maximum of 200 mL/hr, total infusion time approximately 3.25 hr Second infusion started at 200 mL/hr and increased by 200 mL/hr after 30 min to a maximum of 400 mL/hr, for a total infusion time of approximately 1.5 hours.	IV 100 mg methylprednisone , acetaminophen, antihistamine	14 treatment courses resulted in zero AEs; among other courses AEs resulted but all were mild (details of IRRs not available)
Faraawi et al. 2010	10 patients with RA with inadequate response to one TNF inhibitor	RTX, 2 × 1000 mg separated by 2 weeks	First infusion administered per product label followed by second infusion over 120 minutes	IV 100 mg methylprednisone acetaminophen, diphenhydramine	36 infusions followed by 26 rapid infusions; 1 minor IRR
Can et al. 2013	68 patients with autoimmune diseases	RTX, 2 × 1000 mg separated by 2 weeks	First infusion administered per product label followed by second infusion over 120 minutes	IV 100 mg methylprednisone acetaminophen, diphenhydramine	9 patients had AEs (6 had IRRs on first infusion, 2 on second infusion, and 1 on both infusions)

AE = adverse event; IRR = infusion-related reaction; IV = intravenous; RA = rheumatoid arthritis; RTX = rituximab; TNF = tumor necrosis factor; hr = hour; min = minute

[a] Concentration not given

Contents of the clinical dossier

Scope of the clinical dossier

The submission included one pivotal safety study: Study ML25641.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

Study ML25641 appears to have been conducted according to Good Clinical Practice (GCP).

Pharmacokinetics

No new pharmacokinetic data were included in the submission.

Pharmacodynamics

No new pharmacodynamic data were included in the submission.

Dosage selection for the pivotal studies

The dosage selection was based on the currently approved dose, with a new rate of delivery.

Efficacy

No new efficacy data were included in the submission.

Safety

Studies providing safety data

The pivotal study,Study ML25641provided evaluable safety data for this submission.

Patient exposure

There were 351 subjects who received Infusion one, 341 (97.2%) who received Infusion two, 290 (82.6%) who received Infusion three and 278 (79.2%) who received Infusion four (Table 3). A total of 73 (20.8%) subjects discontinued before Week 30: 19 (5.4%) because of adverse event (AE), 20 (5.7%) due to protocol violation and 23 (6.6%) because of the Subject's decision. Not all of the subjects received the intended faster infusion rate for the second and subsequent infusions: 337 (98.8%) of the subjects that received Infusion two, 289 (99.7%) at Infusion three and 278 (100%) at Infusion four.

Table 3: Patient Disposition by Infusion for Study ML25641

	All Patients (N = 351)
Received rituximab Infusion 1	351 (100%) [a]
Complete rituximab infusion (1000 mg) [b]	338 (96.3%)
Discontinued prior to rituximab Infusion 2	
Total	10 (2.8%)
Adverse event	7 (2.0%)
Subject's decision	2 (0.6%)
Lost to follow-up	1 (0.3%)
Received rituximab Infusion 2	341 (97.2%) [a]
Received rituximab at faster infusion rate [b]	337 (98.8%) [a]
Completed rituximab infusion (1000 mg) [b]	333 (97.7%)
Discontinued between Infusions 2 and 3	
Total	51 (14.5%)
Adverse event	10 (2.8%)
Lost to follow-up	3 (0.9%)
Physician's decision to withdraw subject	7 (2.0%)
Protocol violation	15 (4.3%)
Subject's decision	16 (4.6%)
Received rituximab Infusion 3	290 (82.6%) [c]
Received rituximab at faster infusion rate [b]	289 (99.7%)
Completed rituximab infusion (1000 mg) [b]	288 (99.3%)
Discontinued between Infusions 3 and 4	
Total	12 (3.4%)
Adverse event	2 (0.6%)
Protocol violation	5 (1.4%)
Subject's decision	5 (1.4%)
Received rituximab Infusion 4	278 (79.2%)
Received rituximab at faster infusion rate [b]	278 (100%)
Completed rituximab infusion (1000 mg) [b]	277 (99.6%)
Complete the study (Day 210/Week 30)	278 (79.2%)

[a] Infusion rate and dose could not be determined for 4 patients since the site failed to record the infusion volume for both Infusions 1 and 2. Of these 4 patients, one withdrew prior to Infusion 3; three received Infusion 3, and two received Infusion 4 at the faster rate.

[b] Percentages are of the number of patients received rituximab at the corresponding visit.

[c] The infusion was administered at the labeled rate for one patient.

Postmarketing data

MabThera has been licensed and is marketed in over 100 countries including the USA, all EU member states, Norway, Iceland, Japan, Australia, New Zealand, Canada and Switzerland. An estimated 402,372 RA patients have been treated with rituximab via commercially obtained drug and through clinical trials.

The data submitted in Study ML25641 were the only postmarketing data submitted by the sponsor relating to the rapid infusion rate.

The sponsor had also identified through a literature search five studies that described subjects with RA that had received rapid infusions of rituximab but the sponsor considers these data to be only supportive because of the poor quality of the studies and reports. These studies are described in Table 2 and were:

- Faraawi and Roth 2010 was a publication in abstract for describing 10 subjects with RA who between them received 36 infusions of which 26 were rapid infusions of rituximab. One subject experienced an episode of headache, chest tightness and shortness of breath which resolved during the infusion.

- Larsen and Jacobsen 2013 describe 54 subjects who received rapid infusions of rituximab. There were 16 subjects with RA. Ten (18.5%) subjects experienced IRRs: three (5.5%) with both infusions, eight (14.8%) on the first and five (9.2%) on the second. The highest prevalence of IRRs was stated to be in the RA group at 9.2% but this does not correspond to a plausible number of subjects (1.5 subjects).
- Schoeffel et al 2008 was a report in abstract form of a cohort of subjects with RA that were treated with a rapid infusion of rituximab (range 37 to 150 minutes). The methods for identifying and classifying IRRs were not reported. No IRRs were reported.
- Bukh et al was a conference presentation published in abstract form and presented as a poster. It described 13 subjects, 12 with RA that were treated with a rapid infusion of rituximab for their second infusion (1000 mg over 1.5 h). The methods for eliciting and categorising IRRs were not described. One subject experienced mild hypotension. One subject had the infusion stopped temporarily due to sweating, feeling uncomfortable, temperature of 37.9°C and paraesthesiae in the arms.
- Can et al 2012 describes a cohort of 68 subjects, 60 of whom had RA. There were 71 rapid infusions (1000 mg over 2 h) administered in the RA group. There were three (5.9%) subjects with IRRs on the second infusion. The symptoms experienced were pharyngeal discomfort, vertigo, hypotension and cough.

The evaluator agrees with the sponsor's assessment of the quality of the studies and that these studies did not provide sufficient demonstration of safety to support the proposed new rapid dosing regimen. The evaluator also considers that these studies do not raise any additional safety concerns with regard the proposed new rapid infusion dosing regimen.

Evaluator's conclusions on safety

The data primarily address the issue of IRRs, which are the primary concern arising from a more rapid administration rate of intravenous rituximab. The rates of IRRs with the proposed new rapid infusion rate are similar to those observed in previous studies conducted in the RA population. The incidence (95% confidence interval (CI)) of IRRs associated with the rapid infusion rate at the time of the second rituximab infusion was 6.5% (4.1% to 9.7%). The sponsor provided a weighted historical incidence (95% CI) of IRRs associated with the second rituximab infusion of 8.1% (7.2% to 9.1%). The rate of IRRs (95% CI) from Study WA17047 IMAGE and Study WA17045 SERENE was 5.3% (3.4% to 8.0%) for the second infusion.

The incidence (95% CI) of IRRs associated with the rapid infusion rate at the time of the third rituximab infusion was 5.9% (3.5% to 9.3%). The weighted historical incidence (95% CI) of IRRs associated with the third rituximab infusion was 11.5% (10.3% to 12.8%). The rate of IRRs (95% CI) from Study WA17047 IMAGE and Study WA17045 SERENE was 9.2% (6.5% to 12.5%) for the third infusion.

In Study ML25641 there were no SIRRs associated with the rapid infusion rate. There was one CTC Grade 3 or 4 AE reported following the second infusion and none following the third. The incidence (95% CI) of stopping/slowing/interrupting the second rituximab infusion was 3.9% (2.1% to 6.5%) and the third rituximab infusion was 6.6% (4.0% to 10.1%). The adverse event profile reported in the study is consistent with the known AE profile of rituximab.

The proposed new rapid infusion rate dosing regimen in the PI document is the same as that used in Study ML25641.

All subjects in Study ML25641 were treated with methotrexate. Hence, the study results are not generalisable to patients who are not treated with methotrexate. However, this is

consistent with the indication, which includes only those patients with RA who are receiving concomitant treatment with methotrexate.

All subjects in Study ML25641 received the following pre-medication before each rapid rate infusion:

1. Methylprednisolone 100 mg by slow intravenous infusion (over 10 to 15 minutes) administered at least 30 minutes prior to each infusion.
2. Acetaminophen 1 g administered orally 30 to 60 minutes prior to each infusion.
3. An antihistamine (diphenhydramine HCL 50 mg or equivalent dose of alternate) administered orally 30 to 60 minutes prior to each infusion.

The administration of methylprednisolone 100 mg, paracetamol and antihistamine is also recommended in the dosing instructions, according to the same regimen as in Study ML25641.

In Study ML25641 there were 198 (56.4%) subjects treated with concomitant glucocorticoids. However, this would be typical of the RA population and does not impact upon the dosing recommendations.

The study population in Study ML25641 was subjects with RA of ≥ 6 months duration treated with methotrexate who had an inadequate response to a Tumour Necrosis Factor (TNF) inhibitor. However, the indication in Australia is restricted to patients with severe, active RA:

> *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.*

However, in the opinion of the evaluator, the results of Study ML25641, conducted in a general population of subjects with RA are applicable to a population of patients with severe, active RA.

The results of Study ML25641 are only generalisable to patients with RA and not to any other medical conditions. Only subjects with RA were included in Study ML25641.

The study design (single arm, no comparator and using historical data for comparison) was acceptable for evaluation of the safety of the proposed new rapid infusion. The study design would not have been appropriate for the evaluation of efficacy. There were 337 subjects who received the rapid infusion regimen which, in the opinion of the evaluator represents a sufficient number of subjects included in the study. The open nature of the trial may have resulted in measurement bias. However, the primary outcome measure (IRRs) should have been sufficiently objective and robust to overcome this deficiency. The historical incidence (95% CI) of IRRs associated with the second rituximab infusion was 8.1% (7.2% to 9.1%) but the prospective data provided by the sponsor was a rate of IRRs (95% CI) from Study WA17047 IMAGE and Study WA17045 SERENE of 5.3% (3.4% to 8.0%) for the second infusion. This would suggest bias in the elicitation of IRRs for the historical data rather than bias in Study ML25641. The methods used for identifying IRRs from the historical data were different to those for identifying IRRs prospectively[2]. Overall the evaluator was satisfied with the design and conduct of Study ML25641.

[2] The sponsor has commented on the methods used to identify IRRS in the historical and Study ML25641 data on page 30 of this AusPAR.

First Round Benefit-Risk Assessment

First round assessment of benefits

Efficacy was not addressed in the present application but the proposed new rapid administration would be expected to reduce treatment costs and be more convenient to patients.

First round assessment of risks

The proposed alternative, faster infusion schedule of MabThera for rheumatoid arthritis has a similar risk for IRRs as the currently approved administration regimen. There were no other risks identified with the proposed alternative, faster infusion schedule of MabThera.

In the opinion of the evaluator, off-label use of the new rapid infusion is also an Important Potential Risk that should be addressed in the RMP.

First round assessment of benefit-risk balance

The benefit-risk balance of the alternative, faster infusion schedule of MabThera for RA, given the proposed usage, is favourable.

First Round Recommendation Regarding Authorisation

The evaluator has no objection to the approval of the alternative, faster infusion schedule of MabThera for RA.

Clinical Questions

The clinical evaluator did not raise any questions with the sponsor.

Second Round Evaluation of clinical data submitted in response to questions

No second round evaluation was conducted.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted an EU Risk Management Plan (EU-RMP) (Version: 12.0, dated 10 February 2014) with an Australian Specific Annex (ASA) Version: 4.0, dated October 2014 which was reviewed by the TGA's Post-Market Surveillance Branch (PMSB).

Safety specification

The sponsor submitted an EU Risk Management Plan (EU-RMP) (Version: 12.0, dated 10 February 2014) with an Australian Specific Annex (ASA) Version: 4.0, dated October 2014 which was reviewed by the TGA's Post-Market Surveillance Branch (PMSB).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 4.

Table 4: Summary of ongoing safety concerns

Changes compared to EU-RMP version 9.1 are shaded in grey in the tables below.

Important Identified Risks of MabThera

• Infusion related reactions[a]	• Serious viral infections[b]
• Infections[a]	• Gastrointestinal (GI) perforations[b]
• Impaired immune response[a]	• Posterior Reversible Encephalopathy Syndrome (PRES)[b]
• Progressive multifocal leukoencephalopathy (PML)[a]	• Hypogammaglobulinaemia[c]
• Neutropenia (including prolonged)[a]	• Tumour lysis syndrome[b]
• Hepatitis B virus reactivation[a]	• Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis[a]
• Local cutaneous reactions (subcutaneous formulation)[e]	

[a] All indications. [b] NHL/CLL [c] RA and GPA/MPA [d] GPA/MPA [e] NHL

Important Potential Risks of MabThera

• De Novo HBV, and HBV Reactivation[c]	• Second malignancies[b]
• Opportunistic infections[a]	• Off label use in autoimmune disease[c]
• Malignant events[c]	• Off label use in paediatric patients[a]
• Impact on cardiovascular disease[c]	• Relapses[d]
• GI perforations[c]	• AML/MDS[b] (NHL/CLL indications only)
• Prolonged B-cell depletion[a]	• Increased risk of Grade 3/4 and serious blood and lymphatic system AEs in older patients (>70 Years of Age)[b]
• Embryotoxicity resulting from systemic exposure to rHuPH20 (SC formulation)[e]	

[a] All indications. [b] NHL/CLL [c] RA and GPA/MPA [d] GPA/MPA [e] NHL

Important Missing Information about MabThera

• Use in pregnancy and lactation[a]
• Immunogencity and autoimmune disease[c]
• Long term use in GPA/MPA patients[d]
• Immunogenicity associated with the SC formulation[e]
• Effect of greater exposure in patients with low BSA after fixed –dose s.c. administration (NHL indications only)[e]

[a] All indications. [b] NHL/CLL [c] RA and GPA/MPA [d] GPA/MPA [e] NHL

In addition the important potential risks: 'Off label use of the SC formulation' and 'Administration route error' have been included as new ongoing safety concerns to fulfil an assurance provided in the sponsor's correspondence dated 31 October 2013. These changes are reflected in Section 9: 'Pharmacovigilance practice in Australia' and Section 10: 'Risk Minimisation Activities' of the ASA but do not appear to have been captured in Section 8: 'Summary of Safety Concerns' of the ASA.

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities to monitor all the specified ongoing safety concerns, including the use of guided questionnaires to collect data for the important identified risks: 'Progressive Multifocal Leukoencephalopathy (PML)', 'Hepatitis B virus reactivation' and 'Posterior Reversible Encephalopathy Syndrome (PRES)'; and for the important potential risks: 'Second malignancies' and 'Off label use in paediatric patients'. Furthermore additional pharmacovigilance activities are also proposed for the important identified risks: 'Infusion related reactions', 'Infections', 'Progressive Multifocal

Leukoencephalopathy (PML)' & 'Hepatitis B virus reactivation'; for the important potential risks: 'De Novo HBV, and HBV Reactivation', 'Opportunistic Infections', 'Malignant Events', 'Impact on Cardiovascular Disease', 'GI Perforation', 'Prolonged B-cell depletion', 'Off label use in paediatric patients' and 'Relapses' and for the important missing information: 'Use in pregnancy and lactation', 'Immunogenicity and autoimmune disease' & 'Long term use in GPA/MPA patients'.

Risk minimisation activities

The sponsor proposes routine risk minimisation activities for all the specified ongoing safety concerns, except for the important missing information: 'Effect of greater exposure in patients with low BSA after fixed-dose SC administration' for which no risk minimisation activities are proposed. Furthermore additional risk minimisation activities are proposed for the important identified risks: 'Infusion related reactions' and 'Infections'; and for the important potential risks: 'Off label use of the SC formulation' and 'Administration route error.'.

Reconciliation of issues outlined in the RMP report

Table 5 and *Outstanding issues* below summarises the PMSB's first round evaluation of the RMP, the sponsor's responses to issues raised by the PMSB and the PMSB's evaluation of the sponsor's responses."

Table 5: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	PMSB evaluator's comment
2. The summary of the Ongoing Safety Concerns as specified in the ASA is only considered acceptable once the important potential risk: 'Off-label use of the alternative, faster infusion schedule of MabThera is included as a new ongoing safety concern, which need only be reflected in a revised ASA. In addition Section 8: 'Summary of Safety Concerns' of the ASA should be corrected to include the important potential risks: 'Off label use of the SC formulation' and 'Administration route error'.	See above The ASA has been updated to include off label use of the SC formulation and Administration Route Error as potential risks.	See above This is acceptable.
4. The 'Potential for Medication Errors and Overdose' section of the ASA previously accepted for MabThera has been removed from the updated ASA. The *Risk Management Plan (RMP) Questions and Answers (Version 1.3, October 2012)*, as found on the TGA website, states the ASA should include: *"Australian information if available, on potential for medication errors or other risks, for example: if an extension of indication or new*	Information on the "Potential for Medication Errors and Overdose" in relation to the important potential risks of 'Off label use of the SC formulation' and 'Administration route error', has been reinstated in the ASA.	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	PMSB evaluator's comment
dosage form is proposed." Consequently the sponsor should reinstate such a section in a revised ASA, which relates to the important potential risks: 'Off label use of the SC formulation' and 'Administration route error'.		
8. There are no objections to changes to the distribution plan of the additional risk minimisation activities for the important potential risks: 'Off label use of the SC formulation' and 'Administration route error' to what was previously accepted for MabThera. Nevertheless such detail should be captured in a revised ASA.	The ASA has been updated accordingly.	This is acceptable.

Summary of recommendations

It is considered that the sponsor's response to the TGA's consolidated request for further information has not adequately addressed all of the issues identified in the RMP evaluation report.

Outstanding issues

Issues in relation to the RMP

The Clinical Evaluation Report for MabThera stated: *"In the opinion of the Evaluator, off-label use of the new rapid infusion is also an Important Potential Risk."* It was acknowledged that appropriate routine risk minimisation was already applied to the ongoing safety concern of off-label use of the new rapid infusion. Nevertheless to ensure that it is appropriately monitored by routine pharmacovigilance it was reiterated to the sponsor that 'Off-label use of the alternative, faster infusion schedule of MabThera should be included as an important potential risk, which need only be reflected in a revised ASA. Consequently the summary of the Ongoing Safety Concerns as specified in the ASA would only be considered acceptable once the important potential risk: 'Off-label use of the alternative, faster infusion schedule of MABTHERA' was included as a new ongoing safety concern, which need only be reflected in a revised ASA. In response the sponsor has simply restated its position that it considers off-label administration of a faster rate of infusion, in itself, does not represent an important risk for patients and therefore it is not included in the updated ASA. Consequently this remains an outstanding issue and the ASA should be revised accordingly before this application is approved.

It was acknowledged that the sponsor has provided a tabular summary of the 'Studies referenced in the RMP' in the ASA but not all of these additional pharmacovigilance activities have had anticipated dates for their submission in Australia annotated. Given such information has been provided in the EU-RMP in relation to the EU, the sponsor was asked to correct this oversight in a revised ASA. The sponsor has stated: *"The availability of data in Australia is by default linked to the dates provided in the EU RMP."* and *"If changes to the Australian PI are warranted as a result of availability of new data, an appropriate Safety Related Request or Category I submission will be made, accompanied by the relevant study report."* The sponsor should include these assurances in a revised ASA before this application is approved.

The sponsor was advised that there appeared to be a lack of detailed information in either the EU-RMP or the ASA in regard to the communication/distribution plan for the Health Care Professional (HCP) educational materials related to the important identified risk: 'Infusion related reactions' (RA and GPA/MPA indications only). Consequently it was difficult to assess the adequacy of relying upon data from spontaneous adverse drug reactions (ADR) reporting to measure the effectiveness of the proposed additional risk minimisation activities. It is also unclear as to whether patient educational materials are included in this battery. Consequently the sponsor was asked to provide such detailed information relating to the proposed additional risk minimisation activities for the important identified risk: 'Infusion related reactions' (RA and GPA/MPA indications only) in a revised ASA, including compelling justification for relying upon data from spontaneous ADR reporting to measure the effectiveness of these activities.

Similarly the sponsor was advised that there appeared to be a lack of detailed information in the ASA in regard to the communication/distribution plan for the HCP and patient educational materials, as distinct from the Patient Alert Card, related to the important identified risk: 'Infections' (RA and GPA/MPA indications only). Criteria for judging the success of these proposed additional risk minimisation measures also appears to be missing from both the EU-RMP and the ASA. Consequently the sponsor was asked to provide such detailed information relating to the proposed additional risk minimisation activities for the important identified risk: 'Infections' (RA and GPA/MPA indications only) in a revised ASA, including compelling justification for relying upon data from spontaneous ADR reporting to measure the effectiveness of these activities if so suggested.

Finally the sponsor was asked to attach copies of the draft HCP and patient educational material for the important identified risks: 'Infusion related reactions' and 'Infections' and the Patient Alert Card for the important identified risk: 'Infections' to a revised ASA. If these are not yet available, the sponsor was asked to provide an assurance that they will be provided to the TGA once they become available. The sponsor states: *"With the update of the EU RMP from version 9.1 to 9.4, additional EU risk minimisation measures for "Infusion Related Reactions" and "Infection (non-oncology indications)" were listed. Educational materials addressing these risks have been in place for a long time in the EU, commensurate with the fact that Infusion Related Reactions and Infection have been longstanding identified risks however, changes to the new EU RMP template resulted in these now being listed in EU RMP v9.4 as risk minimisation measures. In Australia, RA focused educational materials for patients and health care providers have been in existence since at least 2007. The materials currently available (Patient Information for MabThera and Infusion guidelines for HealthCare Professionals) incorporate information regarding infusion related reactions and infections. These materials are however broader educational / promotional materials rather than specific risk minimisation measures to manage the well-established risks of Infusion Related Reactions and Infections."* and *"We therefore consider that additional, specific, educational risk minimisation measures are not necessary, especially since these risks have been established for a long time. Accordingly, the ASA has been updated to remove the statements in Section 10 of the ASA that "Similar educational materials are employed in Australia" so that there is no implication that available educational / promotional materials in Australia are specific risk minimisation measures to address these risks."*

This response is considered to be inadequate as it makes no attempt to compare what risk minimisation activities included in previously submitted RMP documentation were accepted for MabThera prior to the EU-RMP Version: 9.4. In addition the tabular summary in Section 11: 'Risk Minimisation Activities (RMinA)' of the updated ASA does not identify and provide reasons for any differences between the EU-RMP and the local implementation of risk management activities – in this instance for the important identified risks: 'Infusion related reactions' and 'Infections' (RA and GPA/MPA indications only) the use of additional risk minimisation activities in the EU and not in Australia.

Furthermore Section 8: 'Change history of RMPs submitted to TGA' of the updated ASA does not capture the proposed changes to additional risk minimisation activities from ASA Version: 3.0 onwards and Section 2: 'RMP Version History' of the updated ASA does not include Version: 4.1 of the ASA. Consequently these issues remain outstanding and the ASA should be revised accordingly, including compelling justification for any differences between the EU-RMP and the local implementation of risk management activities, before this application is approved.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

RMP

At this time, no wording can be provided as it is recommended that an acceptably revised ASA be submitted before this application is approved.

Key changes to the updated RMP

In their response to the TGA's consolidated requests for further information the sponsor provided an updated ASA (Version: 4.1 dated November 2014). Key changes from the versions evaluated in the second round evaluation are summarised in Table 6 below.

Table 6: Key changes to the ASA

	Key change
ASA	The important potential risks: 'Off label use of the SC formulation' and 'Administration route error' have been included in Section 9: 'Summary of Safety Concerns'. Section 5: 'Potential for Medication Errors and Overdose' in relation to the important potential risks of 'Off label use of the SC formulation' and 'Administration route error' has been included. Section 11: 'Risk Minimisation Activities (RMinA)' has removed the use of educational materials as additional risk minimisation activities for the important identified risks: 'Infusion related reactions' and 'Infections' (RA and GPA/MPA indications only).

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

Clinical Efficacy

Study ML25641

This single-arm study investigating the proposed 2 h infusion schedule in RA patients was conducted at multiple sites in the USA during 2011-2013.

Patients with previous history of serious infusion related reaction to any biologic agent including rituximab were excluded. Patients with other concomitant serious, uncontrolled systemic diseases were also excluded.

A total of 4 rituximab infusions (one course comprising two 1000 mg doses given 2 weeks apart followed 22 weeks later by a second course) were given to each patient via a dedicated line. All patients received standard pre-medications before each infusion.

The first infusion of the first course (1000mg in 250mL) was administered as the currently approved standard 4 h infusion schedule. If a patient experienced an infusion-related reaction, standard instructions for interruption and slowing the infusion, as currently reflected in the prescribing information document, were to be followed including withdrawal from the study in case of a serious infusion-related reaction. The 4 h standard schedule was as shown in Table 7.

Table 7: Four hour standard schedule

Time (minutes)	Infusion Rate (mg/hour)	Infusion Rate (mL/hour)	Dose in 30 minutes (mg)	Cumulative Dose (mg)
0–30	50	12.5	25	25
31–60	100	25	50	75
61–90	150	37.5	75	150
91–120	200	50	100	250
121–150	250	62.5	125	375
151–180	300	75	150	525
181–210	350	87.5	175	700
211–240	400	100	200	900
241–255 [a]	400	100	200	1000

[a] Should complete at 255 minutes (4 hours, 15 minutes) to complete a 1000-mg total dose.

For second Infusion (1000 mg in 250 mL) of the first course (Day 15) and both first and second infusions of the second course (Day 168 and 182) the new 2 h faster infusion schedule was used as shown in Table 8.

Table 8: New faster infusion protocol

Time (minutes)	Infusion Rate (mg/hour)	Infusion Rate (mL/hour)	Dose in 30 minutes (mg)	Cumulative Dose (mg)
0–30	250	62.5	125	125
31–60	600	150	300	425
61–90	600	150	300	725
91~120[a]	600	150	275	1000

[a] Should complete in just under 2 hours to complete a 1000-mg total dose.

Patients who experienced a moderate-to-severe infusion related reaction (such as fever, chills or hypotension) were to have their infusion interrupted immediately and to receive symptomatic treatment. The infusion was not to be restarted until all symptoms had disappeared. The infusion was to be restarted at half the rate. If the patient tolerated the reduced rate for 30 minutes, the infusion rate was to be increased to the next closest rate following the infusion schedule. If the symptoms did not resolve with treatment, the

patient was to be withdrawn from the study. Any patient experiencing a serious IRR (SIRR) was also to be withdrawn from the study.

The age range of the participating patients (N = 351) was 23 to 88 years. There were 306 (87.2%) patients with no prior rituximab exposure, 24 (6.8%) with one prior rituximab course and 21 (6.0%) with two prior rituximab courses. The mean duration of RA was 12.5 years (standard deviation (SD) 9.7). All patients were receiving concomitant methotrexate and 198 (56.4%) were receiving concomitant glucocorticoids.

A total of 351 patients received standard 4 h Infusion 1. Subsequently, 341/351 (97.2%) received Infusion 2, 290/351 (82.6%) received Infusion 3 and 278/351 (79.2%) received Infusion 4. However, not all patients received the intended faster infusion for the second and subsequent infusions. The 2 h infusion was received by 337/351 (92%) patients at Infusion 2, 289/351 (82%) at Infusion 3 and 278/351 (79%) at Infusion 4.

The primary outcome was the incidence of IRRs associated with the second rituximab infusion. There were a number of related secondary outcomes. The data were also analysed by previously rituximab-naïve and rituximab-experienced status.

The results were as shown in Table 9.

Table 9: Incidence of adverse events associated with Infusions 1-4

Study ML25641	Infusion 1 (Day 1)	Infusion 2 (Day 15)	Infusion 3 (Day 168)	Infusion 4 (Day 182)
Percent (incidence) [95%CI]	N = 351	N = 337	N = 289	N = 278
IRRs	16.2% [12.5%, 20.5%]	6.5% [4.1%, 9.7%]	5.9% [3.5%, 9.3%]	0.7% [0.1%, 2.6%]
SIRRs	0.0 [0.0, 1.0%]	0.0 [0.0, 1.1%]	0.0 [0.0, 1.3%]	0.0 [0.0, 1.3%]
AEs	17.7% [13.8%, 22.1%]	7.1% [4.6%, 10.4%]	7.6% [4.8%, 11.3%]	1.8% [0.6%, 4.1%]
SAEs	0.0 [0.0, 1.0%]	0.0 [0.0, 1.1%]	0.0 [0.0, 1.3%]	0.0 [0.0, 1.3%]
CTC (Grade 3 or 4)	0.6% [0.1%, 2.0%]	0.6% [0.1%, 2.1%]	0.0 [0.0, 1.3%]	0.0 [0.0, 1.3%]
Stopping/slowing/ interrupting the	12.3% [9.0%,	3.9% [2.1%,	6.6% [4.0%,	1.1% [0.2%,

Study ML25641	Infusion 1 (Day 1)	Infusion 2 (Day 15)	Infusion 3 (Day 168)	Infusion 4 (Day 182)
infusion	16.1%]	6.5%]	10.1%]	3.1%]
Stopping/slowing/ interrupting the infusion due to AE	10.3% [7.3%, 13.9%]	2.7% [1.2%, 5.0%]	5.5% [3.2%, 8.8%]	0.7% [0.1%, 2.6%]

IRRs = infusion related reactions; SIRRS = serious infusion related reactions; CTC = common toxicity criteria; AEs = adverse events; SAEs = serious AEs

For analysis by subgroups (rituximab naive versus experienced), please see Attachment 2 Table 12.

Historical data

The weighted average of IRRs incidence (to account for rituximab experienced patients in the Study ML25641) in historical controls was provided for comparison as follows:

Table 10: Expected control incidence of IRR for rituximab administered at the labelled rates.

Incidence of IRRs	Infusion 1 (Day 1)	Infusion 2 (Day 15)	Infusion 3 (Day 168)	Infusion 4 (Day 182)
Historical Incidence	22.2%	8.6%	11.9%	5.2%
95% CI (exact)	20.9% – 23.6%	7.7% – 9.6%	10.7% – 13.2%	4.4% – 6.2%
Weighted Historical Incidence [a]	20.7%	8.1%	11.5%	5.0%
95% CI (exact)	19.4% – 22.1%	7.2% – 9.1%	10.3% – 12.8%	4.2% – 6.0%

CI = confidence interval; IRR = infusion-related reaction.

[a] Based on weighted averages from data presented in Table 16, in which the proportion of patients at the various courses of rituximab are provided.

In a previous study WA17047, the incidence (unique patients) of IRRs (2 x 1.0g rituximab group) was as follows:

- 15.3% (infusion 1) and 4.9% (infusion 2) during Course 1.
- 8.5% (infusion 1) and 2.9% (infusion 2) during Course 2.
- 8.8% (infusion 1) and 3.6% (infusion 2) during Course 3.

In a previous study WA17045, the incidence (unique patients) of IRRs (2 x 1.0g rituximab group) was as follows:

- 25% (infusion 1) and 6% (infusion 2) during Course 1.
- 10% (infusion 1) and 5% (infusion 2) during Course 2.

Note the Infusions 1 and 2 in any course of treatment in this historical dataset are expected to be standard 4 h and 3 h infusions respectively based on the current approval. *The sponsor is requested to confirm this in their pre Advisory Committee on Prescription Medicines (ACPM) response.*

Clinical Safety

No new or unexpected findings were reported compared to the current adverse effects profile of rituximab in RA patients. The infusion related adverse outcomes were treated as

main safety/efficacy outcomes as reported above. No post approval data are available yet with respect to the rapid 2 h infusion. For a number of published reports of rapid rituximab use please see CER Attachment 2.

Clinical evaluator's recommendation

The clinical evaluator has no objection to the approval of the alternative, faster infusion schedule of MabThera for RA.

Risk management plan

This submission is subject to a Risk Management Plan to the satisfaction of RMP evaluation area and will be a condition of regsitration.

Risk-benefit analysis

Delegate's considerations

1. The major limitation of Study ML25641, investigating the proposed 2 h rapid infusion schedule in RA patients, was its uncontrolled design, that is, lack of concurrently treated controls. The selection criteria also excluded patients at high risk at baseline. Although historical data were provided but these are also subject to both selection bias and information bias with no assurance that similar patients under equivalent conditions are being compared.
2. It also needs to be emphasised that a controlled trial was eminently possible, practical and ethical. Thus it is not entirely clear why a single arm design was preferred. Note also that no patient in this study received the currently approved 3 h infusion for which the 2 h infusion is the proposed alternative. The sponsor is requested to comment whether any regulatory advice from any jurisdiction was obtained during the planning of this study.
3. The patient population in Study ML25641 was generally consistent with the approved indication of severe RA patients in Australia. The participants appear to have been given the third and fourth infusions (that is, a second course) without a clinical imperative, which would be inconsistent with the current treatment recommendations. The sponsor is requested to clarify this aspect of the study in their pre-ACPM response.
4. The reported incidence of IRRs in Study ML25641 and the non-concurrent controlled data were as shown in Table 11 below.

Table 11: Reported incidence of IRRs

IRRs (%)	Infusion 1 (4 h)	Infusion 2	Infusion 3	Infusion 4
Study ML25641	16.2%	6.5% (2 h)	5.9% (2 h)	0.7% (2 h)
Historical data	20.7%	8.1% (3 h)	11.5% (4 h)	5.0% (3 h)
Study WA17047	15.3%	4.9% (3 h)	8.5% (4 h)	2.9% (3 h)
Study WA17045	25%	6% (3 h)	10% (4 h)	5% (3 h)

On the face of it, the incidence of IRRs with the 2 h infusion at Infusion 2 was similar to incidence of IRRs with the current standard schedule (3 h) and furthermore appeared to be safer at subsequent administrations compared to the current standard schedule. This may, however, be a reflection of inherent bias in the single-arm trial design.

5. A noted earlier, the changes to the dosing schedule proposed in this submission also aim to limit the 4 h infusion to the first ever infusion in a patient. All subsequent infusions can be standard 3 h infusions or 2 h infusions (where there has been no incidence of SIRRs in the past). All proposed changes apply to the RA indication only.

Advice from ACPM is sought regarding the validity and robustness of the supporting uncontrolled data as acceptable evidence of efficacy and safety of the proposed 2 h alternative schedule for use in RA patients. The Committee is also requested to advice on the clinical suitability of accompanying changes that will result in a recommendation to use the slower 4 h schedule for the first dose in a patient so that in subsequent courses of treatment either a 3 h or a 2 h (where no SIRRs has occurred in the past) infusion schedule may be used.

Summary of Issues

Adequacy of supporting dataset for the new/alternative rapid (2 h) infusion schedule and appropriateness of the consequent proposed changes to the current infusion schedule.

Proposed action

The Delegate is not in a position to say, at this time, that the application for MabThera (rituximab) for addition of an alternative 2 h infusion schedule should be approved for registration

Request for ACPM advice

The Committee is requested to provide advice on the following specific issues:

1. Does the ACPM accept the validity and robustness of the supporting uncontrolled data as reliable evidence of efficacy and safety for the proposed 2 h alternative schedule for use in RA patients?
2. Does the Committee consider the accompanying changes that will result in a recommendation to use the slower 4 h schedule for the first dose in a patient so that in subsequent courses of treatment either a 3 h or a 2 h (where no SIRR has occurred in the past) infusion schedule could be used as clinically desirable?

The Committee is also requested to provide advice on any other issue that may be relevant to a decision on whether or not to approve this application.

Response from Sponsor

Comment on the Delegate's Proposed Action

The Sponsor notes the Delegate's Summary of Issues and requests for ACPM advice in relation to:

1. The adequacy of the supporting dataset for the new alternative rapid (2 h) infusion schedule.
2. The appropriateness of the consequent proposed changes to the current infusion schedule.

Similar issues relating to the adequacy of the supporting dataset and overall clinical benefit (rather than a specific safety concern), were also raised by the FDA as part of a Complete Response Letter issued to the sponsor (US FDA Complete Response Letter 2014).

The sponsor wishes to respond to the Delegate's request for ACPM advice as follows:

1. The adequacy of the supporting dataset for the new alternative rapid (2 h) infusion schedule

Rationale for Use of Historical Controls

Roche decided to use historical data, comprised of a pooled observed case analysis within the global rituximab RA clinical trial program as an external control for Study ML25641. This decision was based on a thorough assessment of study design options prior to initiating Study ML25641. A comparator study was considered not to be operationally feasible because of the complexities involved in managing the bias of different infusion rates in an open label setting. In addition, a controlled trial testing the hypothesis whether a 2 h infusion time is associated with a non-inferior or worse rate of severe IRRs compared to the standard 4.25 h infusion time would require far more than 1000 patients*. Such a large sample size was considered not appropriate and also not feasible.

> *1-sided test of non-inferiority (margin of 0.15) of the 2 h infusion duration compared to 3.25 h infusion assuming a 1.1% severe IRR in the control arm ($\alpha = 0.25$, $1\text{-}\beta = 0.9$, $n = 2616$).

The use of historical data as a control arm holds the potential for more efficient trials in appropriate situations. The benefits include the possibility for an increase in the relative amount of on-treatment safety data available per patient. In clinical practice, expected results are based on the current set of historical studies and it makes statistical sense to capitalise on this historical data, when possible.[3]

Several factors are significant for ensuring a valid historical control including[4]:

- A recent study or studies with the same treatment
- Same eligibility criteria, workup, and evaluations
- Prognostic factors completely known and the same in both treatment groups
- No unexplained factors leading one to expect different results
- Differences in prognostic factors not explaining observed differences in outcome

These factors were part of Roche's consideration for choosing an appropriate comparator from historical data for Study ML25641 in order to help reduce selection bias.

Historical Control Data in Study ML25641

For comparative purposes, a weighted historical incidence of infusion-related reactions (IRRs) was derived from a pooled observed case analysis of safety data from patients with moderate to severe active RA treated with rituximab plus methotrexate (MTX) within the global RA clinical trial program (8 randomized clinical trials, 2 long-term open-label extensions, and 1 open-label prospective study). This clinical trial program has been described previously.

Within these clinical trials, rituximab was administered according to the administration guidelines in the approved product labelling (4.25 h for initial infusion and 3.25 h for

[3] Viele K, Berry S, Neuenschwander B, et al. Use of historical control data for assessing treatment effects in clinical trials. Pharmaceut Statist 2014;13:41–54.
[4] Pocock S. The combination of randomized and historical controls in clinical trials. J Chron Dis 1976;29:175-188.

subsequent infusions). As of September 2012, there were 3595 patients (All-Exposure population) who received rituximab infusions at the standard rate in these clinical trials. The All-Exposure population had been treated over a period of 11 years (14,816 patient-years) with up to 20 courses (one course = 2 infusions) of rituximab and included those patients who had never received any prior methotrexate (MTX), inadequate responders to prior disease-modifying antirheumatic drugs (DMARDs), and inadequate responders to prior tumour necrosis factor inhibitors (TNF-IR) and/or other biologics. TNF-IR and/or other biologic-inadequate responders contributed to approximately 43% (n=1533) of this heterogeneous population.

This robust dataset was considered an appropriate comparator because these patients had the same RA eligibility criteria, workup and evaluations as patients in Study ML25641. Also, a similar process to identify IRRs was used for both the historical and Study ML25641 data and across rituximab clinical studies in RA patients conducted by Roche/Genentech.

The applicability of the historical control data to the ML25641 study population has been further examined by considering the TNF-IR subset of the All-Exposure population. Study populations in two of the pivotal trials that are representative of the TNF-IR subset of the All-Exposure population, Study WA17042 (REFLEX)[5] and Study U3384g (SUNRISE)[6] were comparable to the patients enrolled in Study ML25641 in terms of baseline patient characteristics (see Table 12). These studies were previously submitted to and reviewed by TGA as part of two previous applications.

Table 12: Demographics and baseline characteristics for patients allocated or rituximab treatment in three RA studies.

	Study ML25641 (RATE-RA) N = 351	Study WA17042 (REFLEX) N=308	Study U3384g (SUNRISE) N=318
Age (year)			
Mean (SD)	55.5 (11.5)	52.2 (12.2)	54 (11)
Sex			
Male	72 (20.5%)	57 (19%)	61 (19%)
Female	279 (79.5%)	251 (81%)	257 (81%)
RA Duration (years)			
Mean (SD)	12.5 (9.7)	12.1 (8.3)	12 (9.2)
MTX Dose (mg/week)			
Mean (SD)	17.4 (4.7)	16.4 (8.8)	16.4 (4.6)
Oral steroid use at baseline(mg/day)	150 (42.7%)	200 (65%)	164 (51.6%)
Number if prior anti-TNF agents			
1	187 (53.3%)	186 (60%)	181 (57%)
2	116 (33.0%)	94 (31%)	101 (32%)
3 or more	44 (12.5%)	28 (9%)	35 (11%)

SD = standard deviation.
Source: Study ML25641: Tables 10.1/5 and 10.1/6; Study WA17042: Cohen et al. 2006; Study U3384g: Mease et al. 2010.

The incidence of IRRs observed in the subset of the All-Exposure population (n = 3595) who had inadequate response to at least one prior TNF inhibitor (that is, TNF-IR population, n=1533) was similar to that of the larger dataset of the All-Exposure population (Table 13) for the first two infusions and for subsequent courses, when given. Therefore, the more robust All-Exposure population was chosen as the control for Study ML25641.

[5] Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006;54(9)2793- 2806.
[6] Mease PJ, Cohen S, Gaylis NB, et al. Efficacy and safety of retreatment in patients with rheumatoid arthritis with previous inadequate response to tumor necrosis factor inhibitors: Results from the SUNRISE trial. J Rheumatol 2010;37(5):917-27.

Table 13: Incidence of infusion related reactions associated with rituximab infusion in Study ML25641 versus the Integrated Historical Clinical Data

	Infusion 1 n (%)	Infusion 2 n (%)
Course #1		
All-Exposure population	3595	3523
No. with IRRs	799 (22.2)	304 (8.6)
TNF-IR patients	1533	1506
No. with IRRs	348 (22.7)	137 (9.1)
ML25641 patients	351	293
No. with IRRs	57 (16.2)	22 (6.5)
Course #2		
All-Exposure population	2751	2690
No. with IRRs	327 (11.9)	141 (5.2)
TNF-IR patients	1031	1011
No. with IRRs	139 (13.5)	57 (5.6)
ML25641 patients	289	278
No. with IRRs	17 (5.9)	2 (0.7)

Supporting Data

As indicated in Section 1.2.2 of the Clinical Overview [not in this AusPAR], multiple physicians were motivated to initiate their own studies in rheumatology to investigate the safety and feasibility of administering rituximab using shorter infusion times. Several published studies, which make use of shorter infusion times, were summarized in the original submission.

Since the submission, there have been additional supportive publications providing data on the safety profile of a faster infusion rate for rituximab in patients with RA. The most relevant recent publication evaluating a faster infusion rate with rituximab was a long-term (7 year) comparison study presented by Faraawi et al. at the European League Against Rheumatism (EULAR) meeting in 2014.[7] This data, from a 50 patient study comparing the long-term safety data of patients with RA who were treated using a rapid infusion protocol versus patients with RA treated with a standard infusion, showed no significant difference in the incidence of IRRs between rapid and standard infusions ($p = 0.97$). In both rapid and standard infusions, no patients discontinued rituximab due to IRRs. Overall, symptoms reported were mild and resolved within 24 h after the infusion with no serious AEs reported in either infusion group. Additionally, the author stated that '*patients reported greater satisfaction with the shorter infusion duration*'[7]. Data from this recent study further supports Roche's conclusion that faster infusion of rituximab appears to be well tolerated in patients with RA.

Roche believes that the extensive safety data from previous trials of rituximab in RA, which forms the basis for the established safety profile of rituximab in RA, serves as an appropriate control for Study ML25641 data, which allows adequate comparison to the safety of the faster rate infusion. Roche believes this comparison supports the use of the faster rate infusion. This conclusion is further substantiated by recent literature reports describing the safe use of the faster rate infusion.

2) The appropriateness of the consequent proposed changed to the current infusion schedule

The primary concern related to faster rate infusion is the occurrence of IRRs which might have serious clinical outcomes. Table 13 showed that there was no increase in the incidence of IRRs reported in study ML25641 with 2 h infusion compared to the historical

[7] Faraawi R, Malik S, Roth K. Safety of rapid rituximab infusion in rheumatoid arthritis in a single community practice. Ann Rheum Dis 2014;73(Suppl 2).

data with 4.25 h and 3.25 h infusion. Treatment was withdrawn due to IRR (second infusion) in only one patient. Furthermore, neither Grade 4 IRRs nor IRRs with fatal outcome were reported in study ML25641. Thus, Roche believes that if patients tolerated the first infusion at 4.25 h, subsequent 2 h infusions have been demonstrated to be safe. Should an IRR occur during any infusion, irrespective of infusion rate, appropriate measures are adequately outlined in the Product Information?

Another important and relevant aspect that needs to be considered relating to faster rate infusion is patient preference. As RA is a chronic debilitating disease which also affect individuals who are fully employed and/or have young families, convenience of drug administration plays an important role in drug adherence and therefore subsequent clinical outcome. Poulos et al (2014)[8] conducted an online discrete choice experiment survey (also known as conjoint-analysis) involving 901 respondents with a self-reported physician diagnosis of moderate to severe RA. The results indicate that respondents would accept treatments with lower efficacy and greater safety risks to get lower treatment duration and frequency. Furthermore, a 1 h reduction in duration is more important than reducing the frequency by 1 treatment per year.

Anecdotal feedback from experts in the Australian clinical community also supports the availability of an alternative faster infusion schedule to provide increased flexibility for both the health care professional and patient and an increase in capacity at the infusion centre with no impact on treatment outcomes.

Therefore, Roche considers it appropriate to administer a faster infusion rate (2 h) in second or subsequent infusions if patients tolerated and did not experience IRRs during the first infusion (4.25 h). This proposed change in infusion schedule is based on the dose regimen used in Study ML25641, that is, 4.25 h, 2 h, 2 h and 2 h.

The reader is referred to the response to the Delegate's first question to the ACPM for further information on safety profile of faster rate infusion.

Comments in response to the Delegate's specific requests

1. *The infusions 1 and 2 in any course of treatment in the historical dataset are expected to be standard 4 h and 3 h infusions respectively, based on the current approval. The sponsor is requested to confirm this in its pre-ACPM response.*

The sponsor confirms that Infusions 1 and 2 in any course of treatment in the historical dataset are expected to be standard 4.25 h and 3.25 h infusions respectively. This was specified in the protocols for the pivotal studies, including Study WA17042 (REFLEX)[5] and Study U3384g (SUNRISE)[6] which included repeated dosing and which were included in the All- Exposure population.

An analysis of the infusion times reported for the All Exposure population has been conducted. Each course of rituximab in studies that comprised the historical control for Study ML25641 (RATE-RA) included two infusions to be administered in 4.25 and 3.25 h for the first and second infusion, respectively. The total infusion duration, including time of interruption for the first two courses in these studies, was summarised in Table 14. The mean (median) infusion duration for the first two courses was in the range of 4.29 to 4.42 h (4.25 h) for the first infusion, and 3.39 to 3.45 h (3.25 h) for the second infusion.

[8] Poulos C et al. Patients' Willingness to Trade off Between the Duration and Frequency of Rheumatoid Arthritis Treatments. Arthritis Care and Research 2014 Jul; 66(7):1008-1015

Table 14: Summary of total rituximab infusion duration by Course and Infusion for All Exposure Population

Course	Total Infusion Time (hours) (including time of interruption)	First Infusion	Second Infusion
1	N (N1)	3595 (3595)	3523 (3521)
	Mean (SD)	4.42 (0.59)	3.45 (0.47)
	Median (Min—Max)	4.25 (0.25–9.42)	3.25 (0.47–9.00)
	<3 hours	32 (0.9%)	66 (1.9%)
	3 to <3.5 hours	47 (1.3%)	2498 (70.9%)
	3.5 to <4 hours	77 (2.1%)	515 (14.6%)
	4 to 4.5 hours	2793 (77.7%)	340 (9.7%)
	> 4.5 hours	646 (18.0%)	102 (2.9%)
	unknown	--	2 (0.1%)
2	N (N1)	2751 (2751)	2690 (2689)
	Mean (SD)	4.29 (0.45)	3.39 (0.37)
	Median (Min—Max)	4.25 (0.50–7.98)	3.25 (0.58–8.00)
	<3 hours	17 (0.6%)	39 (1.4%)
	3 to <3.5 hours	82 (3.0%)	2025 (75.3%)
	3.5 to <4 hours	109 (4.0%)	411 (15.3%)
	4 to 4.5 hours	2257 (82.0%)	180 (6.7%)
	> 4.5 hours	286 (10.4%)	34 (1.3%)
	unknown	--	1 (0.0%)

This summary used the integrated data from Phase II and Phase III studies and their open-label extension studies as September 2012. N = number of patients received rituximab infusion; N1 = number of patients received rituximab with infusion time recorded; SD = standard deviation.

2. *It also needs to be emphasised that a controlled trial was eminently possible, practical and ethical. Thus it is not entirely clear why a single arm design was preferred. Note also that no patient in this study received the currently approved 3 h infusion for which the 2 h infusion is the proposed alternative. The sponsor is requested to comment whether any regulatory advice from any jurisdiction was obtained during the planning of this study.*

The reader is referred to Roche's response to the Delegate's first question to the ACPM, in which we provide the rationale for not conducting a controlled study and further information on the validity of our use of the All Exposure population data in the ML25641 study report. The sponsor confirms that no regulatory advice relating specifically to the ML256141 study was obtained from any jurisdiction during study planning. In pre-sBLA advice, which occurred once Study ML25641 was completed, the FDA indicated that an assessment of whether the totality of data is adequate to support the shorter infusion would be a review issue once the application was submitted in the USA. Prior to the conduct of ML256141, a study was conducted with rituximab in the oncology setting using a 90 min duration of infusion leading to a USA approval of a 90 min infusion in 2012. The study design for ML25641 was similar to the oncology study in that a single treatment arm was used.

3).The patient population in Study ML 25641 was generally consistent with the approved indication of severe RA patients in Australia. The participants appear to have been given the third and fourth infusions (that is, a second course) without clinical imperative, which would be inconsistent with the current treatment recommendations. The sponsor is requested to clarify this aspect of the study in their pre-ACPM response.

The Australian label states that the retreatment is based on regular monitoring of the signs and symptoms of the disease. However, the US label specifies that retreatment is every 24 weeks or, based on clinical evaluation, as early as 16 weeks. As Study ML25641 was a US based study the interval of 24 weeks between infusions was chosen as the basis to evaluate the safety of faster infusions of repeat course. Furthermore, the historical safety data used for comparison was reported every 6 months.

Advisory Committee Considerations

The ACPM resolved to recommend to the TGA delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of efficacy and safety, considered MabThera single use vials containing 100 mg/10 mL and 500 mg/ 50 mL of rituximab to have an overall acceptable benefit–risk profile for the proposed new (2 h) dosing schedule for use in patients with rheumatoid arthritis.

The ACPM advised that, despite limited evidence (lack of concurrent controls) in support of the proposed 2 h infusion rate and the trial using historical controls, there were no reported SIRRs with the 2 h infusion in almost 300 patients which was reassuring. However, the committee was of the view that dosage instructions required modification to better reflect the evidence provided.

Proposed conditions of registration

The ACPM noted that the submission was supported by a Risk Management Plan and agreed that monitoring in the post-approval phase will be important.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM specifically advised on the inclusion of the following amendments to the Product Information (PI) and Consumer Medicine Information (CMI):

- The proposed directions for use in the Dosage and Administration section of the PI do not apply to patients who are ineligible for the 2 h infusion and should be appropriately modified to reflect lack of data in this patient population.
- The description of the supporting study in the Clinical Trials section should include a comprehensive definition of SIRR.

Specific Advice

The ACPM advised the following in response to the delegate's specific questions on this submission:

1. *Does the ACPM accept the validity and robustness of the supporting uncontrolled data as reliable evidence of efficacy and safety for the proposed 2 h alternative schedule for use in RA patients?*

While not ideal, the ACPM advised the data can be taken to indicate that the proposed 2 h schedule is safe, under the restricted conditions proposed. With respect to efficacy, there are no grounds to suspect MabThera would not be as effective as a slower first infusion or more rapid subsequent infusions.

2. *Does the Committee consider the accompanying changes that will result in a recommendation to use the slower 4h schedule for the first dose in a patient so that in subsequent courses of treatment either a 3h or a 2h (where no SIRR has occurred in the past) infusion schedule could be used as clinically desirable?*

The 2 h infusion as per the RATE-RA study (ML25641) is acceptable (ie in patients who have not had an SIRR). In order to correctly reflect patients who are not eligible for 2 h infusions the recommended dosing instructions are as follows:

> ***Rheumatoid Arthritis***
>
> *First infusion of each course: The recommended initial rate for infusion is 50 mg/h; after the first 30 minutes, it can be escalated in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h.*
>
> *Second infusion of each course: Subsequent doses of MABTHERA can be infused at an initial rate of 100 mg/h, and increased by 100 mg/h increments at 30 minutes intervals, to a maximum of 400 mg/h.*

Rheumatoid Arthritis only: Alternative Subsequent, Faster, Infusion Schedule:

In RA, with a dose of 1000 mg MABTHERA, if there are no infusion related reactions or other reasons to slow or cease the infusion, the standard infusion schedules shown above result in an estimated duration of infusion of 4h 15 minutes for the first infusion in each course and 3h 15 minutes for the subsequent second infusions in each course.

If patients do not experience a serious infusion related reaction with their first or subsequent infusions administered over the standard infusion schedule, a more rapid infusion can be administered for second or subsequent infusions in each course using a concentration of 4 mg/mL in a 250 mL volume. Initiate at a rate of 250 mg/h for the first 30 minutes and then 600 mg/h for the next 90 minutes. With this infusion schedule, the 1000 mg/250 mL infusion will generally be completed in 2 h

Patients who have clinically significant cardiovascular disease, including arrhythmias or previous serious infusion reactions to any prior biologic therapy or to rituximab, should not be administered the more rapid, 2 h, infusion.

Furthermore, the Committee considered the potential to use the faster infusion in oncology indications as an important risk and supported its inclusion in the RMP/ASA.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of the amendment to the dosing regimen for MabThera (rituximab) for the treatment of Rheumatoid Arthritis (RA) patients regarding the alternative faster infusion schedule in the Dosage and Administration section of the Product Information and other amendments to the Product Information document.

Specific conditions of registration applying to these goods

The MabThera rituximab European Risk Management Plan (EU-RMP), version 12.0, dated 10 February 2014, as qualified by the Australian Specific Annex (version: 4.3, dated March 2015), included with submission PM-2013-04906-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

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

Attachment 2. Extract from the Clinical Evaluation Report

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