Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Rituximab

Proprietary Product Name: Riximyo

Sponsor: Sandoz Pty Ltd

August 2018

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 Report (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; it provides 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

Common abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ADA	Anti-drug antibodies
ADCC	Antibody dependent cellular cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AUC	Area under the concentration-time curve
AUC(0-inf)	Area under the serum concentration-time curve from time zero to infinity.
AUClast	Area under the serum concentration-time curve from time zero to the last measured time point.
AUC(0-last)	The area under the curve calculated from start of dose to the end of the dosing interval, tau.
AUC_{all}	The area under the curve from the time of dosing to the time of the last observation, regardless of whether the last concentration is measureable or not
AUEC	Area under the effect-time curve
$AUEC_{(0-t)}$	The area under the effect-time curve from time zero to time 't'
BOR	Best overall response
BSA	Body surface area
CDAI	Clinical Disease Activity Index
CDC	Complement-dependent cytotoxicity
CER	Clinical evaluation report
CHMP	Committee for Medicinal Products for Human Use
CHOP	Cyclophosphamide, hydroxydaunorubicin, oncovin [vincristine] and prednisone
CI	Confidence interval(s)
CLL	Chronic lymphocytic leukemia
C_{max}	The maximum (peak) observed serum concentration of rituximab

Abbreviation	Meaning
Cmin	Minimum observed concentration
CMI	Consumer medicine information
CR	Complete response
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	The minimum observed serum drug concentration which is measured right before the next infusion dose administration.
CVP	Cyclophosphamide, vincristine, prednisone
DAS	Disease Activity Score
DLBCL	Diffuse large B-cell lymphoma
DMARD	Disease modifying anti-rheumatic
ECG	Electrocardiogram
ECL	Electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	End of treatment
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
FACS	Fluorescence-activated cell sorting
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIMEA	Finnish Medicines Agency
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index

Abbreviation	Meaning
GPA	Granulomatosis with polyangiitis
HACA	Human anti-chimeric antibodies
HAMA	Human anti-mouse antibody
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBV	Hepatitis B virus
HR	Hazard ratio
IMP	Investigational medicinal product
IV	Intravenous
LLOQ	Lower limit of quantification.
MAA	Marketing Authorisation Application
mAB	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MPA	Microscopic polyangiitis
MTX	Methotrexate
NAb	Neutralising antibody
NHL	Non-Hodgkin's lymphoma
NMQ	Novartis MedDRA Query
ORR	Overall response rate
OS	Overall survival
PAS	PK analysis set
PD	Pharmacodynamics
PFS	Progression free survival
PI	Product Information
PMDA	Pharmaceuticals and Medical Devices Agency
PML	Progressive multifocal leukoencephalopathy
PPS	Per Protocol Set

Abbreviation	Meaning
PR	Partial response
PT	Preferred term
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SAE	Serious adverse event
SD	Standard deviation
SDAI	Simplified disease activity index
SmPC	Summary of Product Information
SOC	System organ class
SPD	Sum of the product of the diameters
$T_{1/2}$	Elimination half-life
TEAE	Treatment emergent adverse event
T_{max}	Time to maximum serum concentration
TNF	Tumour Necrosis Factor
TGA	Therapeutic Goods Administration
USA	United States of America

I. Introduction to product submission

Submission details

Type of submission:	Biosimilar
Decision:	Approved
Date of decision:	21 November 2017
Date of entry onto ARTG:	30 November 2017
ARTG number(s):	281781 and 281782
Active ingredient(s):	Rituximab (rch)
Product name(s):	Riximyo
Sponsor's name and address:	Sandoz Pty Ltd PO Box 101 North Ryde NSW 1670
Dose form(s):	Solution concentrated for Injection
Strength(s):	100 mg/ 10 mL 500 mg/mL
Container(s):	Glass vial
Pack size(s):	100 mg/ 10 mL: 3 and 2 vials 500 mg/ 50 mL: 1 and 2 vials
Approved therapeutic use:	***Non-Hodgkin's Lymphoma (NHL)*** *Riximyo (rituximab) 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 (CLL)*** *Riximyo (rituximab) is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia in combination with chemotherapy.* ***Rheumatoid Arthritis (RA)*** *Riximyo (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.*

Rituximab 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) Riximyo (rituximab) 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 rituximab have not been established.

Route(s) of administration:	Intravenous (IV)
Dosage:	Riximyo may be administered in an outpatient setting. Riximyo should be administered as an intravenous infusion in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced healthcare professional. Administration of Riximyo involves intravenous (IV) infusion at varying dose regimens dependent upon the condition being treated. See PI (Attachment 1) for details.

Product background

This AusPAR describes the application by the Sandoz Pty Ltd, the sponsor, to register Riximyo, containing rituximab as the active ingredient, as a biosimilar to MabThera. The proposed indications and dosing regimen/route match those of the already in Australia registered MabThera (Roche Products Pty Ltd): to be used for the treatment of Non-Hodgkin's Lymphoma (NHL), Chronic Lymphocytic Leukaemia (CLL), Rheumatoid Arthritis (RA), or Granulomatosis with polyangiitis (GPA) and Microscopic polyangiitis (MPA):

Non-Hodgkin's Lymphoma (NHL)

Riximyo (rituximab) 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 (CLL)

Riximyo (rituximab) is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia in combination with chemotherapy.

Rheumatoid Arthritis (RA)

Riximyo (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.

Rituximab 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) Riximyo (rituximab) 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 rituximab have not been established.

Riximyo is also known by the global product name Rixathon (for example, in the European Union (EU)). The dosages proposed are identical to those of the innovator, MabThera (intravenous (IV) formulation).

Administration of Riximyo involves IV infusion at varying dose regimens dependent upon the condition being treated with doses of 375 mg/m^2 or 500 mg/m^2 indicated either: once weekly for 4 weeks; day 1 of each chemotherapy cycle or every 2 or 3 months for two years. Indications for rheumatoid arthritis consist of two 1000 mg IV infusions.

Riximyo is to be supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single use vials.

Mechanism of action

The Product Information (PI) for MabThera describes the mechanism of action across haematological malignancies and conditions such as rheumatoid arthritis.

Riximyo binds specifically to the human CD20 molecule expressed on B lymphocytes which can trigger cell death mediated by at least one of three mechanisms. Thus direct binding of Riximyo has been shown to induce apoptosis in target cells, alternatively it may recruit the complement component C1q and induce complement dependent cytotoxicity, or antibody binding may recruit Fc receptor bearing immune effectors which lyse the target cell.

The following diagram is taken from the Jaglowski et al, 2010[1]:

Figure 1: Mechanism of action
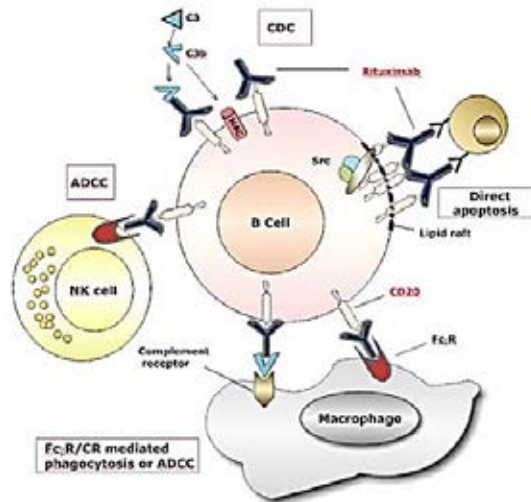
Rituximab coated B cells are killed by at least 4 different mechanisms. (A) Binding of rituximab to CD20 on B cell surface causes activation of the complement cascade, which generates the membrane attack complex (MAC) that can directly induce B-cell lysis by complement-mediated cytotoxicity (CDC). (B) Binding of rituximab allows interaction with NK cells via Fc receptors III (FcRIII), which leads to antibody-dependent cell-mediated cytotoxicity (ADCC). (C) The Fc portion of rituximab and the deposited complement fragments allow for recognition by both FcR and complement receptors on macrophages, which lead to phagocytosis and ADCC. (D) The crosslinking of several molecules of rituximab and CD20 in the lipid raft determine the interaction of these complexes with elements of a signaling pathway involving Src kinases that mediate direct apoptosis (From Jaglowski et al 2010).

This biosimilar product Riximyo is also referred to as 'GP2013' in some parts of this AusPAR and Attachment 2.

Regulatory status

This is an application to register a new biosimilar in Australia. The originator, MabThera was registered on the Australian Register of Therapeutic Goods (ARTG) in 1998.

The same product has the tradename Rixathon in the EU. This was approved on 15 June 2017, with indications across the following areas: NHL; CLL; RA; GPA/MPA (see Table 1 below).

Table 1: International regulatory status

Country Region Trade-name	Status Date	Indications
EU Rixathon	Approved 15 June 2017	Identical to approved indications for reference medicine in the EU (MabThera) in adults for the following: ***Non-Hodgkin's lymphoma (NHL)*** · *Treatment of previously untreated patients with Stage III-IV follicular lymphoma in combination with chemotherapy.*

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[1] Jaglowski SM, Alinari L, Lapalombella R, Muthusamy N, Byrd JC. The clinical application of monoclonal antibodies in chronic lymphocytic leukemia. Blood. 2010 Nov 11;116(19):3705-14.

Country Region Trade-name	Status Date	Indications
		· *Maintenance therapy for the treatment of follicular lymphoma patients responding to induction therapy.* · *Monotherapy treatment of patients with Stage III-IV follicular lymphoma who are chemo resistant or are in their second or subsequent relapse after chemotherapy.* · *Treatment of patients with CD20 positive diffuse large B cell NHL in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.* ***Chronic lymphocytic leukaemia (CLL)*** · *In combination with chemotherapy for the treatment of patients with previously untreated and relapsed/refractory CLL. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including rituximab or patients refractory to previous rituximab plus chemotherapy.* ***Rheumatoid arthritis (RA)*** · *In combination with methotrexate for the treatment of adult patients with severe active RA who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies.* · *Rituximab has been shown to reduce the rate of progression of joint damage as measured by X-ray & to improve physical function, when given in combination with methotrexate.* ***Granulomatosis with polyangiitis & microscopic polyangiitis*** · *In combination with glucocorticoids for the induction of remission in adult patients with severe, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA).*
Switzerland Rixathon	Pending	Identical to approved indications for reference medicine in Switzerland (MabThera): ***Non-Hodgkin's lymphoma (NHL)*** · *Monotherapy in patients with CD20 positive follicular NHL (Stage III or IV) who have relapsed or are unresponsive to chemotherapy.* · *Treatment of previously untreated patients with CD20 positive follicular NHL (Stage III-IV) with high tumour load, in combination with CVP or CHOP. If responsive to the therapy, maintenance therapy with rituximab monotherapy over 2 years can be administered.* · *Maintenance treatment of patients with CD20 positive relapsed or refractory follicular NHL (Stage III-IV) who have responded to induction treatment with CHOP with or without*

Country Region Trade-name	Status Date	Indications
		rituximab. · *Treatment of patients with CD20 positive diffuse large B-cell NHL (DLBCL) in combination with standard CHOP (8 cycles of cyclophosphamide, doxorubicin, vincristine, prednisone).* ***Chronic lymphocytic leukaemia (CLL)*** · *Treatment of patients with CLL in combination with fludarabine and cyclophosphamide (R-FC). Patients should first be treated with fludarabine over a period of at least 6 months.* ***Rheumatoid arthritis*** *In combination with methotrexate (MTX) for the treatment of adult patients with moderate to severe active rheumatoid arthritis (RA) after failure of one or more therapies with tumour necrosis factor (TNF) inhibitors.* ***ANCA-associated vasculitis*** *In combination with corticosteroids for the treatment of patients with severe, active ANCA-associated vasculitis (granulomatosis with polyangiitis (also known as Wegener's disease) and microscopic polyangiitis.*
US	Pending	Not applicable

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR and Attachment 2.

Submission dossier accepted and first round evaluation commenced	30 November 2016
First round evaluation completed	11 May 2017
Sponsor provides responses on questions raised in first round evaluation	3 July 2017
Second round evaluation completed	7 August 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	6 September 2017

Sponsor's pre-Advisory Committee response	18 September 2017
Advisory Committee meeting	5 and 6 October 2017
Registration decision (Outcome)	21 November 2017
Completion of administrative activities and registration on ARTG	30 November 2017
Number of working days from submission dossier acceptance to registration decision*	209

*The statutory time frame is 255 working days

III. Quality findings

Drug substance (active ingredient)

Structure

The active ingredient of Riximyo (GP2013/rituximab) is a genetically engineered murine/human chimeric immunoglobulin G1 (IgG1) kappa type monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The antibody has a molecular mass of 145 kilo Daltons (kDa) and is composed of two light chains (213 amino acids) and two N-glycosylated heavy chains (451 amino acids), which are covalently associated with one another at defined cysteine residues via disulphide bridges. This chimeric anti-CD20 antibody is produced by recombinant deoxyribonucleic acid (DNA) technology in a Chinese Hamster Ovary (CHO) mammalian cell expression system.

A schematic diagram of the chimeric antibody is shown below in Figure 2.

Figure 2: Schematic diagram of the chimeric antibody
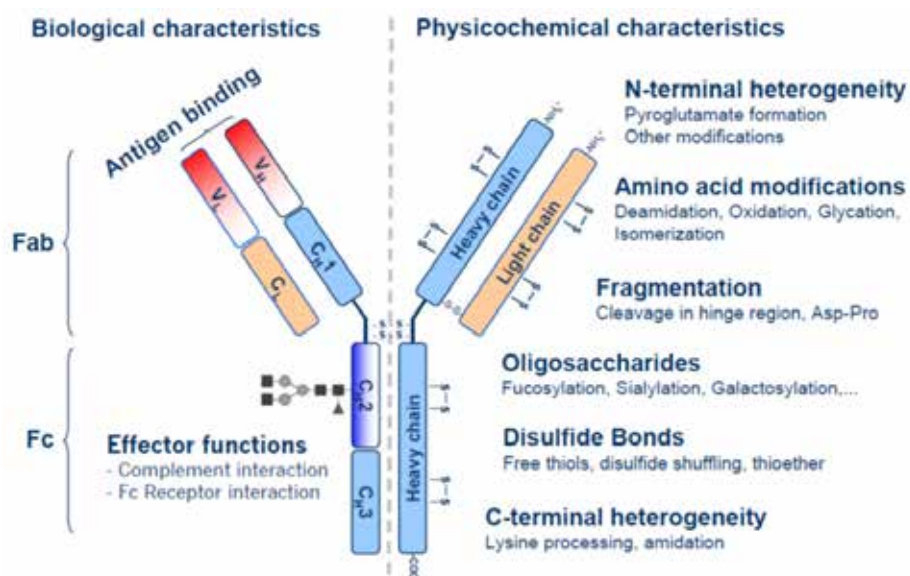
Physical and chemical properties

As noted above, analysis of Riximyo using multiple orthogonal assays indicates that shows features (from analysis of secondary and tertiary structure) of a typical human IgG1 antibody.

Potency assays are primarily based on complement dependent cytotoxicity (CDC) assays.

Drug product

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product.

The proposed shelf life is 3 years when stored at 5 ± 3°C.

The main degradation pathways of Riximyo include decrease in purity (monomer) and accumulation of high molecular weight variants as detected by size exclusion chromatography, redistribution of charged species from main and basic to acidic variants as detected by cation exchange chromatography, purity by non-reducing capillary electrophoresis (SDS), particulate contamination subvisible particles (compendial European Pharmacopeia 2.9.19), and decreased function in CDC assays.

Biosimilarity

The active substance of Riximyo (formerly Rixathon), rituximab, has been developed as a similar biological medicinal product (biosimilar) to that of the currently registered reference product MabThera (intravenous presentation).

During the development of Riximyo, the reference medicines MabThera and Rituxan (EU and US sourced originator material respectively) were used as the main reference product to demonstrate biosimilarity in terms of quality and non-clinical comparability. Note, batches of EU sourced MabThera were primarily used for comparison to Riximyo. An additional bridging comparability study was performed between the EU/US sourced MabThera/Rituxan and Australian sourced MabThera to present EU/US sourced MabThera/Rituxan as representative of the Australian registered product (MabThera).

Extensive characterisation studies involving comparison of primary, secondary and tertiary structures, physicochemical properties and biological activities showed that Riximyo and MabThera/Rixathon are generally similar. However, several differences have been noted as highlighted below:

· Subtle differences are seen in glycan species found in Riximyo and the originator product. The levels of these are mostly within limits set by analysis of batches of the originator product. Alternatively other species are found at low frequencies such that the sponsor believes these are not relevant.

· Small differences were seen in charged variants as judged by cation exchange chromatography, where originator material had higher frequencies of acidic species compared to Riximyo. These were likely due to pyroglutamte formation and lower levels of deamidation. Such acidic species are known to increase with during storage.

These observed differences between Riximyo and MabThera appear minor. The differences in glycan species potentially are important as they can influence functional activity of the antibody, most notably Fc receptor binding and antibody dependent cellular cytotoxicity (ADCC). However when tested in in vitro assays, GP2103 results were within ranges generated using MabThera or Rituxan. This suggests the differences have a minimal effect in these assays.

Fractionation of the different charged molecules showed all had functional activity in CDC assays, suggesting by this measure these changes are not relevant.

Overall, the sponsor has demonstrated that Riximyo is comparable to MabThera/Rituximab in terms of structure, species, function and degradation profile (that is, physico-chemically and biologically).

Quality summary and conclusions

Recommendations to the delegate

There are objections on quality grounds to the approval of Riximyo (initially presented as Rixathon; company code Riximyo).

Riximyo is a biosimilar of the anti-CD20 monoclonal antibody rituximab. Riximyo has been developed to have the same applications as the currently registered originator products MabThera 100 mg/10 mL and 500 mg/50 mL (ARTG numbers 60318 and 60319 respectively). Further details are provided below in the biosimilar section.

Two issues were identified which require action from the sponsor:

The first relates to Good Manufacturing Practice (GMP) certification, where licences have expired or require replacement. Applications for these are currently under consideration for approval.

Secondly, the sponsor has altered their labelling to be compliant with TGO91[2]; however this will require a machine readable bar code being placed on the label of the 500 mg presentation.

During stability studies an increase in particulate matter was noted by the sponsor. The sponsor plans to use a higher grade of excipient which lacks this substance and still complies with European Pharmacopeia specifications. It may be proactive of the sponsor to inform end users of the Drug Product using the original excipient as this may contain visible particulate matter.

Proposed conditions of registration (for delegate)

1. Batch Release Testing and Compliance with Certified Product Details (CPD)

    a. It is a condition of registration that all batches of Riximyo rituximab (rch) imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

    b. It is a condition of registration that each batch of Riximyo rituximab (rch) imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

    The sponsor must supply:

    i. Certificates of Analysis of all active ingredient (drug substance) and final product.

    ii. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).

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[2] Therapeutic Goods Order No. 91. Standard for labels of prescription and related medicines.

iii. Evidence of the maintenance of registered storage conditions during transport to Australia.

iv. Five vials of each batch for testing by the TGA Laboratories Branch together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.

Certified product details

The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm], in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

IV. Nonclinical findings

Introduction

The scope of the nonclinical testing program for Riximyo is in general in accordance with the relevant accepted guidelines on nonclinical testing of similar biological medicinal products. Data presented in the nonclinical part of the submission consisted of comparative in vitro pharmacology studies on biosimilar rituximab (referred to herein as Riximyo) relative to EU sourced MabThera or US sourced Rituxan comparators. Other studies included a Good Laboratory Practice (GLP) pharmacokinetic and pharmacodynamic study and a repeat dose toxicity study conducted in cynomolgus monkeys with concomitant toxicokinetic assessments and a Riximyo cross reactivity study in a panel of human tissues. A number of in vitro comparability studies were also included. These studies included in vitro cell based bioassays to compare biological attributes of Riximyo relative to EU sourced MabThera and included: CD20 binding activity; ADCC; CDC activity; C1q binding and apoptosis induction which all are rituximab's mode of action for B cell depletion. These functional in vitro comparisons are evaluated and assessed by the Quality evaluator.

The EU sourced MabThera or US sourced Rituxan were used as comparators in these nonclinical studies. The Australian sourced MabThera was not used and the sponsor indicated that the data provided in the submission validated that the Australian sourced MabThera is comparable to EU sourced MabThera and the US sourced Rituxan. However, it needs to be noted that no nonclinical data were provided to verify the comparability of the various sources of reference rituximab. Provided adequate comparability of the EU/US sourced and Australian sourced versions of reference rituximab is demonstrated in the quality part of the submission, the submitted nonclinical dossier is considered adequate.

Pharmacology

Rituximab is a monoclonal antibody that binds to the transmembrane antigen CD20 and mediates B cell lysis (leading to B cell depletion) by ADCC, CDC and apoptosis. As a biosimilar, Riximyo is expected to exhibit the same pharmacological action as MabThera

(EU and Australian authorised) and Rituxan (US authorised). Since the pharmacological activity of Rituximab is already well characterised in the original assessment of MabThera, the objective of primary pharmacology studies was to demonstrate comparable pharmacology of Riximyo relative to the comparators (EU sourced MabThera and US sourced Rituxan). It needs to be noted a comprehensive set of in vitro binding and functional assays were completed to fully characterise the biological function of rituximab and were evaluated by the Quality evaluator.

In vitro comparison of ADCC potency using freshly purified effector cells

The functional activity of Riximyo against malignant B cells was compared to that of MabThera alone or with both MabThera and Rituxan in three in vitro ADCC assays using human B cell lymphoma cell lines. In the first study the relative in vitro ADCC potencies of Riximyo and MabThera were compared at a wide concentration range (0 to 10000 ng/mL) using SU-DHL-4 (DLBCL) and Daudi (Burkitt lymphoma) cell lines as target cells. Riximyo and MabThera were comparable in their ability to mediate ADCC in Daudi (the 50% effective concentration (EC_{50})) values were 2.19 and 1.32 ng/mL in Daudi cells with Riximyo and MabThera respectively) and SU-DHL-4 (the EC_{50}) values were 0.72 and 0.47 ng/mL in SU-DHL-4 cells with Riximyo and MabThera, respectively) cell lines. An additional study was conducted to compare the relative ability of various batches of Riximyo (5 batches), MabThera (4 batches), and Rituxan (2 batches) to mediate ADCC in SU-DHL-4 target cells. The EC_{50}) values of Riximyo (of all tested batches ranged between 66 to 165% of the reference standard) were within the range of activities seen with the tested batch samples of MabThera and Rituxan (which ranged between 52 to 188%). In the third in vitro study, the combined FcγRII and FcγRIII mediated effects on ADCC activity of Riximyo was compared to that of MabThera and Rituxan in Raji B target cells. Based on the dose response curves the peripheral blood mononuclear cell (PBMC) mediated ADCC activity of Riximyo (of all tested batch samples) was comparable to that of MabThera and Rituxan. From these three studies it can be concluded that Riximyo and MabThera were comparable in their ability to mediate ADCC in vitro.

In vitro comparison of B cell depletion in a whole blood assay

In a separate in vitro study, B cell depletion activity of Riximyo was compared to that of MabThera and Rituxan in human whole blood from healthy donors. Various batches of Riximyo (4 batches), MabThera (2 batches) and Rituxan (1 batch) were tested. Based on the dose response curves, Riximyo (of all tested batch samples) was comparable in its ability to deplete B cells when compared to MabThera and Rituxan.

Comparative anti-tumour efficacy studies in mouse xenograft tumour models

To evaluate the comparability of anti-tumour activity in vivo, two studies were conducted in xenograft SCID mouse models[3] of Non-Hodgkin's Lymphoma (NHL) with the SU-DHL-4 (DLBCL) and Jeko-1 (mantle cell lymphoma) cell lines. In the SU-DHL-4 NHL model, Riximyo or MabThera was administered to mice at dose levels of 3 or 30 mg/kg (equivalent to 0.02 to 0.2 times the clinical dose based on mg/m^{2}) at once weekly via intraperitoneal (IP) administrations for four weeks. All four treatment dose groups had significant (p < 0.001) survival extensions, with no significant differences between survival at equivalent dose levels of Riximyo and MabThera. Treatment with Riximyo or MabThera showed no significant differences in short term and overall efficacy results, early tumour growth and progression and relative anti-tumour efficacies at equivalent

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[3] SCID = severe combined immunodeficiency. Lympho-deficient (scid/scid) mice.

dose levels. In the Jeko-1 mantle cell lymphoma xenograft model, Riximyo or MabThera was administered once weekly via IP administrations at subclinical dose levels of 0.03, 0.1, 0.3, or 1 mg/kg for three weeks. Riximyo and MabThera showed comparable dose dependent tumour growth inhibition, with no statistical differences in efficacy. Data from both these studies indicated that treatment with Riximyo or MabThera results in comparable tumour growth inhibition in both these xenograft models.

Efficacy of Riximyo was evaluated in mouse xenograft models of human B cell lymphoma. Two studies were conducted in mouse xenograft tumour models to compare survival following treatment with Riximyo or MabThera. In the first study the effects of Riximyo and MabThera on survival were compared in a Granta-519 human B cell lymphoma in a mouse xenograft tumour model. Riximyo or MabThera was administered by IV at dose levels of 5 or 40 mg/kg on Days 6, 10, and 14. Animals were observed until Day 52 for mortality and clinical observations (including score for paralysis). Survival time, onset of paralysis, and period of paralysis development were comparable between Riximyo and MabThera at equivalent dose levels. Riximyo and MabThera showed significant (p < 0.001) increases in mean and median survival times, and delay in in the onset of paralysis, when compared to values for the control group. Interestingly, the duration of paralysis and the paralysis score were increased for both test materials. In a second study, the effects of Riximyo and MabThera on survival were compared in the systemic Raji human Burkitt lymphoma CB17 SCID mouse xenograft tumour model. Riximyo or MabThera was administered by IP injection to mice twice weekly at doses of 0.25, 1.25, or 5 mg/kg for 3 weeks. Treatment with Riximyo or MabThera resulted in statistical significant but dose independent increases in survival compared to the control group; the lifespan relative to control was 80, 107, and 67% with 0.25, 1.25 and 5 mg/kg Riximyo, respectively, and 80, 67 and 73% with 0.25, 1.25 and 5 mg/kg MabThera, respectively. Riximyo at a dose level of 1.25 mg/kg statistically significantly increased survival time in animals (p<0.05) compared to MabThera at the same dose but no statistically significant differences were noted between Riximyo and MabThera at 0.25 and 5 mg/kg. Generally in both these studies using mouse xenograft models of human lymphomas, animal survival was comparable between Riximyo and MabThera. The only exception was the statistically significant increase in survival with Riximyo observed with mid dose (1.25 mg/kg) in the second study (using Raji-human Burkitt lymphoma CB17 SCID mouse xenograft tumour models). No possible explanation or biological significance was identified by the sponsors and this was possibly an outlier give the comparability demonstrated by all other pharmacology studies.

B cell depletion occurred in all monkey studies. Comparable B cell depletion was detected in the single dose pharmacokinetic study 5 days after dosing at 5 mg/kg and in the 4 week repeat dose toxicity study in cynomolgus monkeys at 20 and 100 mg/kg. Monkeys dosed with Riximyo had higher B cell counts 10 days after dosing in the single dose pharmacokinetic study than the MabThera group and difference in B cell depletion might be due to differences in anti-drug antibody levels in individual animals.

Overall, pharmacological comparability between Riximyo and MabThera was demonstrated by nonclinical in vitro and in vivo studies.

Pharmacokinetics

Toxicokinetic assessments were determined up to 9 days following a single dose or up to 14 days following the first repeated weekly doses (that is, prior administration to the third dose) due to observed development of anti-drug antibodies which interfered with the assay. The single and repeat dose studies showed similar Area under the serum concentration-time curve (AUC) values between Riximyo and MabThera. However peak plasma concentrations (C_{max}) values were lower by 13% in the single dose study and by 6

to 20% in the repeat dose study for Riximyo compared to MabThera. These observed differences had no impact on the pharmacology of the two drugs (measured as B cell depletion). A number of factors could contribute to the difference in C_{max} which include heterogeneity among individual monkeys as only a small number of animals were tested and variations in the initial sampling time point. Overall the pharmacokinetics data generally showed good overall comparability.

Toxicology

Toxicity testing was limited to one 4 week repeat dose toxicity study with 4 weeks observation and a 21 week recovery period.

In the repeat dose study either Riximyo or EU sourced MabThera were administered as weekly IV doses of either 20 or 100 mg/kg for four weeks. The doses tested were low, however similar to or higher than what was used in the original MabThera application. Despite low doses used, there was almost complete depletion of B cells after two doses, demonstrating that a near maximum pharmacodynamics response had been achieved. The number of animals that developed anti-rituximab antibodies was comparable at equivalent dose levels of Riximyo and MabThera. Anti-rituximab antibodies were detected in the 20 mg/kg Riximyo and MabThera groups starting 14 days after the first dose in all animals. In the 100 mg/kg treatment group most of the animals from Days 15 to 36 showed no or only marginal immune response which the sponsor suggests is likely due to rapid and marked depletion of B cells or high drug concentration induced tolerance.

In the repeat dose study completed to term there were no mortalities or adverse clinical signs noted in any of the animal groups. Serum chemistry and urinalysis measurements were comparable while haematological assessments indicated the expected decrease in total lymphocytes (as a result of B cell depletion) at all dose levels in both the test items, which recovered at the end of the 25 week recovery period. Both Riximyo and MabThera showed a similar course for B cell depletion and recovery. In all treatment groups, decreases in NK cell numbers (also expected as a result of ADCC activity of both the testing products) were noted during the dosing period, which returned to near baseline values from Day 29 (one week after the last dose). Necropsy assessments at interim sacrifice (Day 57) revealed reversible foamy histiocytes in lungs of animals treated with high dose Riximyo (1 animal) and MabThera (2 animals), which was not observed post the 25 week recovery period. The sponsors suggested the reported histiocytosis were likely to be related to cytokine release syndrome as a result of rituximab treatment. It needs to be noted, formation of histiocytes has not been previously reported for MabThera.

Other notable changes in the repeat dose study included absence of germinal centres in the spleen and some lymphatic organs (mesenteric lymph nodes, mandibular lymph node and axillary lymph node) occasionally accompanied by minimal to slight lymphoid depletion of spleen or axillary lymph node in individual animals. These observations were noted in all treatment groups and were considered to be due to the pharmacological effect of rituximab. While partial recovery (reduced incidences) was observed at the terminal sacrifice (following a 25 week recovery period) in some of these interim microscopic findings, germinal centres of follicles were still lacking (with great inter-individual variability) in the spleen and in some lymphatic organs (mesenteric lymph nodes, mandibular lymph node and axillary lymph node) in some animals of all treatment groups. These changes were likely to be an outcome of an incomplete recovery of B cells in the peripheral blood. No reactions at the injection site were observed. Overall, in vivo toxicity studies did not identify any unexpected toxicity findings for Riximyo compared with MabThera.

Tissue cross-reactivity assay study

Cross-reactivity was assessed by histologically prepared cryosections from > 35 human tissues from 3 donors stained with biotinylated Riximyo at concentrations of 1.25, 2.5 and 5 μg/mL (and optimal concentration of biotinylated Riximyo was determined to be 2.5 μg/mL). Cross reactivity was assessed in three donors for each tissue. Specific positive staining was observed within cells of lymphoid tissues consistent with B lymphocytes. All binding was related to the pharmacology of Riximyo and its ability to bind to CD20-expressing lymphocytes and no off target binding was observed which was similar to what was observed with MabThera in the original studies.

Nonclinical summary and conclusions

·   The scope of the nonclinical testing program was in general in accordance with EU guidelines on similar biological medicines. Data consisted of comparative studies on the pharmacology, pharmacokinetics and toxicity of Riximyo against EU sourced MabThera or US sourced Rituxan as the comparators. Bridging comparability studies between the Australia supplied MabThera and EU sourced MabThera and US sourced Rituxan are provided in the submission.

·   Pharmacological activity of Riximyo, as assessed in a series of in vitro functional assays which included determining ADCC potency and B cell depletion efficacy were comparable to the MabThera and Rituxan comparators. In vivo anti-tumour efficacy and survival studies were carried out in various relevant xenograft tumour models and both the efficacy and survival were generally comparable to MabThera.

·   A single dose pharmacokinetic study in cynomolgus monkeys showed comparability between Riximyo and MabThera.

·   A four week GLP comparative toxicity study was conducted in cynomolgus monkeys using the clinical (IV) route. This study did not identify any finding inconsistent with those seen with MabThera. Toxicity findings and toxicokinetic parameters were comparable between the biosimilar and comparator.

·   There are no nonclinical objections to the registration of Riximyo, provided adequate comparability of the EU sourced and Australia sourced MabThera is demonstrated by quality data.

V. 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

Riximyo has been developed as a similar biological medicinal product to the EU authorised reference product MabThera sponsored by Roche. Riximyo is being proposed for the same indications as those approved for MabThera in the EU and in Australia. The sponsor states that the proof biosimilarity of Riximyo to MabThera is based on a totality-of-data approach, including physicochemical, nonclinical (functional parameters tested in in vitro bioassays as well as animal studies) and clinical data (pharmacodynamic (PK)/ pharmacodynamic (PD), efficacy and safety including immunogenicity from an immunology indication (rheumatoid arthritis (RA)) and from an oncology indication

[previously untreated advanced follicular lymphoma [FL]). The sponsor submitted a justification for extrapolating the clinical data for Riximyo in patients with RA and in patients with previously untreated non-Hodgkin's FL to all other proposed indications. This justification is discussed later in the clinical evaluation report (CER) [see Attachment 2]. An overview of the step-wise Riximyo development program is provided below in Figure 3.

Figure 3: Overview of the Riximyo development program
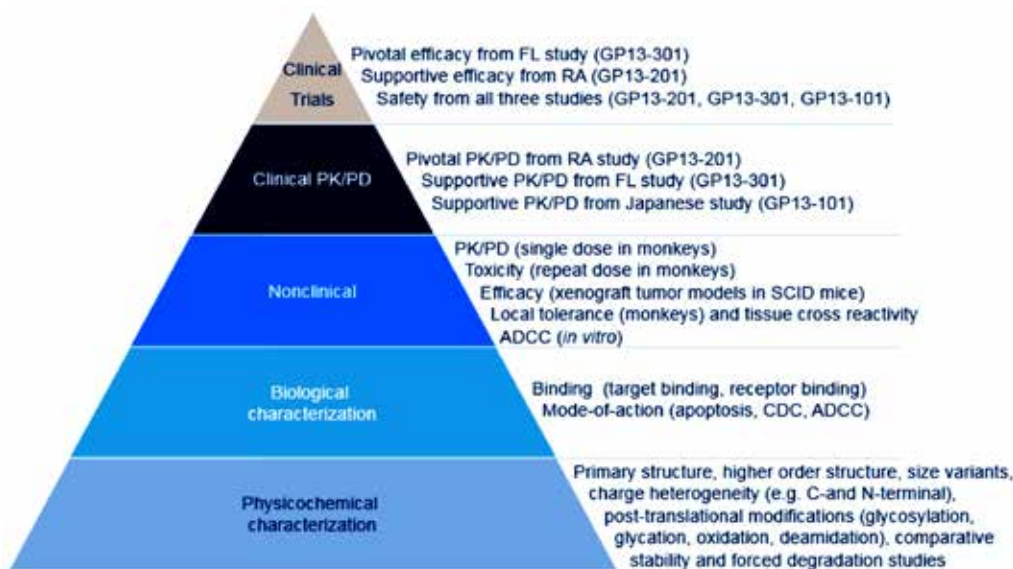
Contents of the clinical dossier

Scope of the clinical dossier

The clinical dossier consisted of an abridged submission aimed at demonstrating bioequivalence, pharmacodynamic comparability, and efficacy and safety similarity of Riximyo to MabThera (EU) in patients with advanced RA and non-Hodgkin's FL. There were no clinical studies supporting approval of Riximyo for all proposed indications. The sponsor has provided a justification supporting extrapolation of the submitted clinical comparability data in patients with advanced RA and non-Hodgkin's FL to all proposed indications.

· Study GP13-201 (Part I): The pivotal Phase II PK/PD study in patients with RA, primarily designed to assess PK equivalence of Riximyo and MabThera (EU). The study also included comparative PD, efficacy, safety and immunogenicity data for Riximyo and MabThera (EU). Part II of the study, which is the same design as Part I, is currently ongoing and compares Riximyo to Rituxan (US). No data from Part II of the study was provided in the clinical part of the submission. The 24 week report for Part II is expected in January 2017 and the 52 week report is expected in January 2018.

· Study GP13-301: The pivotal Phase III efficacy and safety study compared Riximyo and MabThera (EU) in patients with non-Hodgkin's disease FL. In addition to efficacy and safety comparability data, the study also provided comparative immunogenicity data and supportive PK and PD equivalence data. The submission included data for the primary efficacy and safety analysis for the combination phase of the study (Week 24) and interim efficacy and safety results for the maintenance phase of the study (planned duration of 2 years).The final study report for Study GP13-301 is expected in August 2018.

· Study GP13-101: This was a supportive Phase I study assessing the safety and PK of Riximyo monotherapy in Japanese patients with CD20+ low tumour burden indolent

B-cell NHL. The study was requested by the Japanese regulatory authorities (PMDA). The study included only 6 patients and no direct comparative data were provided (that is, Riximyo versus Rituxan (Japanese comparator)). The data for Riximyo from this study were compared with the data for Rituxan from the approved Japanese prescribing for this product.

· Reports of bioanalytical and analytical methods for Studies GP13-101, GP13-201 and GP13-301.

· Literature references.

Paediatric data

No paediatric data were submitted.

No statements regarding paediatric development plans submitted to other regulatory agencies could be identified in the dossier. In the Clinical Overview, the sponsor stated that clinical studies in the paediatric population were not conducted '*since the overall objective of the biosimilar development program is to establish comparability, and therefore the selection of the primary patient population is driven by the need for homogeneity and sensitivity (EMA/CHMP/BMWP/403543/2010)*'. The sponsor refers to the EU Summary of Product Characteristics (SmPC) for MabThera, which states that the safety and efficacy of MabThera in children below 18 years of age has not been established and that no data in this population are available.

The absence of paediatric data in the submitted clinical dossier is considered to be acceptable, given the proposed usage of Riximyo.

Good clinical practice

The sponsor states that all three clinical studies were designed and conducted in full compliance with Good Clinical Practice (GCP) and according to the ethical principles of the Declaration of Helsinki.

Pharmacokinetics

Studies providing pharmacokinetic data

The submission included three studies providing PK information in patients. These three studies were:

· Study GP13-201 (Part 1): This was the pivotal Phase II PK/PD study designed to assess the bioequivalence of Riximyo and MabThera (EU reference product). The study was undertaken in 173 patients with rheumatoid arthritis (RA) refractory or intolerant to standard disease modifying anti-rheumatic drugs (DMARDs) and 1 to 3 anti-tumour necrosis factor (anti-TNF) therapies. The two rituximab formulations were each administered in combination with methotrexate. The sponsor stated that the study was designed in accordance with the European Medicines Agency (EMA) Guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev 1), and demonstrated bioequivalence of Riximyo and MabThera in accordance

with the EMA Guideline on Bioequivalence.[4] Both of these guidelines have been adopted by the TGA.

·   Study GP13-301: This was the pivotal Phase III efficacy and safety study in patients with previously untreated non-Hodgkin's advanced follicular lymphoma (FL). The study included supportive (descriptive) comparative PK/PD data for the two rituximab formulations. The study included PK data (C_{trough} and C_{max}) on 196 patients following sparse sampling and 54 patients with PK data (the area under the curve from the time of dosing to the time of the last observation, regardless of whether the last concentration is measureable or not (AUC_{all}) and area under the serum concentration-time curve from time zero to Day 21 (AUC_{0-21d})) following more extensive sampling. The two formulations were each administered in combination with cyclophosphamide, vincristine and prednisone. The study was undertaken in accordance with the TGA adopted EMA guideline on similar biological medicinal products containing monoclonal antibodies.[5]

·   Study GP13-101: In this Phase I safety study, limited supportive PK data for Riximyo were provided for 6 Japanese patients with CD20 positive low tumour burden indolent B-cell NHL. In this study, no contemporaneous comparative data for MabThera versus Rituxan (Japan) were provided. Instead, the study included a comparison of the observed PK results for Riximyo with those from the Japanese package insert for Rituxan (rituximab).

Evaluator's conclusions on pharmacokinetics

It is considered that the pivotal PK/PD Phase II Study GP13-201 in patients with RA has satisfactorily established the bioequivalence of Riximyo and MabThera (EU approved). The pivotal PK bioequivalence results from Study GP13-201 in patients with RA are supported by the descriptive PK data from Study GP13-301 in patients with FL. There were limited descriptive PK data relating to Riximyo from the Phase I Study GP13-101 in Japanese patients with CD20+ low tumour burden indolent B-cell NHL.

Pivotal PK/PD study (GP13-201) Phase II study

The pivotal PK/PD study (Study GP13-201 (Part 1)) included patients with RA (n = 173) who were refractory or intolerant to standard DMARDs and 1 to 3 anti-TNF therapies. In this study, patients were treated with either Riximyo or MabThera (EU approved) in combination with methotrexate (MTX). The decision to use patients with RA to provide pivotal PK/PD data rather than patients with oncological indications was appropriately justified by the sponsor.

The primary PK variable in the pivotal study was area under the serum concentration-time curve from time zero to infinity (AUC_{0-inf}) at Week 24 following two IV infusions of Riximyo or MabThera at doses of 1000 mg administered 2 weeks apart (Day 1 and Day 15). The geometric mean ratio (Riximyo/MabThera) of the AUC_{0-inf} was 1.064 (90% confidence interval (CI): 0.968, 1.169). The 90% CI was enclosed entirely with the pre-specified bioequivalence interval of 0.80 to 1.25, which indicates that Riximyo was bioequivalent to MabThera (EU approved) based on the AUC_{0-inf}. The analysis was adequately powered to detect a statistically significant difference between the two products. The choice of AUC_{0-inf} as the primary PK variable for assessment of bioequivalence was satisfactorily justified by the sponsor.

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[4] CPMP/EWP/QWP/1401/98 Rev. 1/Corr**
[5] EMA/CHMP/BMWP/403543/2010

The key secondary PK variable ($C_{max,1}$) failed to demonstrate bioequivalence of the two formulations as the 90% CI of the geometric ratio was outside the pre-specified bioequivalence interval of 0.80 to 1.25. The geometric mean ratio (Riximyo/MabThera) of $C_{max}1$ was 1.133 (90% CI: 1.017, 1.262). The results indicated that the geometric mean $C_{max}1$ for Riximyo was approximately 13% higher than for MabThera, with the upper 90% CI for the geometric ratio being marginally greater than the standard upper 90% CI for bioequivalence (that is, 1.262 > 1.25). In contrast, the results for $C_{max,2}$ indicated that the two formulations were bioequivalent based on this parameter as the 90% CI was enclosed entirely within the pre-specified bioequivalence interval of 0.80 to 1.25 (that is, geometric mean ratio ((Riximyo/MabThera) = 1.036 (90% CI: 0.944, 1.138)). The sponsor provided an acceptable explanation for $C_{max}1$ missing the standard bioequivalence criteria based on greater variability in the rate and duration of the infusion associated with the first infusion/first course compared to the second infusion/first course. Both the infusion rate and the duration of the infusion are known to affect end-infusion drug serum concentrations.

Overall, it is considered that the pivotal PK study has satisfactorily established the bioequivalence of Riximyo and MabThera (EU approved) in patients with RA refractory or intolerant to standard DMARDs and 1 to 3 anti-TNF therapies. The primary PK variable of AUC_{0-inf} satisfactorily demonstrated bioequivalence. In addition, it is considered that although Riximyo and MabThera were not bioequivalent based on the $C_{max}1$ results, the observed difference in this parameter between the two rituximab formulations is unlikely to be clinically significant. Furthermore, the 90% CI values for the geometric mean ratios for all the other secondary PK variables (C_{max}, AUC_{0-14d}, AUC_{0-12w} and AUC_{0-24w}) met the standard bioequivalence criteria. Time to maximum serum concentration ($T_{max,1}$) was similar for Riximyo and MabThera, as was $T_{max,2}$

Supportive PK/PD studies

Supportive PK bioequivalence data were provided by the pivotal Phase III efficacy and safety study (Study GP13-301) in patients with FL. The study was not powered for bioequivalence and, therefore, all PK data were presented descriptively. The PK of Riximyo and MabThera (EU approved) at Cycle 4/Day 1 were evaluated as the secondary objective of the study. The PK variables C_{max} and C_{trough} on Day 1 for Cycles 1, 4 and 8 were calculated from sparse sampling after administration of Riximyo or MabThera at an IV dose of 375 mg/m^2, in combination with Cyclophosphamide, vincristine, prednisone (CVP), in approximately 100 patients in each treatment arm. In addition to C_{max} and C_{trough} levels based on sparse sampling, AUC_{0-21d}) and AUC_{all} (steady state) were calculated using extensive sampling after study drug administration on Day 1 of Cycle 4 in a subset of approximately 20 patients in each treatment arm.

In Study GP13-301, the C_{max} values at Cycle 1/Day 1, Cycle 4/Day 1 and Cycle 8/Day 1 were similar for the two formulations. There were some differences between the two formulations in mean C_{trough} levels in Cycle 4/Day 1 and Cycle 8/Day 1, with marked inter-subject variability of this variable being observed with both formulations. Both the AUC_{0-21d}) and AUC_{all} (steady state) were similar for the two formulations, with moderate to marked inter-subject variability being observed for both PK variables with both formulations.

Limited supportive PK data relating to Riximyo were provided in a Phase I study (Study GP13-101) in Japanese patients with CD20+ low tumour burden indolent B-cell NHL. The PK variables (AUC_{0-7d}; C_{max}; AUC_{0-last}; C_{min}; T_{max}) were assessed on Week 1/Day 1 and Week 8/Day 1 after administration of Riximyo IV at a weekly dose of 375 mg/m^2. The PK results were reported to be consistent with the PK results in the package insert for Rituxan (Japanese-approved). No patients in this study were treated with an approved rituximab formulation.

Pharmacodynamics

Studies providing pharmacodynamic data

The submission included two studies providing PD data comparing Riximyo to MabThera:

- The pivotal Phase II, PK/PD study (Study GP13-201 (Part 1)) in patients with RA included PD data on depletion of peripheral B-cells based on the area under the effect-time curve from time zero to Day 14 ($AUEC_{0-14d}$). The two formulations were considered to be equivalent if the 95% CI of the ratio of the geometric means (Riximyo/MabThera) of the area under the effect-time curves for 14 days ($AUEC_{0-14d}$) was within the pre-specified equivalence limits of 0.8 to 1.25.

- The supportive PK/PD data from the Phase III, efficacy study (Study GP13-301) in patients with FL included PD data on depletion of B-cells based on the AUC_{0-21d}). The two formulations were considered similar as the 95% CI of the ratio of the geometric means (Riximyo/MabThera) of the AUC_{0-21d}) was within the equivalence limits of 0.8 to 1.25. The PD in this study were considered exploratory.

Evaluator's conclusions on pharmacodynamics

- It is considered that the submitted PD data have satisfactorily established the PD equivalence of Riximyo and MabThera (EU approved). In the pivotal PK/PD study (Study GP13-201) both Riximyo and MabThera were administered in combination with MTX and in the supportive PK/PD study (GP13-301) both Riximyo and MabThera were administered in combination with CVP. The PD of the two formulations were assessed using depletion of CD19+ B-cells relative to baseline, which is an acceptable surrogate biomarker for CD20+ B-cell depletion. In the following discussion, B-cell depletion refers to CD19+ B-cell depletion.

- The pivotal PK/PD study (Study GP13-201) in patients with RA demonstrated that the PD of Riximyo (n=72) and MabThera (n = 75) were equivalent, based on the 95% CI for the geometric mean ratio for the $AUEC_{0-14d}$ of percent depletion in B cells relative to baseline being entirely within the pre-specified PD equivalence limits of 0.80 to 1.25. The geometric mean ratio (Riximyo/MabThera) for the $AUEC_{0-14d}$ was 1.019 (95% CI: 0.997, 1.042).

- In the pivotal PK/PD study (Study GP13-201), mean percent depletion of B cells relative to Baseline at 72 hours after the infusion (that is, study Day 4) was 4.3% in the Riximyo arm and 6.7% in the MabThera arm, and was less than 1% in both arms at study Day 15 (that is, before second infusion). The percent B cell depletion relative to baseline versus time curves from baseline through to study Day 15 were almost superimposable for the two treatment arms. In addition, the percent B cell depletion relative to baseline curves through to Week 52 were similar for the two treatment arms. The mean percent B cell counts relative to baseline were less than 1% on Day 15 in both treatment arms, remained below 20% up to Week 24 for both formulations, and were 19.7% in the Riximyo arm and 21.1% in the MabThera arm at Week 52.

- In the pivotal PK/PD Study GP13-201, the proportion of patients with B cell counts below the limit of quantification (LoQ) (< 3 cells/µL) was comparable between the Riximyo and MabThera arms on Days 4, 8 and 14. More than 50% of patients by Day 8 and more than 70% patients by Day 15 were below the LoQ (< 3 cells/µL) in both treatment arms.

- In Study GP13-301, the PD equivalence of the two formulations was supported by the exploratory data in approximately 20 patients with FL in each treatment arm in the pivotal Phase III efficacy and safety study (Study GP13-301). In this study, the

geometric mean ratio (Riximyo/MabThera) with associated 90% CI for $AUEC_{0-21d}$ for B-cell depletion relative to baseline was 0.939 (90% CI: 0.845, 1.04). In a post hoc analysis undertaken to meet EMA requirements the geometric mean ratio (Riximyo/MabThera) for with associated 95% CI for $AUEC_{0-21d}$ 0.939 (95% CI: 0.827, 1.065). The 90% CI and the 95% CI were both enclosed entirely within the pre-specified equivalence limits of 0.80 to 1.25. The arithmetic mean plots of percentage B-cell reduction relative to baseline from end of infusion through to 504 hours post infusion were similar for the two treatment arms.

Dosage selection for the pivotal studies

The rituximab + CVP treatment regimens used in the combination phase of Study GP13-301 are consistent with the approved recommended treatment regimen of MabThera plus chemotherapy for 8 cycles as induction therapy for the treatment of patients with previously untreated Stage III/IV non-Hodgkin's FL (MabThera PI). Based on the data from Marcus et al (2008);[6] it is considered that comparison of Riximyo+CVP to MabThera+CVP in patients with previously untreated non-Hodgkin's FL is sufficiently sensitive to identify efficacy differences between the two regimens arising from differences between the two rituximab formulations. Similarly, it can be anticipated that differences in the safety profiles of the two regimens used in the combination phase of Study GP13-301 are likely to be due to differences between the two rituximab formulations.

The maintenance regimen used in Study GP13-301 of Riximyo or MabThera for 8 times 3 month cycles for 2 years, differs from the recommended MabThera maintenance regimen of treatment every 2 months for 2 years (see approved MabThera PI). However, this is not a major issue as it can be reasonable inferred that differences in the efficacy outcomes and safety profiles between single agent Riximyo and single agent MabThera regimens in the maintenance phase of Study GP13-301 will be due to differences between the two rituximab formulations.

Data from the Clinical trials section of the approved MabThera PI indicates that ACR response[7] (20, 50, 70) at Week 24 in patients with RA is consistently better (statistically and clinically) across studies in patients treated with MabThera in combination with MTX compared to patients treated with placebo in combination with MTX. In addition, the Clinical trials section of the approved MabThera PI provides data showing that both the mean change in DAS28[8] and the EULAR[9] responses at Week 24 across studies are superior in patients treated with MabThera in combination with MTX compared to patients treated with placebo in combination with MTX. The approved MabThera PI also states that the *'efficacy and safety of further courses [of rituximab in combination with MTX [are] comparable to the first course [of rituximab in combination with MTX]]'*. Based on the data in the Clinical trials section of the approved MabThera PI, it is considered that the

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[6] Marcus et al (2008). Phase III study of R-CVP plus rituximab compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol; 26(28):4579-4586.

[7] ACR (American College of Rheumatology) responses are presented as the numerical improvement in multiple disease assessment criteria. For example, an ACR 20 response is defined as a ≥20% improvement in (1) swollen joint count (66 joints) and tender joint count (68 joints) and (2) ≥20% improvement in 3 of the following 5 assessments - patient's assessment of pain (VAS), patient's global assessment of disease activity (VAS), physician's global assessment of disease activity (VAS), patient's assessment of physical function as measured by the HAQ and CRP. ACR 50 and ACR 70 are similarly defined.

[8] DAS = Disease activity score and DAS28 is a measure of the activity of rheumatoid arthritis. The DAS is based upon treatment decisions of rheumatologists in daily clinical practice.

[9] The EULAR (European League against Rheumatism) response criteria are based on the assessment of disease activity using the Disease Activity Score (DAS), a statistically-derived index consisting of number of tender joints, number of swollen joints, erythrocyte sedimentation rate, and global disease activity.

treatment regimens of Riximyo or MabThera (both in combination with MTX) are sufficiently sensitive to detect clinically meaningful efficacy and safety differences between the two rituximab formulations. This is considered to be the case even though the criteria for patients with RA treated in Study GP13-201 differed from the Australian approved criteria for patients with RA eligible for treatment with MabThera.

The rituximab treatment regimen used in Study GP13-201 in patients with active RA intolerant or resistant to DMARDs and 1-3 anti-TNF therapies is consistent with, but not identical to, the regimen recommended for MabThera in the approved Australian PI. In Australia, MabThera in combination with methotrexate is indicated for the treatment of adult patients with severe, active RA who have had an inadequate response or intolerance to at least one TNF-inhibitor therapy. The RA indication in Study GP13-201 requires patients to have had an inadequate response or be intolerant to non-biological DMARDs and 1 to 3 anti-TNF therapies. However, the difference in the indications is not considered to be a major clinical issue. It is considered reasonable to infer that if there are no clinically meaningful differences in efficacy and safety between Riximyo and MabThera in patients with RA treated in Study GP13-201 then there are unlikely to be clinically significant efficacy and safety differences between the two rituximab formulations for treatment of patients with RA meeting the approved indication. In addition, further support for the acceptability of the two rituximab formulations for the treatment of both groups of RA patients arises from the finding that Riximyo and MabThera are bioequivalent based on the PK data and equivalent based on the PD data in patients with RA studied in GP13-201.

All patients in the study were required to have been on a stable dose of MTX of 7.5 to 25 mg per week for at least 4 months prior to randomisation and with a stable dose for 4 weeks prior to randomisation. At Baseline, the mean ± Standard deviation (SD) dose of MTX in the total population was approximately 15 ± 4.9 mg/week, and the mean dose in both treatment groups was approximately 15 mg/week with a similar SD of 5 mg/week. MTX at baseline was used by all patients in accordance with the protocol, with the exception of 2 patients who had not been taking MTX for at least 4 months prior to randomisation or who had not been taking MTX (both in the Riximyo group) and 3 patients who had not been on a stable dose of MTX for 4 weeks prior to randomisation (1 in the Riximyo group; 2 in the MabThera group).

In patients with RA, the maintenance dose of MTX is generally within the range of 7.5 mg to 20 mg per week (methotrexate PI) and the dose of MTX to be given concurrently with MabThera is the dose tolerated by the patient (MabThera PI). In Study GP13-201, all patients received MTX at a dose of between 7.5 mg and 15 mg per week (oral dose recommended), which was to remain unchanged throughout the study. It is considered that the dose of MTX administered with rituximab in Study GP13-201 is appropriate.

Efficacy

Studies providing efficacy data

There were two studies in the submission providing evaluable efficacy data comparing Riximyo with MabThera (EU approved). The two studies with evaluable efficacy data are outlined below in Table 2.

Table 2: Brief outline of the two studies with evaluable efficacy data

Study	Design	Study population	Treatment
GP13-301 Phase III Pivotal efficacy	Randomised, double-blind, active-control, 3 year, multinational, multicentre, study comparing PK, PD, efficacy, and safety of Riximyo vs MabThera in patients with previously untreated non-Hodgkin's stage III/IV follicular lymphoma. Efficacy was the primary objective; primary efficacy variable was comparison of the two study drug with respect to ORR in the combination phase; secondary efficacy variables included BOR of CR, PR, SD and PD for the combination phase and PFS and OS covering the whole study (i.e., combination phase, maintenance phase, and post-treatment phase (if applicable).	Patients with untreated FL, mean age 56.9 years (range: 23, 84 years), Caucasian 67.1%, Asian 24.9%, Black 1.4%. Total N = 627 (330 F, 289 M); Riximyo N = 312 (181 M, 131 F); MabThera N = 315 (169 F, 146 M).	Combination Phase (6 months); Riximyo (n = 312) or MabThera (n = 315) 375 mg/m^2 administered by IV infusion on day 1 of 8 x 21 day cycles in combination with cyclophosphamide, vincristine and prednisone. Maintenance Phase (2 years) treatment with single-agent Riximyo (n=231) or MabThera (n=231) 375 mg/m^2 for 8 x 3 month cycles for responders to combination phase treatment. Follow-up phase (6 months) for patients completing 2 years of maintenance treatment or discontinuing treatment prematurely.
GP13-201 (Part 1) Phase II Supportive efficacy	Randomised, double-blind, active-control, 52-week, multinational, multicentre study comparing PK, PD, efficacy and safety of Riximyo vs MabThera in patients with active RA refractory or intolerant to standard non-biologic DMARDs and 1-3 anti-TNF therapies. Efficacy was a secondary objective in this study; key variable was non-inferiority of Riximyo to MabThera with respect to change from baseline in DAS28 at week 24. There were a large number of other secondary efficacy variables.	Patients with active RA, mean age 53.7 years (range: 21, 82 years), Caucasian 80.9%, Asian 13.9%, Black 4.0% Total N = 173 (149 F, 24 M); Riximyo N = 86 (76 F, 10 M); MabThera N = 87 (73 F, 14 M).	Riximyo or MabThera: 1000 mg, two single IV infusions two weeks apart (days 1 and 15) in combination with MTX (7.5-25 mg/week); treatment could be repeated for responder between week 24 and week 52. Follow-up to week 52 or 26 weeks after the first infusion of second course of study medication for re-treated patients. Primary analysis at week 24, responders could then be re-treated between Week 24 and Week 52.

Evaluator's conclusions on efficacy

Pivotal Phase III Study GP13-301 Follicular Lymphoma (FL)

·   Pivotal efficacy data for comparability of the two formulations were provided in patients with untreated Stage III/IV non-Hodgkin's FL in the Phase III Study GP13-301. The study met its primary objective, which was to show equivalence between Riximyo-CVP and MabThera CVP based on the overall response rate (ORR) assessed by the Modified Response Criteria for Malignant Lymphoma using central blinded review of the radiological response and liver/spleen enlargement assessments in patients with FL (Per Protocol Set (PPS)). The ORR was 87.1% (271/311) in the Riximyo arm and 87.5% (274/313) in the MabThera arm, with the difference between the two arms being -0.40% (95% CI: -5.94%, 5.14%). The 95% CI for the difference in ORR between the two arms was entirely enclosed within the pre-specified ORR equivalence margin of -12% to +12%.The study was adequately powered (90%) to show equivalence based on the pre-specified equivalence margin of 12% to +12% at a two one-sided significance level of 2.5%. The results for the analysis in the full analysis set (FAS) were consistent with the results in the PPS.

·   In a pre-specified subgroup analysis testing ORR equivalence between the two treatment arms in patients with FL stratified by baseline Follicular Lymphoma International Prognostic Index (FLIPI) score (PPS), the 90% CI of the difference between the two treatment arms for both FLIPI subgroups (scores 0-2; scores 3-5) were not enclosed entirely within the equivalence margin of -12% to +12%. Of note, the ORR notably favoured the MabThera arm compared to the Riximyo arm in patients with a FLIPI score of 0 to 2 (91.2% versus 82.8%, respectively), while the ORR notably favoured the Riximyo arm compared to the MabThera arm in patients with a FLIPI score of 3 to 5 (90.4% versus 84.7%, respectively). The results of this subgroup analysis do not support the primary analysis, as the 90% CI of the difference between the two treatment arms was not enclosed entirely within the equivalence margin of -12 to +12% for either of the two subgroups. However, the inconsistent results in the two FLIPI subgroups make interpretation of the analysis problematic. No firm conclusions concerning the comparability of the two treatment arms can be made based on the results of the FLIPI subgroup analysis. However, the ORR was high in both the Riximyo and the MabThera arms suggesting that both products are effective in both subgroups.

·   The sponsor states comments that the FLIPI score was developed as a prognostic factor for overall survival and, therefore, the difference between the two treatment arms observed in the analysis of ORR by FLIPI score may not be clinically relevant. However, it is considered that there is no reason to assume that the FLIPI score is not a relevant prognostic factor for all efficacy endpoints in patients with FL, given that it is based on scores relating to age > 60 years, Ann Arbor Stage III & IV[10], involvement of more than 4 lymph node groups, elevated lactate dehydrogenase (LDH), and

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[10] Ann Arbor staging is the staging system for lymphomas, both in Hodgkin's lymphoma (formerly designated Hodgkin's disease) and non-Hodgkin lymphoma (abbreviated NHL). The principal stage is determined by location of the tumor:
Stage I indicates that the cancer is located in a single region, usually one lymph node and the surrounding area. Stage I often will not have outward symptoms.
Stage II indicates that the cancer is located in two separate regions, an affected lymph node or lymphatic organ and a second affected area, and that both affected areas are confined to one side of the diaphragm—that is, both are above the diaphragm, or both are below the diaphragm.
Stage III indicates that the cancer has spread to both sides of the diaphragm, including one organ or area near the lymph nodes or the spleen.
Stage IV indicates diffuse or disseminated involvement of one or more extralymphatic organs, including any involvement of the liver, bone marrow, or nodular involvement of the lungs.

haemoglobin level < 12 g/dL. Furthermore, it is reasonable to infer that the sponsor considered that the FLIPI score was an important prognostic factor for ORR in the pivotal study, given that it was one of the factors used to stratify randomised patients and the pre-defined primary efficacy endpoint was the ORR.

· In the pre-specified subgroup analysis assessing ORR equivalence between the two treatment arms stratified by baseline age (PPS), the 90% CI of the difference between the two treatment arms for both subgroups (< 60 years; ≥ 60 years) was within the equivalence margin of -12% to +12%. The results of the subgroup analysis in the FAS were consistent with the results in the PPS. The results in the subgroup analysis based on age support equivalence of the two treatment arms observed in the primary analysis.

· The logistic regression analysis of the ORR based on central blinded review of the tumour assessment during the combination treatment phase (PPS) determined the odds ratio (CP2013/MabThera) to be 0.96 (90% CI: 0.65, 1.43).The results showed no statistically significant difference between the two treatment arms based on the 90% CI (that is, the interval includes an odds ratio of 1). The results of the logistic regression with explanatory variables of treatment and FLIPI score support the primary analysis of the ORR showing equivalence of the two treatments.

· The results of the Best overall response (BOR) based on central review of tumour assessments (Complete response (CR), Partial response (PR), SD, PD) in the combination phase were comparable in the two treatment arms in both the PPS and the FAS. The results support the primary analysis of the ORR showing equivalence of the two treatments.

· Overall, it is considered that the primary analysis of the ORR established the equivalence of Riximyo-CVP and MabThera-CVP based on central blinded review of tumour assessment in the combination treatment phase of the study (8 x 21 day treatment cycles) in patients with FL. However, while the pre-specified subgroup analyses of the ORR based on age (< 60 years; ≥ 60 years) demonstrated equivalence of the two treatments, the pre-specified subgroup analyses of the ORR based on FLIPI prognostic scores (0-2; 3-5) failed to demonstrate equivalence of the two treatments. The logistic regression analysis of the ORR demonstrated no statistically significant difference between the two treatment arms in BOR of CR or PR, based on modelling with explanatory variables of treatment and FLIPI score.

· The preliminary data for PFS and OS are too immature to conclude comparability of the two treatments for the two parameters. Therefore, it is considered that although the primary analysis of the ORR demonstrated equivalence of the two treatments, the absence of confirmatory comparability data for PFS and OS preclude GP013 and MabThera being declared therapeutically equivalent. It is suggested that this matter be re-visited when the final results for PFS and OS from Study GP13-301 become available.

Supportive Phase III Study GP13-201 Rheumatoid Arthritis (RA)

· Supportive efficacy data for comparability of the two formulations were provided in patients with advanced RA in the Phase II Study GP13-201. In this study, the assessment of efficacy in patients with RA was a secondary objective. The study met its key efficacy objective, which was to show non-inferiority of change from baseline in DAS28 (C-reactive protein (CRP)) at Week 24 in the PPS. The LS mean change from baseline in DAS28 (CRP) at week 24 in the PPS was similar for the Riximyo and the MabThera arms (-2.16 and -2.23, respectively), and the LS mean difference between the two treatment arms was 0.07 (95% CI: -0.328, 0.462). The upper 95% CI of 0.462 was below the pre-defined non-inferiority margin of 0.6. The arithmetic mean change from baseline in DAS28 (CRP) from baseline over the 52 weeks of the study was

similar in the two treatment arms, with marked inter-subject variability in the parameter being observed in both treatment arms.

- The criterion for non-inferiority of averaged change from baseline in DAS28 (CRP) between Week 4 and 24 in the PPS was not met, with the upper 95% CI for the LS mean difference between the two treatment arms of 0.639 being marginally higher than the pre-specified non-inferiority margin of 0.6. The criterion for non-inferiority of ACR20 (CRP) response at Week 24 in the PPS was met, with the lower 95% CI for the difference between the two treatment arms of -14.74% being greater than the pre-specified non-inferiority margin of -15.0%. The criteria for non-inferiority of averaged change from baseline in ACR20 (CRP) using a logistic repeated measures mixed model and a non-linear mixed effect longitudinal model in the PPS were met, with the respective lower 95% CIs for the difference between the two treatment arms for the two analyses of -12.5% and -12.8% being greater than the pre-specified non-inferiority margin of -15%.

- The study included a number of other secondary efficacy variables which were summarised descriptively. There were some numerical differences between the two treatment arms in some of these variables. However, the observed differences are considered not to be clinically meaningful.

- Overall, based on the totality of the RA data it is considered that Study GP13-201 satisfactorily demonstrated that the efficacy of the two formulations were comparable with the differences between the two formulations being not clinically meaningful.

Switching data

The were no data in the submission comparing efficacy in patients with either RA or FL initially treated with MabThera and switched to Riximyo to the efficacy of patients continuing with MabThera. The submission indicates that there is an ongoing safety study (GP13-302) in patients with RA designed to identify potential risks (general safety and immunogenicity) associated with transitioning from the originator product (Rituxan [US approved] or MabThera [EU approved]) to Riximyo compared to continuous treatment with the originator product. The main safety and immunogenicity analysis in this study will take place at Week 12 with an additional follow-up analysis at Week 24. No efficacy analyses are planned for this study. The study is planned to randomise approximately 100 patients in the USA and EU.

Other indications

The sponsor submitted a scientific justification for extrapolating the data for Riximyo and MabThera in patients with RA and FL to all other TGA approved indications of MabThera. This justification was based on the totality-of-data submitted to establish the comparability of Riximyo and MabThera. The results of the comparability exercise based on the clinical data (PK, PD, efficacy [RA, FL]) are considered to be promising and suggest that Riximyo and MabThera are therapeutically for all proposed indications. However, it is considered that confirmation of clinical comparability of the two products should await the final results of Study GP13-301 relating to progression free survival (PFS) and overall survival (OS). The submitted data for these two important time-to-event endpoints are too immature to demonstrate comparability of Riximyo and MabThera for the treatment of FL.

Safety

Studies providing safety data

The three studies providing evaluable safety data were:

- Pivotal Phase II PK/PD study in patients with active RA (Study GP13-201);
- Pivotal Phase III clinical efficacy and safety study in patients with FL (Study GP13-301); and
- Phase I study in Japanese patients with indolent B-cell NHL (Study GP13-101).

The safety analysis sets defined for each of the three studies with evaluable safety data are summarised below in Table 3.

Table 3: Safety analysis sets defined for safety analysis of three studies with evaluable safety data

Study	Definition	Number of patients in SAF[1]
GP13-201 (Part I)	The **Safety Analysis Set** consisted of all patients who received study drug at least once. Patients were analyzed according to treatment received.	N=173 (100%) GP2013=86 (100%) MabThera=87 (100%)
GP13-301 (data until cut-off 10-Jul- 2015)	The **Safety Set** population consisted of a subset of the patients in the Full Analysis Set who actually received at least one (partial or complete) dose of investigational treatment (MabThera or GP2013) and had at least one post-baseline safety evaluation (e.g., lab, vital signs, AEs)[2]. All safety analyses that included safety information limited to the Combination Phase were based on the Safety Set.	N=627 (99.7%) GP2013=312 (99.4%) MabThera=315 (100%)
	The **Maintenance Set** consisted of all patients who agreed to participate in the Maintenance Phase of the study and received at least one dose of investigational treatment (MabThera or GP2013) in the Maintenance Phase.	N=462 (73.4%) GP2013=231 (73.6%) MabThera=231 (73.3%)
GP13-101	The **Safety Set** was identical to Full Analysis Set which included all patients who received at least one dose of GP2013	N=6 (100%) GP2013=6 (100%)

The submission included no pooled safety analysis of the data from the three studies with evaluable safety data. The sponsor stated that a pooled analysis was not performed due to diverse indications, comorbid conditions and concomitant medications across the three studies. The absence of a pooled safety analysis is considered to be acceptable for the reasons provided by the sponsor.

The approach to evaluation of the safety data in the CER has been to separately evaluate the comparative safety data (Riximyo versus MabThera) for Studies GP13-201 and GP13-301. The safety data for Study GP13-101 included information from 6 Japanese patients treated with Riximyo. The safety data from this study have been examined and raise no concerns. Therefore, the safety data in the 6 Japanese patients from Study GP13-101 treated with Riximyo are not included in the review of safety presented below.

Patient exposure

The safety of Riximyo has been evaluated in 504 patients, comprising 133 Riximyo treatment naïve patients with active RA (Study GP13-201, Parts I and II), 53 patients with active RA transitioned to Riximyo after being treated with Rituxan/MabThera (Study GP13-302), 6 Japanese patients with indolent NHL (Study GP13-101) and 312 patients with FL up to cut-off date of 10 July 2016 (Study GP13-301). Patients with RA have been followed for up to 52 weeks, and patients with FL haven been followed for up to 3 years.

In Study GP13-201, 133 patients with RA were randomised to treatment with Riximyo (Parts I and II) and 123 (92.5%) have completed the study up to 24 weeks and 89 (66.9%) have completed the study up to 52 weeks. In Study GP13-302, 53 patients with RA were randomised to treatment with Riximyo following prior treatment with Rituxan/MabThera and 22 (41.5%) have completed the planned 24 weeks. In Study GP-301, 312 patients with FL were randomised to Riximyo and 87 (27.9%) have completed 6 months, 52 (16.7%)

have completed 12 months, 45 (14.4%) have completed 18 to < 24 months, 45 (14.4%) have completed 24 to < 30 months and 1 (0.3%) has completed 30 to < 36 months.

For further details see the *Patient exposure* section in Attachment 2.

Safety issues with the potential for major regulatory impact

The effects of intrinsic factors, extrinsic factors and drug interactions on the safety of the two rituximab products were not assessed in either Study GP13-201 or Study GP13-301. There were no pregnancies in the studies. There were no cases of Riximyo overdose. There were no data on the potential for drug abuse with Riximyo but abuse with the drug is unlikely. There were no data on withdrawal and rebound for Riximyo. There were no studies on the effects of the drugs on the ability to drive and use machinery.

Postmarketing data

Not applicable. Riximyo has not yet been registered in any country.

Evaluator's conclusions on safety

· The submitted safety data in patients with FL and RA suggest that there are no clinically meaningful differences in the safety profiles of Riximyo and MabThera. In patients with RA (Part I (Study GP13-201)) and FL (combination phase (Study GP13-301)) the safety profiles for the two treatment arms were comparable, while in patients with FL (maintenance phase (Study GP13-301)) most of the AE categories were reported marginally more frequently in the Riximyo arm than in the MabThera arm.

· In the pivotal Phase III efficacy and safety study in patients with FL (Study GP13-301), safety data were reported for a total of 627 patients in the combination phase treated with 8 x 21 day cycles of either Riximyo or MabThera in combination with CVP for approximately 6 months (n=312, Riximyo + CVP; n=315, MabThera + CVP). In addition, safety data in GP13-301 were also provided for a total of 462 patients continuing treatment in the maintenance phase, with 8 x 3-month cycles planned for 2 years (n = 231, Riximyo; n = 231, MabThera). The safety data reported for the maintenance phase of Study GP13-301 were treated as interim as the study is ongoing.

· In the supportive Phase II efficacy and safety study in patients with RA, safety data (Part I) were reported for a total of 173 patients (n = 86, Riximyo; n = 87 MabThera) treated for up to 52 weeks (two initial infusions separated by 2-weeks (Day 1 and Day 15), followed by two infusions separated by 2 weeks initiated from Week 24 to Week 52 for selected patients). In addition to safety data from the studies in patients with FL and RA, the submission also included safety data on 6 Japanese patients with low grade CD20+ NHL treated with Riximyo from the Phase 1 Study GP13-101.

· In Study GP13-301, the median duration of exposure for both treatment arms in the combination phase was 168 days, and the median cumulative dose of study drug was similar in the two treatment arms (5172 mg, Riximyo versus 5205 mg, MabThera). In the combination phase, 89.7% (280/312) of patients in the Riximyo arm received 8 treatment cycles compared to 90.2% (284/315) of patients in the MabThera arm. In the maintenance phase, the median cumulative dose of study drug was lower in the Riximyo arm than in the MabThera arm (2261 mg versus 2705 mg, respectively) with the difference being due to the higher rate of discontinuations due to AEs in the Riximyo arm than in the MabThera arm. In the maintenance phase, 16.5% (38/231) of patients in the Riximyo arm received 8 treatment cycles compared to 19.0% (44/231) of patients in the MabThera arm.

- In Study GP13-301, based on the number of cycles of investigational treatment in the maintenance phase it can be estimated that approximately 195 patients have been treated with Riximyo for 12 months (that is, combination plus maintenance phase) compared to approximately 194 patients treated with MabThera, with the corresponding number of patients treated for 30 months (combination plus maintenance phase) being 38 and 44 patients, respectively.

- The duration of exposure to Riximyo in patients with RA (Study GP13-201; Part I) was 1 month for 84 patients, 3 months for 82 patients, 6 months for 77 patients, and 12 months for 49 patients. The total person-years of exposure to Riximyo in Study GP13-201 (Part I) was 87.1 person-years. In Study GP13-201 (Part I), the number of patients receiving the maximum number of 4 infusions was similar in the Riximyo and the MabThera arms (n = 59 (68.6%) versus n = 58 (66.7%), respectively).

- Data from the draft Risk management plan (RMP) indicates that the total number of patients exposed to Riximyo was 470 (submitted trials and not submitted ongoing trials), which based on the 'rule of 3s' is too low to detect rare adverse drug reactions (that is, ≥ 1/10,000 to < 1/1,000). However, the available safety data suggest that rare adverse drug reactions for Riximyo and MabThera are unlikely to be notably different.

- There were no general safety or immunogenicity data in patients with RA or FL treated initially with MabThera and then switched to Riximyo. However, there is a study (Study GP13-302) currently underway in patients with RA comparing general safety and immunogenicity in patients switched from Rituxan (US approved) or MabThera (EU approved) to Riximyo to patients continuing treatment with Rituxan (US approved) or MabThera (EU approved).

Study GP13-201 RA

- In patients with RA (GP13-201), AEs were reported in a similar proportion of patients in the Riximyo and the MabThera arms (65.1% vs 65.5%, respectively), as were AEs suspected to be study drug-related (32.6% versus 33.3%, respectively). The most commonly occurring AEs by SOC in both treatment arms were 'infection and infestations' (31.4%, Riximyo versus 35.6%, MabThera). Overall, the AE profiles of the two treatment arms were similar and the observed differences are not considered to be clinically meaningful.

- The incidence of post-baseline ADAs was lower in patients in the Riximyo arm than in patients in the MabThera arm (11.0% vs 21.4%), while NAbs were reported in 3.7% and 1.2% of patients, respectively. Infusion related reactions (sponsor MedDRA Query) were reported more frequently in the MabThera arm than in the Riximyo arm (42.5% versus 37.2%, respectively).

For further details on the evaluator's assessment of this study *Evaluator's overall conclusions on clinical safety* (see Attachment 2).

Study GP13-301 - FL - Combination and maintenance phases

- Immunogenicity was assessed in 551 patients (n = 268, Riximyo; n = 283, MabThera). The frequency of ADAs in the combination phase was 1.5% in the Riximyo arm and 1.1% in the MabThera arm and in the maintenance phase was 0.4% and 0%, respectively. Overall, ADAs were detected in 5 (1.9%) of patients in the Riximyo arm and 3 (1.1%) patients in the MabThera arm. NAbs were detected in 2 out of 268 (0.7%) patients in the Riximyo arm and 2 out of 283 (0.7%) patients in the MabThera arm.

- There were no clinically meaningful differences between the two treatment arms in the combination and maintenance phases as regards AEs of particular regulatory interest including hepatic, renal, cardiovascular and skin toxicity or immune system

disorders. No notable clinically significant differences between the two treatment arms were observed as regards vital signs or clinical laboratory tests (haematology and chemistry).

· There were no studies in special groups specifically comparing safety in patients by age, sex or race. There were no special studies in patients with hepatic, renal impairment or cardiac impairment. However, based on the currently available data it is unlikely that the safety profile of the two products will significantly differ in patients treated with Riximyo or MabThera.

For summaries of safety findings in the individual studies (Study GP13-201-RA and Study GP13-301) see the *Evaluator's overall conclusions on clinical safety* in Attachment 2. See also *First round benefit-risk assessme*nt in Attachment 2 and *Second round benefit-risk assessmen*t below.

Second round evaluation

For details of the second round evaluation including the issues raised by the evaluator (Clinical questions), the sponsor's responses and the evaluation of these responses please (see Attachment 2).

Second round benefit-risk assessment

Second round assessment of benefits

It is considered that the original and the updated efficacy data provided in the sponsor's response to the first round CER data show that the benefits of treatment with Riximyo for the proposed indications are comparable to the benefits of treatment with MabThera.

The pivotal Phase III clinical efficacy and safety Study GP13-301 showed that treatment with Riximyo (375 mg/m^2, IV) and MabThera (375 mg/m^2, IV) in combination with CVP chemotherapy for approximately 6 months (8 x 21 day cycles) had equivalent effects on the ORR based on Modified Response Criteria for Malignant Lymphoma using central blinded review of the radiological response and liver/spleen enlargement assessments in patients with FL (PPS). In the combination phase, the ORR was 87.1% (271/311) in the Riximyo arm and 87.5% (274/313) in the MabThera arm in the PPS, with the difference in the ORR between the two arms being -0.40% (95% CI: -5.94%, 5.14%). The 95% CI for the difference in ORR between the two arms was entirely enclosed within the pre-specified ORR equivalence margin of -12% to +12%. The results for the analysis in the FAS were consistent with the results for the primary analysis in the PPS.

For further details on the evaluator's *Second round benefit assessment* (see Attachment 2).

There was no switching study in the original submission. However, in the sponsor's response of 28 June 2017 interim safety results were provided from a Phase III descriptive safety study (Study GP13-302) comparing outcomes in patients with active RA switched from Rituxan/MabThera to Riximyo to patients continuing treatment with Rituxan/MabThera. This study did not investigate efficacy, but focussed primarily on development of ADAs, hypersensitivity reactions, infusion-related reactions and anaphylactic reactions following switching. The sponsor commented that relevant TGA/EU biosimilar guidelines do not require specific efficacy studies investigating the effects of switching from the innovator to the biosimilar. The sponsor noted that the development of ADAs following a switch from the innovator to the biosimilar could theoretically result in decreased efficacy. However, the sponsor considered that the totality of the comparability data indicates that loss of efficacy will not be an issue for

patients switching from MabThera to Riximyo. The sponsor also commented that, to date, no drug regulatory agency has requested a study investigating the effects on efficacy of switching from MabThera to Riximyo. The sponsor's justification for not submitting efficacy data exploring the effects of switching from MabThera to Riximyo is acceptable.

The sponsor submitted a scientific justification for extrapolating the proposed indications of Riximyo from the data in RA and FL to all other TGA approved indications of MabThera based on the totality-of-data submitted to establish the comparability of Riximyo and MabThera. The results of the comparability exercise based on the clinical data (PK, PD, efficacy (RA, FL)) are considered to be acceptable. The data indicate that there are unlikely to be clinically meaningful differences between the two formulations, as regards the benefits of treatment for all proposed indications.

Second round assessment of risks

Study GP13-201 (Part I); RA

In patients with RA (Study GP13-201) the risks of treatment with Riximyo in combination with MTX were comparable to the risks of treatment with MabThera in combination with MTX, following similar exposures (dose and duration) from baseline through to 24 weeks (first course/2 infusions) and baseline through to 52 weeks (first and second courses / 4 infusions). The study included 84 patients randomised to Riximyo and 86 patients randomised to MabThera, with 49 and 50 patients, respectively, completing 12 months. The risks of treatment are based on the safety analysis set, which comprises 86 patients in the Study GP2103 arm and 87 patients in the MabThera arm.

The overall incidence of AEs, regardless of the relationship to the study drug was 65.1% in the Riximyo arm and 65.5% in the MabThera arm. The most commonly reported AEs by SOC in ≥ 10% of patients in the Riximyo arm compared to the MabThera arm, respectively, were 'Infections and infestations' (31.4% versus 35.6%), 'Musculoskeletal and connective tissue disorders' (18.6% versus 16.1%), 'Gastrointestinal disorders' (15.1% versus 17.2%), 'General disorders and administration site conditions' (14.0% versus 10.3%), 'Injury, poisoning, and procedural complications' (10.5% versus 12.6%), and 'Skin and subcutaneous tissue disorders' (10.5% versus 12.6%).

The incidence of post-baseline ADAs was lower in patients in the Riximyo arm than in patients in the MabThera arm (11.0% (9/82) versus 21.4% (18/84)), while NAbs were reported in 3.7% (n = 3) and 1.2% (n = 1) of patients, respectively, in the two arms. There were no relevant differences observed in terms of general safety in patients with and without NAbs, but the efficacy data in patients with NAbs were too limited to make meaningful conclusions. Infusion related-reactions (NMQ) were reported more frequently in patients in the MabThera arm than in patients in the Riximyo arm (42.5% versus 37.2%, respectively). No infusion related-reactions (AEs preferred term) were reported in ≥ 5% of patients in the Riximyo arm.

For further details on the evaluator's *Second round risk assessment* of this study (see Attachment 2).

Study GP13-201 (Part II); RA

The sponsor's response of 28 June 2017 presented the Week 24 report for Study GP13-201 (Part II). Patients in Part II were randomised to either Riximyo or Rituxan (originator rituximab as licensed in the USA). The design of Part II the study (Riximyo versus Rituxan) was the same as Part I of the study (Riximyo versus MabThera).

The following safety analyses were presented in the study report: (i) up to the Week 24; and (ii) from Week 24 to data cut-off (that is, up to 19 January 2016). In the safety analyses up to Week 24, all patients in the Riximyo arm recruited in Parts I and II of the study were included (n = 133), while in the safety analyses from Week 24 to data cut off

only Riximyo patients from Part II of the study were included (n = 47). In both the Week 0 to Week 14 and Week 24 to data cut-off safety analyses Rituxan patients from Part II of the study were included (n = 92).

The safety analysis for Part II of Study GP13-201 did not give rise to new safety signals. The risk profiles of Riximyo and Rituxan are considered to be comparable.

AEs from week 0 to week 24

The overall incidence of AEs up to Week 24, regardless of the relationship to the study drug, was 60.2% (n = 80) in the Riximyo arm and 54.3% (n = 50) in the Rituxan arm. The most commonly reported AEs by SOC in ≥ 10% of patients in either of the two treatment arms (Riximyo versus Rituxan), in descending order of frequency in the Riximyo arm, were 'Infections and infestations' (25.6% versus 22.8%), 'Musculoskeletal and connective tissue disorders' (14.3% versus 13.0%), 'General disorders and administration site conditions' (13.5% versus 6.5%), 'Gastrointestinal disorders' (11.3% versus 12.0%), 'Skin and subcutaneous tissue disorders' (10.5% versus 6.5%), and 'Nervous system disorders' (7.5% versus 10.9%).

The overall incidence of AEs from Week 24 to data cut-off, regardless of the relationship to the study drug, was 23.4% (n = 11) in the Riximyo arm and 25.0% (n = 23) in the Rituxan arm. The most commonly reported AEs by SOC in ≥ 5% of patients in either treatment arm (Riximyo versus Rituxan) were 'Infections and infestations' (6.4%, n = 3 versus 15.2%, n = 14) and 'Injury, poisoning and procedural complications' (6.4%, n = 3 versus 4.3%, n = 4).

The overall incidence of binding anti-rituximab antibodies up to Week 24 was similar in the Riximyo and Rituxan arms (10.0% (12/120) versus 8.9% (7/79), respectively). Overall, from Week 4 post-baseline ADA was detected in 12 (9.4%) out of 127 patients in the Riximyo arm and 7 (8.5%) out of 82 patients in the Rituxan arm. None of the ADAs were confirmed to be neutralising except for one patient in Riximyo group. The patient showed neutralising antibody 154 days after the second dose of the study drug and completed the study as planned.

AEs of regulatory significance

There were no clinically meaningful differences in the AE profile of patients in the two treatment arms as regards events of particular regulatory significance including haematological, hepatic, renal, or cardiovascular toxicity, immune system disorders, serious skin disorders or neoplasms.

For further details on the evaluator's *Second round risk assessment* of this study (see Attachment 2).

Study GP13-301; FL

Combination phase (Riximyo + CVP versus MabThera + CVP) 6 months

The sponsor's response of 28 June 2017 included an updated study company study report (CSR) for GP13-301 based on a cut-off of 10 July 2016. The CSR for this study in the initial submission had a cut-off date of 10 July 2015. There was no significant difference in the safety profiles of the two drugs in the combination phase between the initial and updated reports. This is not unexpected as the final assessment of safety in the combination phase at Week 24 was presented in the initial CSR with no additional patients being treated in the combination phase. There were some small numerical differences for some AE categories between the safety data reported in the original and updated reports. However, these were too small to affect the conclusions based on the original data. Therefore, the safety data for the combination phase provided in the first round CER (primary analysis) has been included unchanged in the second round CER (see Attachment 2).

Maintenance phase (Riximyo versus MabThera) 2 years

The sponsor's response of 28 June 2017 included updated safety data for Study GP13-301 with a cut-off of 10 July 2016 (first interim analysis). The updated safety data provided 12 additional months of maintenance phase treatment compared to the data reported in the first round CER (cut-off 10 July 2015). The data reviewed below relate to the updated safety information at the cut-off date of 10 July 2016 (first interim analysis). The updated safety data were similar to the originally submitted safety data and no new or unexpected safety signals were identified. Final safety data from the maintenance phase are anticipated in 2018.

> *Immunogenicity anti-drug antibodies (ADAs)*

In this study, immunogenicity was assessed for all patients at screening (or pre-dose or both), EOT combination phase, and EOT maintenance phase. In total, ADAs were detected in 8 out of 559 patients (1.4%), comprising 5 out of 274 (1.8%) patients in the Riximyo arm and 3 out of 285 patients (1.1%) in the MabThera arm. Neutralising antibodies were detected in a total of 4 patients (n = 2, Riximyo versus n = 2, MabThera). PFS events (documented disease progression or death) were observed in 3 of the 5 ADA positive patients in the Riximyo group, and in 1 of 3 ADA positive patients in the MabThera group. Additionally, clinical signs of immunogenic reactions evaluated with the incidences of potential infusion related reactions did not reveal any new safety signal and the incidences were similar between treatment groups. As the number of ADA positive patients was low, no definite conclusion can be drawn for the impact of observed immunogenicity on the efficacy or safety outcomes of the study.

For further details on the evaluator's *Second round risk assessment* of this study (see Attachment 2).

Study GP13-302

The company's report of Study GP13-302 (descriptive safety) was provided in the sponsor's response of 28 June 2017. The study was undertaken in patients with RA and was designed to identify potential risks associated with switching from Rituxan/MabThera to Riximyo. It is considered that the safety profile of patients switched from Rituxan/MabThera to Riximyo is comparable to the safety profile of patients continuing Rituxan/MabThera. The observed numerical differences between switched and continuing patients are considered to be not clinically meaningful.

For further details on the evaluator's *Second round risk assessment* of this study (see Attachment 2).

Second round assessment of benefit-risk balance

It is considered that the totality of the submitted clinical data have satisfactorily demonstrated that that the benefit-risk assessment for Riximyo is comparable to the benefit-risk assessment for MabThera. The additional data submitted by the sponsor in its response of 28 June 2017 have adequately addressed the concerns relating to the benefits and risks of Riximyo raised in the first round CER.

Second round recommendation regarding authorisation

Approval of Riximyo is recommended for the following listed indications:

> ### Non-Hodgkin's Lymphoma (NHL)

> *Riximyo (rituximab) 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 (CLL)

Riximyo (rituximab) is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia in combination with chemotherapy.

Rheumatoid Arthritis (RA)

Riximyo (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.

Rituximab 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)

Riximyo(rituximab) 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 rituximab have not been established.

The second round authorisation differs from the first round authorisation, which recommended rejection of the application. The reasons for the change in recommendation from rejection to approval are summarised below:

- Data provided in the sponsor's response of 28 June 2017 demonstrate that the Overall Response Rate (ORR) selected as the primary efficacy endpoint for Study GP13-301 is a more appropriate and sensitive endpoint in patients with follicular lymphoma for the assessment of comparability between Riximyo and MabThera than progression free survival (PFS) or overall survival (OS).

- Data provided in the sponsor's response of 28 June 2017 demonstrate that the size and duration of an adequately powered study designed to demonstrate equivalence of Riximyo and MabThera based on PFS makes such a study impractical.

- Data provided in the sponsor's response of 28 June 2017 demonstrate that the design of Study GP13-301 will result in both PFS and OS still being immature at the completion of the study (that is, 36 months from randomisation), with median time-to-event for both endpoints not being reached for either Riximyo or MabThera.

- Additional 12 months safety data up to 10 July 2016 for the maintenance phase of Study GP13-301 in patients with FL provided in the sponsor's s31 response of 28 June 2017 continue to demonstrate comparable safety profiles for Riximyo and MabThera. As of 10 July 2016, a total of 67.4% (n = 506) patients who entered the maintenance phase had reached end of treatment (30.7%, n = 78, Riximyo; 34.5%, n = 87, MabThera). Based on the current safety data from Study GP13-301 and safety data in patients with RA it is considered unlikely that new or unexpected safety signals will emerge from the 78 (30.7%) ongoing patients with FL in the Riximyo arm still to complete the maintenance phase in Study GP13-301.

- Data from Study GP13-201 (Part II) provided in the sponsor's response of 28 June 2017 demonstrated that Riximyo and Rituxan were bioequivalent in patients with RA based on AUC_{0-inf} up to Week 24, as were MabThera and Rituxan. In addition, the primary efficacy endpoint analysis of change from baseline in DAS28 (CRP) at Week 24 showed that Riximyo and Rituxan were therapeutically equivalent. No new or unexpected safety signals were observed based on the main comparison between Riximyo and Rituxan at Week 24, and the supportive comparison between the two treatment arms from Week 24 through to data cut-off (that is, 19 January 2016).

- Safety data from Study GP13-302 provided in the sponsor's response of 28 June 2017 demonstrated that patients with RA can be safely switched from Rituxan/MabThera to Riximyo without an increase in hypersensitivity reactions, potential infusion-related reactions, anaphylactic reactions and development of ADA antibodies occurring at Week 12 (main analysis) or Week 24 (supportive analysis). In addition, the general safety data from Week 0 through to Week 24 demonstrated comparability between Riximyo and Rituxan/MabThera.

- Based on the totality of the clinical data provided by the sponsor in the original submission and the response of 28 June 2017 it is considered the Riximyo is comparable to MabThera, as regards PK, PD, efficacy and safety. Therefore, the known safety and efficacy data for MabThera can be safety extrapolated to Riximyo.

VI. Pharmacovigilance findings

- The sponsor submitted EU-RMP version 1.0 (dated 3 March 2016; data lock point (DLP) 3 March 2016) and Australian Specific Annex (ASA) version 1.0 (dated 24 October 2016) in support of this application. In the sponsor's response of 28 June 2017, the sponsor provided updated EU-RMP version 1.4 (dated 17 March 2017; DLP 17 March 2017) and ASA version 1.1 (dated 24 June 2017).

- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised in the table below. Safety concerns are relevant to all indications, except where indicated. There is one Australian-specific safety concern which is indicated by the yellow highlight.

Table 4: Sponsor's summary of ongoing safety concerns

R = Routine and A = Additional

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		R	A	R	A
Important identified risks	Infusion-related reactions	ü	ü*/**	ü	ü**/***
	Infections (including serious infections)	ü	ü*/**	ü	ü**/***
	Serious viral infections*	ü	ü*	ü	–
	Impaired immunization response	ü	ü**	ü	–
	PML	ü	ü	ü	ü**/***

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	Neutropenia (including prolonged)	ü	ü*/**	ü	–
	HBV reactivation	ü	ü	ü	–
	Tumour lysis syndrome*	ü	–	ü	–
	GI perforation*	ü	–	ü	–
	Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis	ü	–	ü	–
	Hypogammaglobulinemia**/***	ü	–	ü	–
Important potential risks	PRES	ü	ü	ü	–
	Opportunistic infections	ü	ü*/**	ü	–
	Prolonged B-cell depletion	ü	ü**	ü	–
	Increased risk of Grade 3/4 serious blood and lymphatic system AEs in patients > 70 years (applicable for CLL only /relevant for marketing authorizations with indication CLL)*	ü	–	ü	–
	AML/MDS*	ü	–	ü	–
	Second malignancies*	ü	ü*	ü	–
	Off-label use in paediatric patients	ü	ü	ü	–
	Administration route error*	ü	–	ü	ü*
	Malignant events**/***	ü	ü**/***	ü	–
	Impact on cardiovascular disease**/***	ü	ü**	ü	–
	GI perforation**/***	ü	ü**	ü	–
	Off-label use in autoimmune disease**/***	ü	–	ü	–
	Relapses***	ü	–	ü	–
	ASA only: off-label use of the faster infusion schedule	ü	–	ü	–

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
Missing information	Use in Pregnancy and Lactation	ü	–	ü	–
	Immunogenicity and autoimmune disease**/***	ü	ü**	ü	–
	Long term use in GPA/MPA patients***	ü	–	ü	–

* NHL/CLL indication only; ** RA indication only; *** GPA/MPA indication only

· Routine pharmacovigilance is proposed for all safety concerns and missing information. Additional pharmacovigilance is proposed for the specified safety concerns and missing information as indicated in the table above, and consists of:

   – 3 clinical studies (Studies GP13-201, GP13-301, and GP13-302);

   – Patient registries (RA indication); and

   – Targeted follow-up questionnaires.

   There is Australian involvement in Study GP13-301, which is investigating the efficacy, safety and pharmacokinetics of Riximyo compared to MabThera when either agent is given in combination with cyclophosphamide, vincristine, prednisone, followed by Riximyo or MabThera maintenance therapy in patients with previously untreated, advanced stage follicular lymphoma.

· Routine risk minimisation is proposed for all safety concerns and missing information. Additional risk minimisation is proposed to address specified safety concerns (see Table 4, above), and consists of healthcare professional and patient educational materials, a Patient Alert Card (PAC) and a healthcare professional alert card relating to the risk of administration route error.

Outstanding recommendations

There are no outstanding issues. The sponsor is reminded to collect Australian Indigenous demographic data where possible in targeted adverse event follow-up.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

   Implement EU-RMP (version 1.4, date 17 March 2017, data lock point 17 March 2017) with Australian Specific Annex (version 1.1, date 24 June 2017) and any future updates as a condition of registration. Specifically, the ASA must be revised to include the approved educational materials, which the sponsor has committed to providing to the TGA for review prior to marketing the product.

Other advice to the delegate

The sponsor has committed to providing the TGA with the additional risk minimisation materials prior to launch. This includes Health Care Professional (HCP) and patient educational materials and HCPs and PACs.

VII. Overall conclusion and risk/benefit assessment

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

Quality

Some Good Manufacturing Practice (GMP) clearances are required before approval can be given. Otherwise, from a quality perspective, there are no objections to registration.

Regarding physico-chemical comparability, the quality evaluator concluded that comparability had been demonstrated across a wide range of test methodologies. A few probably minor differences were noted. Multiple in vitro tests of biological function were conducted, included tests of products' capacity to trigger antibody-mediated cellular cytotoxicity, ADCC. The Advisory Committee on Medicines' (ACM's) attention is drawn to the degree of comparability across rituximab 'versions' seen for ADCC (detailed later).

The quality evaluator noted that not all GMP clearances had been obtained:

· All outstanding GMP clearances will need to be issued before any approval can be given. Clearances were still outstanding as of 18 August 2017.

The quality evaluator also noted that a machine-readable bar code is required on the label of the 500 mg presentation. The sponsor has accepted this in principle, as per 'Notification of Errors/Omissions' document dated 18 August 2017.

The quality evaluator noted an 'out of specification event' affecting the product – visible particulate matter. The evaluator stated:

> *While this does not appear to be a safety issue, and indeed some of these batches were administered in trials with no obvious adverse effects, it may be proactive of the Sponsor to inform end users of the Drug Product using the original… [excipient as it] may contain these visible … particles.*

The sponsor's comment in the 'Notification of Errors/Omissions' document dated 18 August 2017 is noted:

Implementation of the use of [a higher grade of excipient] is considered a measure to consistently guarantee the required quality profile… By way of background, the impurity has a structure similar to long chain fatty acids. The issue appears to be resolved.

Physicochemical comparability

Of note:

· Batches of EU MabThera were primarily used for comparison to Riximyo.

· An additional bridging comparability study was performed between the EU/US sourced MabThera/Rituxan and AU sourced MabThera to present EU/US sourced MabThera/Rituxan as representative of the Australian product (MabThera)

The evaluator described Riximyo and MabThera/Rituxan as 'generally similar' but highlighted several issues, outlined below.

There were subtle differences in glycan species with levels '*mostly within limits set by analysis of batches of the comparator product*'. An impression of differences in N-glycosylation was given. The evaluator writes:

[information redacted]

The sponsor's perspective on glycan species is copied from the Quality Summary:

> *…No potentially immunogenic glycoforms such as NGNA or Gal-α1,3-Gal could be detected in both, Riximyo and originator product. The glycosylation pattern of the major abundant glycans bG0, bG1 and bG2 was comparable in both products. When looking at the low abundant glycans the heterogeneity was lower in Riximyo than in the originator product, for which two additional glycans were observed (hNG2M5F or hSA2NG1M5F). In addition, Riximyo showed lower amounts of mannose structures* [information redacted].

There were also small differences in charged variants, '*likely due to pyroglutamate formation and lower levels of deamidation*' (post-translational modifications). All different charged variants had functional activity in CDC assays.

These observed differences in physico-chemical characteristics were described by the evaluator as 'minor', though the evaluator also notes:

> *The differences in glycan species potentially are important as they can influence functional activity of the antibody, most notably Fc receptor binding and antibody dependent cellular cytotoxicity (ADCC).*

This serves to emphasise the importance of in vitro characterisation of ADCC across the two rituximab products.

Biological function in vitro was compared for the biosimilar and the reference product. For ADCC, the view was that potency of Riximyo as measured by the ADCC assay was 'within the range' of that seen with the innovator. A key figure from the sponsor's dossier was based on the ADCC assay using NK effector cells. [information redacted]

A figure in the dossier summarised an ADCC assay with PBMCs (not NKs as per above) as effectors, where there was no obvious difference across versions.

This serves, in turn, to emphasise the importance of PD/efficacy outcomes in nonclinical and clinical studies.

Recommended conditions of registration for quality issues

Standard conditions are recommended.

Nonclinical

Studies examined comparability across biosimilar and innovator of PK outcomes, PD outcomes (B cell depletion), anti-tumour efficacy, and toxicology outcomes, in animal models. Acceptable similarity was seen.

There were no nonclinical objections to registration. Animal studies found no meaningful difference between Riximyo and MabThera. These studies generated PK, PD, anti-tumour efficacy and toxicology data.

Clinical

Regulatory guidelines

The TGA has adopted various EU Guidelines relating to biosimilars:

· https://www.tga.gov.au/multidisciplinary-guidelines

There is no product-specific guidance, other than for monoclonal antibodies:

· Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012 /06/WC500128686.pdf

· Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012 /06/WC500128688.pdf

Other relevant guidelines are mentioned in the EPAR for this product and is listed in Table 5, below.[11]

Table 5: Relevant guidance to this submission

Guideline	Document Reference	Topic
Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues	EMEA/CHMP/BMWP/4283 2/2005 Rev 1, 2014	Development plan
Guideline on Similar Biological Medicinal Products	CHMP/437/04 rev 1, 2014	Development plan
Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues	EMEA/CHMP/BMWP/4035 43/2010	Development plan
Guideline on the investigation of bioequivalence	CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **	PK trial design
Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins	CHMP/EWP/89249/2004	PK trial design
Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins	EMEA/CHMP/BMWP/1432 7/2006	PK and efficacy/safety trial design

[11] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_- _Public_assessment_report/human/004729/WC500232539.pdf

Guideline	Document Reference	Topic
Guideline on the evaluation of anticancer medicinal products in man	EMA/CHMP/205/95/Rev. 4	Efficacy trial design
Draft Guideline on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis	CPMP/EWP/556/95 Rev. 2	Efficacy trial design
Guideline on the choice of the non-inferiority margin	EMEA/CPMP/EWP/2158/99	Efficacy trial design

Sourced from EPAR page 13/114

In addition, there is overarching TGA guidance at:

· https://www.tga.gov.au/publication/evaluation-biosimilars

The TGA has also adopted:

· The EU Guideline on the evaluation of anticancer medicinal products in man, EMA/CHMP/205/95/Rev.4 (and relevant appendices).

· The EU Points to Consider on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis, CPMP/EWP/556/95rev1/final

Guidelines are not binding but variation from their recommendations may suggest a need for close examination of particular quality, efficacy and/or safety issues.

Several key concepts about the TGA's biosimilar framework are mentioned below.

A step-wise approach is used to establish comparability (sufficient to leverage off the innovator's pivotal studies, without replicating them). Extent and nature of the non-clinical and clinical programme depends on the level of evidence obtained *in the previous step(s).*[12]

In clinical studies, the aim is not to repeat the innovator's study programme but in each therapeutic area (or each area sharing a mechanism of action for the product) to find a sufficiently sensitive study design and patient population in order to show comparability of effect (or, confidently exclude clinical inferiority).

A comparative PK study is a typical first step; a therapeutic equivalence study is a next step (TGA adopted EU Guidelines explore specific aspects of trial design in the cancer setting; see in particular, Section 5.3.1 of the EU Guideline on biosimilars containing monoclonal antibodies, EMA/CHMP/BMWP/403543/2010).

Extrapolation of indications is permitted under this framework. See page 15 of the EU Guideline on biosimilars containing monoclonal antibodies, where it states:

> *Extrapolation of clinical efficacy and safety data to other indications of the reference mAb, not specifically studied during the clinical development of the biosimilar mAb, is possible based on the overall evidence of comparability provided from the comparability exercise and with adequate justification...*

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[12] Guideline on biosimilars containing monoclonal antibodies, EMA/CHMP/BMWP/403543/2010

Figure 3 above lists the clinical studies provided by the sponsor in the dossier, and shows the step-wise approach used to establish comparability.

Clinical studies

There were four key clinical studies and these are summarised in Table 6 below.

Table 6: Key clinical studies

Name of study	Patient population	Comparison	Key endpoints (all studies had safety data)
GP13-201 Part I	Rheumatoid arthritis	Riximyo versus MabThera (EU) 24 and 52 week data	Primary: PK Secondary: PD, efficacy
GP13-201 Part II (provided at the second round)	Rheumatoid arthritis	Riximyo versus Rituxan; also MabThera (EU) versus Rituxan 24 week data	Primary: PK Secondary: PD, efficacy
GP13-301 (combination and maintenance phases)	Follicular lymphoma, with CVP backbone	Riximyo versus MabThera (EU) Analyses using July 2015, July 2016 and December 2016 data cuts provided.	Primary: efficacy (ORR) Secondary: PK, PD, other efficacy (PFS, OS)
GP13-302 (provided at and after the second round)	Rheumatoid arthritis	From innovator to Riximyo versus remaining on innovator 24 week data	Immunogenicity (not efficacy)

Using the step-wise framework for clinical comparisons:

· There was acceptable evidence of comparability of exposure, based on PK data from Study GP13-201 Part I, supported by PK data from other studies. Different C_{trough} results at Cycle 4 in the FL study were a source of uncertainty but in the context of AUC, C_{max} and other C_{trough} results across studies, the conclusion that Riximyo provides similar ('bioequivalent') exposure to rituximab, compared to MabThera, is acceptable.

· B cell depletion was the pharmacodynamic endpoint, and there was acceptable comparability of outcomes where tested.

· Therapeutic equivalence takes efficacy and safety into account.

  – For efficacy, the pivotal study was Study GP13-301 in treatment-naïve follicular lymphoma. Comparison of objective response rates at the end of 8 cycles of induction (in conjunction with CVP chemotherapy) was the primary endpoint. There was close similarity of ORR across arms. PFS was a secondary endpoint. There was *not* close similarity of PFS across arms. PFS outcomes are immature, although relatively stable across three data cut-points spanning July 2015 through

December 2016. OS outcomes in this typically indolent lymphoma are entirely too immature to contribute to comparison of therapeutic efficacy.

- Efficacy was assessed in Study GP13-201 (Parts I and II) in RA patients. There was, broadly speaking, non-inferiority of the biosimilar versus innovator, to 52 weeks in Part I.

- Safety was assessed across all studies. There was no alarming signal of any meaningful divergence in safety outcomes, across studies.

- Immunogenicity was assessed across studies. ADAs were commoner in RA patients than FL patients, possibly due to concomitant CVP in the 6 month induction phase for FL patients, and/or due to the higher doses of rituximab given in FL patients. In RA and FL, neutralising antibodies were infrequent and there was no signal that ADAs or neutralising antibodies were associated with decreased efficacy or increased toxicity.

A switching study tested safety and immunogenicity up to 24 weeks after either switching from innovator to Riximyo, or continuing on the innovator (the clinical evaluator only had access to 12 week data). While there were no major issues identified, some uncertainties arose (for example, one report of serum sickness in a patient switched to Riximyo; and more musculoskeletal AEs, such as arthralgia, in patients switched to Riximyo).

Clinical evaluator's view

The evaluator's final view is that approval is recommended. This differs from the first round recommendation.

The 'Second Round Risk Benefit' is a summary (but in fair detail [in Attachment 2]) of the clinical dataset and the evaluator's view. This section also includes details of the new clinical data supplied for certain studies at the second round stage of the TGA evaluation.

Overview of clinical data

The evaluator describes the scope of the initial Dossier. Some clinical data mentioned below were introduced at the second round or beyond:

- Study GP13-201 (Part I) is a PK/PD study in RA, designed *primarily* to assess PK equivalence of Riximyo and MabThera (EU), with 24 and 52 week data included in the dossier

- Study GP13-201 (Part II) is the same except in comparing Riximyo with Rituxan (US). *24 week data were included at the second round evaluation* (52 week data are due in January 2018);

- Study GP13-301 is an efficacy study comparing Riximyo and MabThera (EU) in NHL (follicular lymphoma, FL). Final data were provided for the *combination phase* (that is, induction, with CVP; 8 x 3 week cycles, to Week 24). Interim data were provided for the *maintenance phase* (rituximab monotherapy for 2 years). The main report used a July 2015 data cut-off but two subsequent analyses were also provided, using a July 2016 and a December 2016 data cut-off. The maintenance phase is scheduled to have a last-patient-last-visit date in January 2018 and a final Clinical Study Report in August 2018. PK data were also generated.

- Study GP13-101 is a supportive Phase I study, n = 6 (Japanese) with no control arm, not discussed further here.

- Study GP13-302, a switching study in RA patients (switch from MabThera (EU) or Rituxan (US) to Riximyo versus continuing treatment with MabThera (EU) or Rituxan

(US)) – *a first interim analysis of this study was included at the second round evaluation* and 24 week data were included after the evaluation phase.

Formulation

The main reference product in clinical studies was '*an EU formulation of MabThera'*. The sponsor provided in vitro bridging data comparing Australian approved MabThera with EU approved MabThera.

Pharmacology

Studies providing PK data are listed in Attachment 2.

Study GP13-201 (Part I) is the pivotal PK/PD study. 173 patients with RA refractory or intolerant to standard DMARDs and 1 to 3 anti-TNFs were enrolled and randomised 1:1 to receive Riximyo or MabThera (EU). The two rituximab versions were given with methotrexate. Study design and timing of rituximab administration is shown in the following figure (also in the Attachment 2 and in the EPAR).

Figure 4: Study design and timing of treatments
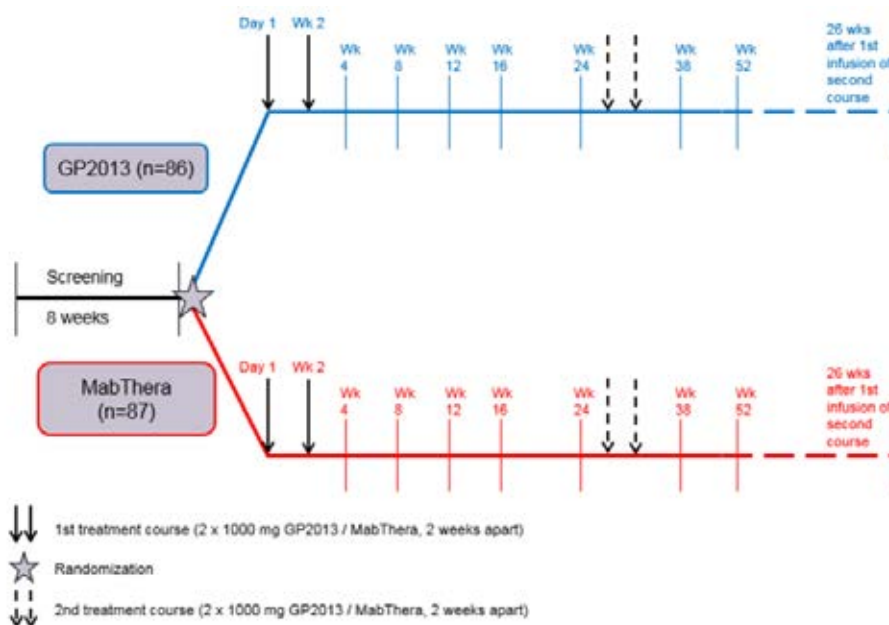
The primary PK endpoint (AUC_{0-inf}) was at Week 24, reflecting treatment on Days 1 and 15. The geometric mean ratio (test/reference) was 1.064 (90% CI 0.968 to 1.169) and similar to the geometric mean ration (GMR) in cynomolgus monkeys (1.06). 5 to 8 patients in each arm were excluded due to confirmed immunogenicity up to Week 24.

C_{max} after infusion 1 was also compared; the GMR was 1.133 (90% CI 1.017 to 1.262), with the upper limit slightly outside the standard bioequivalence range of 0.8 to 1.25. Other secondary variables, including C_{max} for infusion 2, fell within this range. The sponsor attributed the bioinequivalence of $C_{max,1}$ to increased variability in infusion rates and durations after the first infusion. The evaluator agreed that the totality of data supported the claim of bioequivalence in this study.

Study GP13-301 provided supportive PK and PD data (from sparse sampling in n=196 with previously untreated FL; 54/196 had extensive sampling). The two rituximab versions were given with cyclophosphamide, vincristine and prednisone (CVP). Some differences between this study and Study GP13-201 (Part I) are outlined in Table 7, below.

Table 7: Differences between Studies GP13-301 and GP13-201 (Part I)

Study GP13-201 (Part I) – pivotal for PK	Study GP13-301 – supportive for PK
Rheumatoid arthritis (pre-treated)	Follicular lymphoma (first line)
Rituximab is given in a first course of 1000 mg IV on days 1 and 15, and possibly a second course after 26 weeks	Rituximab is given at a 375 mg/m^2 dose on Day 1 every 21 days for 8 cycles (there is also a maintenance phase)
MTX (fixed dose) + folic acid is given	CVP is given during the 8 cycles

The study was not powered to show bioequivalence; results are descriptive. There were some differences across arms (for example, Cycle 4 C_{trough}: median 67 µg/mL for Riximyo, 81 µg/mL for MabThera, with high inter-subjects variability in both arms).

Studies providing pharmacodynamic (PD) data are listed in Attachment 2. A key PD outcome was depletion of peripheral B cells. In Study GP13-201 (Part I), B cell depletion was very comparable across arms (GMR 1.019, 95% CI 0.997 to 1.042 based on percentage change in peripheral blood B cell count from day 0 to prior to second infusion on day 15). The secondary PD outcomes (such as longer-term measures) were also very similar. PD results in Study GP13-301 also supported similarity.

Efficacy

There is a summary tabulation of both main efficacy studies in Attachment 2.

Pivotal efficacy study: Study GP13-301 (Follicular Lymphoma)

Study GP13-301 is described in Attachment 2. Patients had previously untreated, advanced stage, follicular lymphoma (Grade 1 to 3a). Rituximab treatment was double-blinded.

Patients received CVP and either MabThera (EU) or Riximyo, across 8 cycles, then the same rituximab version in the maintenance phase (every 3 months for 2 years). 629 patients were randomised 1:1.

A discussion of the 'assay sensitivity' inherent in this trial design is in Attachment 2. The sponsor argued that adding rituximab to CVP has been shown to increase the objective response rate and other efficacy endpoints, relative to CVP alone (Marcus et al, 2008).[6] The implication is that any potential clinically important difference in efficacy between Riximyo + CVP and MabThera (EU) + CVP should be detectable. The evaluator accepted this view.

A 'temperature out of range' (TOR) issue affected some medicine used in the study; this is discussed in Attachment 2. The TOR issue did not appear to diminish the study's capacity to compare the two biosimilar versions for efficacy/safety, although for both versions, the few patients given TOR product had a moderately higher rate of infusion-related reactions than patients given compliant product.

The primary objective was to show comparability in ORR (at the end of 8 cycles) across arms; ORR is defined on in Attachment 2. ORR was based on central radiology review, but factored in investigator review of other aspects. The evaluator discusses the use of ORR as the primary endpoint in the context of a study comparing biosimilar/reference products for therapeutic equivalence and concludes that the use of ORR is appropriate in this setting.

The evaluator discusses the choice of a ±12% equivalence margin and concludes this margin is appropriate. The value of 12% was based on the Marcus et al (2005) paper;[13] that showed a difference in FL between R-CVP and CVP of 24% (95% CI 14 to 34%) in ORR. Strictly, this means an actual difference as low as 14% between R-CVP and CVP cannot be excluded with confidence, yet the current equivalence study's delta (inferiority margin) allows an up to 12% difference in ORR between rituximab versions. However, the non-inferiority margin is accepted.

The primary efficacy outcome is discussed in Attachment 2. ORR was 87.1% for Riximyo, 87.5% for MabThera (difference, -0.4%; 95% CI -5.94%-5.14%). Confidence limits were within the pre-specified equivalence margin. A sensitivity analysis of ORR in FLIPI subgroups showed some differences across rituximab versions; with higher risk patients having better outcomes with Riximyo and lower risk patients having better outcomes with MabThera. The EPAR[11] notes that patients in Study GP13-301 had a higher risk at baseline (FLIPI score 3 to 5 in 56% of patients), than in key historical trials (22 to 38%). However, it is not clear the ORR difference in FLIPI subgroups is a real effect.

CR rates were very similar across arms and best overall response of progressive disease was seen 0.3% (Riximyo) versus 1% (MabThera).

Investigator-assessed PFS outcomes differed somewhat across arms; at the July 2015 cut-off, the HR for PFS was 1.33 (90% CI 0.98 to 1.80) favouring MabThera. At the July 2016 cut-off, this had shifted slightly to HR 1.25 (90% CI 0.96 to 1.61); and at the December 2016 cut-off, the HR was 1.31 (90% CI 1.02-1.69). Thus, despite the immaturity of PFS outcomes, there was fair stability of this result over an approximately 18 month period.

The evaluator considered PFS outcomes too immature to allow comparisons to be drawn, for example, median PFS values had not been reached. In the first round evaluation the evaluator's view was that PFS was more appropriate than ORR as an endpoint for the purpose of comparing therapeutic equivalence. The most recently updated analysis of OS and PFS (cut-off December 2016) is also referenced in Attachment 2.

The PFS curve from the initial data cut-off is included below in Figure 5.

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[13] Marcus R, Imrie K, et al (2005). CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood; 105:1417-1423.

Figure 5: PFS curve from the initial data cut-off
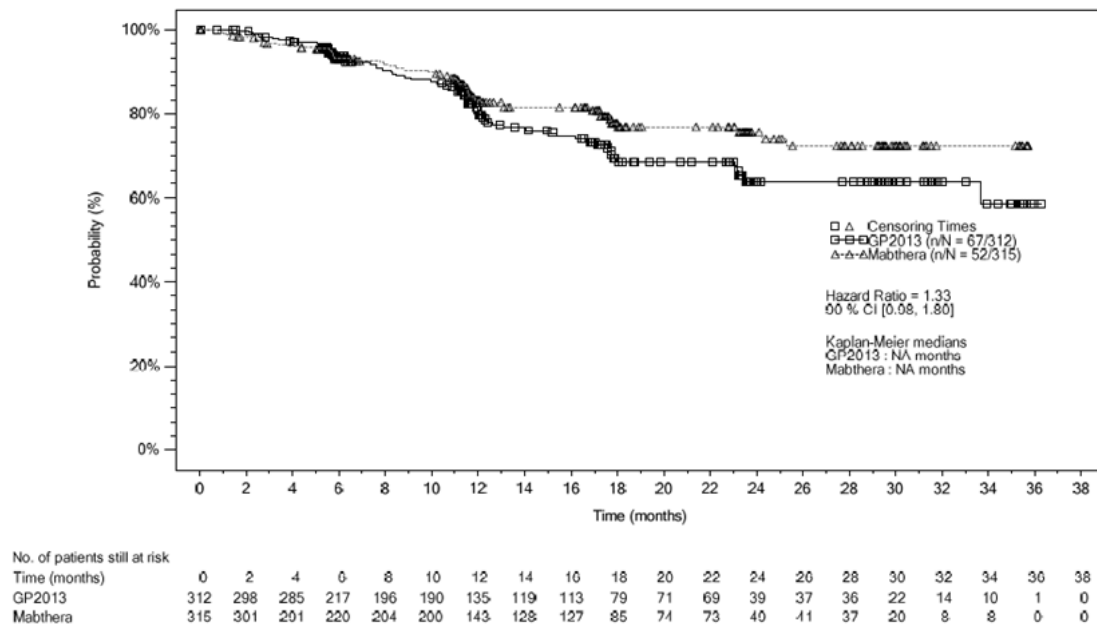
While the sponsor claims these curves violates an assumption used to calculate the HR statistic that curves do not cross, in the view of this Delegate the curves are not crossing over to any appreciable extent.

If this divergence in PFS were 'real', biosimilarity should be ruled out (unless the difference has no impact at all on FL patients, and no implications at all for efficacy in other conditions). This outcome seems to be ascribed to chance by the sponsor. Consistent with PFS findings (and based on the same underlying patient response data), 20.9% of Riximyo patients ended treatment *due to disease progression* versus 14.3% for MabThera, at the July 2016 data cut-off.

It could be argued that ORR is a more sensitive way to identify real differences in efficacy across biosimilar versions. However, *measurement of PFS identified a difference* but measurement of ORR did not. Is it plausible ORR could be closely similar, but PFS could diverge to the extent seen? And, how is a PFS HR confidence interval that excludes 1 to be interpreted given the large amount of censoring, that is, the PFS data immaturity.

December 2016 data cut-off overall survival outcomes present a different picture, with the HR being 0.77 (90% CI 0.49-1.22), but these outcomes are so immature in an indolent lymphoma like FL as to be quite meaningless (and as reflected in the fluctuating OS HRs at different cut-offs). At the December 2016 cut-off, 23/312 GP2103 arm patients had died, versus 29/315 MabThera patients.

The worst case scenario may be that this PFS signal reflects real waning of efficacy over time for the biosimilar version, relative to MabThera. This is discussed below.

· In Study GP13-301, C_{trough} at C4 D1 was lower in patients on Riximyo than in patients on MabThera; possibly, if this PK difference were real, it would be accentuated when rituximab is given every 3 months (in maintenance). However, C_{trough} before cycle 8 was much more comparable.

· Decreasing efficacy over time in the Riximyo arm could be due to late onset of anti-drug antibodies, for example if co-administration of CVP limits ADAs. The sponsor supplied information about the propensity for rituximab versions to provoke anti-drug antibodies, and no particular difference was seen:

- In the RA Study GP13-201 Part 1, there was a *higher* frequency of ADAs in the MabThera arm; but 3/82 had neutralising antibodies to Riximyo, versus 1/84 for MabThera. Only the MabThera patient had neutralising antibodies with potential links to AEs (an infusion-related reaction was reported).

- There was no marked imbalance in frequency of neutralising antibodies in the FL study. This study assessed ADAs at end of treatment in the maintenance phase, though sample size at this time-point dropped off to n = 62 in the Riximyo arm (from n=231 entering maintenance) and n=47 in the MabThera arm (from n = 231). This does not allow rigorous exclusion of the risk of longer-term development of ADAs for Riximyo relative to MabThera but the risk does seem limited. PFS events (disease progression or death) were recorded in 3/5 Riximyo patients who had ADAs, and in 1/3 MabThera patients with ADAs but no conclusions can be drawn from samples so small.

- There is further discussion from Attachment 2 (ADAs in FL versus RA).

- In Part II of GP13-201 one patient had neutralising antibodies to Riximyo (154 days after the second dose).

It is possible the PFS result is a chance finding, not a real effect. Is there *sufficient assurance* that is the case, whether via implausibility of mechanisms invoked to explain such a divergence in the context of equivalent ORR, or from more general consideration of PFS data immaturity? The EPAR**Error! Bookmark not defined.** states regarding the PFS findings:

The divergence is considered due to patient heterogeneity or random data variation rather than a real treatment effect; the study was not powered to demonstrate similarity (nor to detect a difference) in PFS between the products, and that the PFS results should be interpreted with caution. Moreover, the potential PFS difference is not reflected by an effect in CR rates at various time points (month 15, 27, 33 and at end of study). CR has been shown to correlate with OS (even as surrogate marker when measured at week 30) whereas PFS has not. [Shi Q, Flowers CR, Hiddemann W et al (2017); Thirty-months complete response as a surrogate end point in first-line follicular lymphoma therapy: An individual patient-level analysis of multiple randomized trials. J Clin Oncol 35(5): 552-560]. Furthermore, the interpretability of the PFS results is hampered by the study design (PFS assessment at only 6 month time interval, and no planned assessment for disease progression beyond 3 years follow up), the immaturity of the data, the high level of censoring (70% of the patients with main reason for censoring 'adequate assessment no longer available', ~50% of censored patients), and median follow up time of less than 2 years.

However, the EPAR acknowledges that the PFS signal introduces uncertainty:

In Study GP13-301 at (data cut-off: 31-Dec-2016) more patients in the MabThera arm are on ongoing treatment whereas a higher number of patients treated with Rixathon than MabThera ended treatment in the maintenance phase with the primary reason for discontinuation being disease progression (20.9% versus 14.3%). The HR for PFS (Rixathon/MabThera) was 1.31 (90% CI [1.02, 1.69]), at the December cut-off, in the same range as observed with the first PFS analysis (data cut off: 10-Jul-2016) where the PFS HR was calculated to be 1.25 (90% CI: [0.96, 1.61]). However, as Study GP13-301 was not powered for time-to-event outcomes, hence, for PFS and OS the currently observed data are still immature. Moreover, the follow-up time up to now is too short to allow for an estimation of median PFS and the number of PFS events low and the rate of censoring high. The availability of the study report will provide further information on PFS (see RMP).

The advice of the ACM is requested regarding PFS outcomes (see below).

Supportive efficacy Study GP13-201 (Part I) (Rheumatoid Arthritis)

Study GP13-201(Part I) is described in Attachment 2. Patients had established RA, with inadequate response or intolerance to non-biologic DMARDs and 1-3 TNF antagonists. Concomitant MTX was used. 173 patients were randomised to either Riximyo or MabThera.

The study was 52 weeks long, with responders at Week 24 eligible for re-treatment at the discretion of the investigator, if they had at least residual disease activity.

Non-inferiority of Riximyo to MabThera with respect to *change from baseline in Disease Activity Score* (DAS28) at week 24 was a secondary objective. A non-inferiority margin of 0.6 was pre-specified (the upper 95% CI of the difference in DAS28^{CRP} had to be ≤ 0.6). Other efficacy measures were also used, but radiological assessment of structural joint damage was not included.

The key secondary efficacy result (change in DAS28 at week 24) is reported in Attachment 2. The difference across arms was 0.07 (95% CI -0.328 to 0.462) (for context, the baseline DAS28^{CRP} scores per arm were 5.81-5.85). Non-inferiority was claimed on this basis. The figure *GP13-201 – Arithmetic mean (SD) of DAS28 (CRP) by treatment over 52 weeks, PPS* in Attachment 2 indicates that at other time-points, similarity was not so exact; non-inferiority was not obtained for '*averaged change from baseline in DAS28 (CRP) between Week 4 and 24*'. In comparison of ACR20, non-inferiority was also seen. Other measures of efficacy did not reveal distinct differences across arms. Overall, the evaluator's view was that this study established comparable efficacy across the two rituximab versions.

Supportive efficacy Study GP13-201 (Part II) (Rheumatoid Arthritis)

Data to Week 24 were included in the second round evaluation. The study's aim was to provide a clinical PK bridge between MabThera (EU) and Rituxan, to facilitate a submission to the FDA. The PK analysis in this Part II study included n=124 (Riximyo), 80 (Rituxan) and 79 (MabThera) patients. The GMR for Riximyo/Rituxan at Week 24 for AUC was 1.02 (90% CI 0.925-1.108), indicated bioequivalence. The GMR for Rituxan/MabThera was 1.09 (90% CI 0.99-1.21), indicating bioequivalence. For C_{max}, bioequivalence was also shown.

Comparison of Riximyo and MabThera was not a primary objective but the GMR would not have varied dramatically from that seen for Rituxan/MabThera.

B cell depletion (based on AUEC$_{0-14d}$, the area under effect curve) was 'equivalent' for Riximyo/Rituxan and for Rituxan/MabThera.

Change from baseline in DAS28^{CRP} at Week 24 was assessed and non-inferiority was declared (based on a non-inferiority margin of 0.6 as discussed for Part I).

Extrapolation of indications

The evaluator discusses the sponsor's justification for extrapolation of indications. The sponsor has conducted efficacy trials in haematological malignancy (FL) and autoimmunity (RA), although the trial in RA was presented as supportive as far as efficacy outcomes were concerned (the primary outcome was PK-related). A consequence is that extrapolation can be seen, crudely, as 'from FL to DLBCL/CLL' and 'from RA to GPA/MPA'.

The sponsor justified extrapolation of the comparability across rituximab versions of *PK* in RA (and also FL) to other settings. Some circumstances can be envisaged where PK aspects may differ across diseases (such as higher B cell load in CLL than FL; [sporadic] use of IVIG in CLL to treat recurrent infection, since IVIG might saturate FcRn-mediated clearance). Comparability of biosimilar version PK is not, however, called into question by such situations.

The sponsor justified extrapolation of the comparability of *PD* seen in RA (and in FL) to other settings. Extrapolation would be contentious if in unstudied patient populations (DLBCL; CLL; GPA/MPA) the importance of different mechanisms of B cell depletion varied from what is known for FL and RA, *and* if there were large differences across rituximab versions in outcomes of functional assays of these different mechanisms of B cell depletion. This is not known to be the case, though in vitro data seemingly do not exclude modest difference in ADCC (see discussion of quality data). It is also suggested that in CLL, ADCC may have a greater role than in FL. Given close therapeutic equivalence (in terms of ORR) in FL, these uncertainties are probably not sufficient to disallow extrapolation to CLL, but the ACM's view is asked.

Presented information about variation across RA, GPA and MPA in mechanism of action was more limited still but extrapolation to GPA and MPA is probably reasonable given the totality of comparability data provided.

Switching

12 week data from switching Study GP13-302 in 107 RA patients were supplied for the second round evaluation, along with a comment that incidence of hypersensitivity reactions and general AEs did not change meaningfully between Week 12 and Week 24. No efficacy data were gathered in this study.

Study GP13-302 12 week data are evaluated in Attachment 2. Some highlights are mentioned below.

· An AE of anaphylaxis was reported in a patient continuing initial rituximab.

· Hypersensitivity was reported in a similar percentage of patients across arms.

· Infusion-related reactions were reported in 11.3% (in those switching to Riximyo) versus 18.5% (in those remaining on their existing rituximab).

· No patient transitioning to Riximyo developed ADAs.

· More patients in the Riximyo arm reported AEs. There was an imbalance in musculoskeletal/connective tissue AEs (20.8% for Riximyo versus 3.7% for Rituxan/MabThera), including reports of arthralgia. It would be unreasonable to place too much weight on this, given other AE categories were imbalanced in the other direction (for example, gastrointestinal disorder), *except* the study did not examine efficacy, and possibly some musculoskeletal AEs reflect loss of control of RA.

· There was imbalance in 'AEs suspected to be immunologically mediated' with 5.7% of patients in the Riximyo arm having such AEs (paraesthesia, asthma and allergic pruritus) versus no patients in the other arm having such AEs.

· There was also an AE of serum sickness in the Riximyo arm, occurring 6 hours after first infusion (for some reason this did not make the list of AEs suspected to be immunologically mediated). The patient had muscle aches/pains/fever, resolving on Day 11 but causing study drug discontinuation. Some features of serum sickness also fall into the category musculoskeletal AEs (polyarthralgia, polyarthritis), and rituximab induced serum sickness may mimic exacerbations of rheumatological conditions.[14] Serum sickness with rituximab may occur earlier than the 7-21 days commonly reported for drugs (6.6 ± 3.8 days in 33 cases retrieved from the literature by Karmacharya et al.[14]) but this AE occurred 6 hours after infusion, so it is not clear if the AE is a classic example of rituximab-induced serum sickness.

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[14] Karmacharya P, Poudel DR, et al (2015). Rituximab-induced serum sickness: A systematic review. Seminars in Arthritis and Rheumatism; 45: 334-340

Question for sponsor

Can other instances of serum sickness be ruled out in this study, based on review of grouped signs and symptoms and investigator diagnoses?

The 24 week outcomes were supplied after the TGA evaluation phase and have therefore not been seen by the clinical evaluator. The Delegate has conducted a limited review:

· ADAs up to Week 24 remained infrequent, with the only baseline negative ADA seen in a patient in the Rituxan/MabThera arm.

· AEs were reported in 69.8% (Riximyo) versus 51.9% (Rituxan/MabThera) but AEs suspected of being drug-related were seen in 11% versus 20% respectively.

· An imbalance in musculoskeletal AEs remained (20.8% versus 7.4%); the imbalance in GI disorders remained. Within preferred terms, it is noted the specific AE of 'worsening of RA' was seen in 3.7 to 3.8% across arms. However, 'arthralgia' was reported in 5.7% (Riximyo) versus 0% (innovator).

· One patient in the Riximyo arm who received high dose corticosteroids to treat a hypersensitivity event was excluded from the per protocol analysis.

Safety

Studies noted in relation to PK and efficacy formed the safety dataset. Exposure is discussed in Attachment 2. In RA patients, follow-up was for 52 weeks; in FL patients, for up to 3 years.

In RA (Study GP13-201, Part I), the safety profile was comparable, with no clear sign of increased drug-related SAEs or infusion-related reactions with Riximyo. In FL (Study GP13-301), there was again comparability of the toxicity profile, with drug-related SAEs and potential infusion-related reactions occurring at similar rates across arms.

At the preferred term level, there were many differences across arms (for example see RA Study GP13-201 in Attachment 2) but the evaluator concluded these were unlikely to be clinically meaningful.

In the FL study, there was no sign of an increase in neutropenia with Riximyo in the induction phase. There were more AEs of neutropenia with Riximyo than with MabThera in maintenance, and febrile neutropenia was imbalanced (6.1% versus 3.2%) but the difference narrowed for 'drug-related' events.

The evaluator concluded there were no clinically meaningful differences in safety for the two rituximab versions.

For the second round evaluation, the sponsor provided updated safety information that did not change this conclusion of similar safety across the two rituximab forms.

Risk management plan

The RMP evaluator had no major objections to registration. There were several second round recommendations and the RMP evaluation area is currently reviewing the sponsor's response to these recommendations.

The EPAR noted plans to use multiple European registries to provide additional safety data in RA patients.[11]

Recommended condition/s of registration

> Implement EU-RMP (version 1.4, date 17 March 2017, data lock point 17 March 2017) with Australian Specific Annex (version 1.1, date 24 June 2017) and any future updates as a condition of registration. Specifically, the ASA must be revised

to include the approved educational materials, which the sponsor has committed to providing to the TGA for review prior to marketing the product.

Risk-benefit analysis

Delegate's considerations

Background

The TGA has adopted a framework for the assessment of biosimilar medicines that in large part copies that of the EMA. A step-wise approach is required: physico-chemical comparability data; nonclinical comparability data; clinical comparability data. The sponsor of Riximyo has followed this approach.

A key point is that clinical trials are designed not to copy pivotal studies conducted by the innovator but to study comparability of effect, using populations, endpoints and methods that will allow detection of meaningful differences if they exist.

Another point is that trials are not required in all indicated groups; extrapolation of indications is accepted, where a suitable scientific justification is provided.

There are no rituximab products on the ARTG other than MabThera and MabThera SC. MabThera (IV) was the reference product, for biosimilarity comparisons. Most MabThera used in the different comparisons with Riximyo was EU or US sourced (Rituxan is the tradename for the innovator product in the US). Physico-chemical/in vitro data were used to bridge EU/US innovator to the Australian MabThera.

If Riximyo were registered, it would be the first rituximab biosimilar in Australia.

This product has market authorisation in the EU, under the tradename Rixathon. It is not currently approved by the FDA.

Issues

Manufacturing and quality control

Some GMP clearances are required before approval can be given. Otherwise, from a quality perspective, there are no objections to registration.

Regarding physico-chemical comparability, the quality evaluator concluded that comparability had been demonstrated across a wide range of test methodologies. A few probably minor differences were noted. Multiple in vitro tests of biological function were conducted, included tests of products' capacity to trigger ADCC. The ACM's attention is drawn to the degree of comparability across the rituximab 'versions' seen for ADCC (see details below).

Nonclinical

Studies examined comparability across biosimilar and innovator of PK outcomes, PD outcomes (B cell depletion), anti-tumour efficacy, and toxicology outcomes, in animal models. Acceptable similarity was seen.

Clinical

There were four key clinical studies (Table 6 above).

Using the step-wise framework for clinical comparisons:

· There was acceptable evidence of comparability of exposure, based on PK data from Study GP13-201 Part I, supported by PK data from other studies. Different C_{trough} results at Cycle 4 in the FL study were a source of uncertainty, but in the context of

AUC, C_{max} and other C_{trough} results across studies, the conclusion that Riximyo provides similar ('bioequivalent') exposure to rituximab, compared to MabThera, is acceptable.

- B cell depletion was the pharmacodynamic endpoint, and there was acceptable comparability of outcomes where tested.

- Therapeutic equivalence takes efficacy and safety into account.

  – For efficacy, the pivotal study was Study GP13-301 in treatment-naïve follicular lymphoma. Comparison of objective response rates at the end of 8 cycles of induction (in conjunction with CVP chemotherapy) was the primary endpoint. There was close similarity of ORR across arms. PFS was a secondary endpoint. There was NOT close similarity of PFS across arms. PFS outcomes are immature, although relatively stable across three data cut-points spanning July 2015 through December 2016. OS outcomes in this typically indolent lymphoma are entirely too immature to contribute to comparison of therapeutic efficacy.

  – Efficacy was assessed in GP13-201 (Parts I and II) in RA patients. There was, broadly speaking, non-inferiority of the biosimilar versus innovator, to 52 weeks.

  – Safety was assessed across all studies. There was no alarming signal of any meaningful divergence in safety outcomes, across studies.

  – Immunogenicity was assessed across studies. ADAs were commoner in RA patients than FL patients, possibly due to concomitant CVP in the 6 month induction phase for FL patients, and/or due to the higher doses of rituximab given in FL patients. In RA and FL, neutralising antibodies were infrequent, and there was no signal that ADAs or neutralising antibodies were associated with decreased efficacy or increased toxicity.

- A switching study tested safety and immunogenicity up to 24 weeks after either switching from innovator to Riximyo or continuing on the innovator (note: the clinical evaluator only had access to 12 week data). While there were no major issues identified, some uncertainties arose (for example, one report of serum sickness in a patient switched to Riximyo; and more musculoskeletal AEs, such as arthralgia, in patients switched to Riximyo).

Risk management plan

Several RMP issues remain unresolved after the second round evaluation but overall there were no major objections to registration of Riximyo.

Pre-ACM preliminary assessment

There is sufficient evidence of biosimilarity to approve Riximyo as a biosimilar.

Despite the immaturity of PFS outcomes in Study GP13-301, the PFS outcomes to date should be clearly communicated in the PI, as important empirical findings.

Proposed action

There is sufficient evidence of biosimilarity to approve Riximyo as a biosimilar.

Despite the immaturity of PFS outcomes in Study GP13-301, the PFS outcomes to date should be clearly communicated in the PI, as important empirical findings.

Request for ACM advice

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

1. In Study GP13-301 (the FL study), can therapeutic equivalence be concluded, despite the PFS outcomes to date? Should PFS outcomes be included in the PI?

2. Regarding the switching Study GP13-302, what weight should be placed on the single event of serum sickness in a patient switched to Riximyo? This AE is already listed in the proposed PI but should it be more prominent?

   Please also note that the sponsor has been asked an additional question, re-copied below, and the answer in the Pre-ACM Response may be of interest.

   Can other instances of serum sickness be ruled out in [Study GP13-302], based on review of grouped signs and symptoms and investigator diagnoses?

3. Considering physicochemical comparisons (including *in vitro* tests of biological function) and nonclinical and clinical studies, does the ACM consider Riximyo to be sufficiently comparable to MabThera to allow approval as a biosimilar?

4. Does the ACM have any concerns about extrapolation of indications beyond RA and FL?

5. Does the ACM have any comments about the proposed PI?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

In answering these questions, it is important that the ACM takes into account the sponsor's response to the Delegate's Overview, that is, the 'Pre-ACM Response'.

Response from sponsor

Introduction

The Delegate has sought the Advisory Committee on Medicines (ACM)'s advice on five issues related to this approval. The sponsor has taken this opportunity to provide comments to assist the ACM in its deliberations. The sponsor also responds to the 'Question to the sponsor'.

Regarding delegate's questions to the ACM

Question 1

> *In GP13-301 (the FL study), can therapeutic equivalence be concluded, despite the PFS outcomes to date? Should PFS outcomes be included in the PI?*

Sponsor's position

The sponsor's position is that therapeutic equivalence of Riximyo to MabThera (reference medicine) has been established based on Study GP13-301 primary endpoint of ORR given the endpoint was met. The purpose of this study was not to re-establish efficacy of rituximab but to demonstrate therapeutic equivalence as part of a step-wise approach recommended for clinical comparisons for registration of biosimilars. The sponsor considers ORR the appropriate primary endpoint in this setting.

For biosimilar development, reference medicinal drug product indications with a large add-on- effect to standard treatment provide a sensitive clinical setting. In FL, rituximab has shown the largest add-on effect for overall response rate when combined with the chemotherapeutic regimen CVP. ORR is a more sensitive endpoint than progression-free survival (PFS) since the add-on effect of rituximab to ORR (+24%);[15] in the study setting

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[15] Marcus R, Imrie K, et al (2005). CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood; 105:1417-1423.

exceeds the add-on effect on PFS at 3 years follow up which can be considered to be less than 17%. In addition, while the ORR responses in studies comparable to GP13-301 were in a robust range of 81% to 88%;[16][15,17,18,19] very limited data are available on the variability of PFS in follicular lymphoma. Only the SAKK 35/05 trial;[20] indicated a difference in both treatment arms after 8 months of a PFS rate of 3.7% versus 12.2%, despite the treatment being exactly the same, putting the reliability of PFS as a precise outcome measure for a comparability trial into question. The primary endpoint of ORR at the end of the combination phase is considered sensitive and thus appropriate to establish clinical similarity between Riximyo/Riximyo and MabThera.

Therapeutic equivalence was demonstrated by the end of the combination phase. The maintenance phase was added for ethical reasons as maintenance was standard of care. As a maintenance phase was added, the expectation was to report PFS and OS as secondary endpoints, even if not powered. The power for PFS is less than 1%. A biosimilar trial in the setting of Study GP13-301 appropriately powered (power 80%) for PFS would require more than 2,500 patients and is thus not feasible in a biosimilar setting as recruitment would take more than 10 years. ORR is an endpoint that can be assessed earlier and is a direct measure of drug anti-tumour activity.

With regard to the PFS outcomes to date, the low statistical power mentioned above and the immaturity of the PFS data leads to the conclusion that the separation in the treatment arms in PFS is a chance finding in the PFS curve. The clinical evaluator considered PFS outcomes too immature to allow comparisons to be drawn. The sponsor agrees with this conclusion. The event rate is still low in total (about 27%) with more than 70% of patients censored, of which more than 30% are ongoing in the study without event at the last data cut (31 December 2017). The median PFS has not been reached yet. The follow-up time in Study GP13-301 is not appropriate to reach the median PFS, which is 6 to 8 years for previously untreated FL patients.[21] Hence, even at study end, PFS and OS will remain immature.

Based on literature data and additional analysis submitted along with the sponsor's responses to TGA, the sponsor considers that the PFS data are influenced by patient heterogeneity and random data variation rather than treatment differences. Also, a high level of censoring influenced the results. Further support for this by chance finding is the observation of the similarity of the CR rate for different study periods, especially at up to month 33 (CR rate 28.2% in Riximyo arm, 28.6% in MabThera arm, difference -0.37, 90% CI (-6.61, 5.88)), which is strongly correlated with PFS.[21]

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[16] Federico M, Luminari S, et al (2013). R-CVP Versus R-CHOP Versus R-FM for the Initial treatment of Patients With Advanced-Stage Follicular lymphoma: Results of the Foll05 Trial Conducted by the Fondazione Italiana Linfomi. J Clin Oncol. 2013 Apr 20;31(12):1506-1513.

[17] Moccia A, Hoskins, et al (2010). Front-line therapy with rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) followed by 2 years of rituximab maintenance for follicular lymphoma (FL) is associated with excellent outcomes and improved progression-free survival (PFS) in comparison to no maintenance. Blood (ASH Annual Meeting Abstracts) 2010 116: abstract 1803.

[18] Nastoupil L, Sinha R, et al (2015). Comparison of the effectiveness of frontline chemoimmunotherapy regimens for follicular lymphoma used in the United States. Leukemia & Lymphoma, May 2015; 56(5):1295-1302.

[19] Salles G, Seymour JF, et al (2011). Rituximab maintenance for 2-years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. The Lancet, January 1, 2011, 377: 42-51.

[20] Taverna C, Martinelli G, Hitz F, et al (2016) Rituximab maintenance for a maximum of 5 years after single-agent rituximab induction in follicular lymphoma: results of the randomized controlled phase III trial SAKK 35/03. J Clin Oncol 34(5): 495-500.

[21] Shi Q, Flowers CR, Hiddemann W et al (2017). Thirty-months complete response as a surrogate end point in first-line follicular lymphoma therapy: An individual patient-level analysis of multiple randomized trials. J Clin Oncol 35(5): 552-560.

Lastly, the sponsor is of the opinion that the PFS outcomes for Riximyo compared to MabThera from GP13-301 should not be included in the PI as it is likely to be misinterpreted in a biosimilar setting. In general, PFS is not a surrogate endpoint for OS, as PFS prolongation may not result in OS prolongation.[22]

In conclusion, despite the PFS outcome, no clinically meaningful differences between the reference product and the biosimilar were seen in Study GP13-301 and thus therapeutic equivalence can be concluded.

Question 2

> *Regarding the switching Study GP13-302, what weight should be placed on the single event of serum sickness in a patient switched to Riximyo? This AE is already listed in the proposed PI (Table 24), but should it be more prominent?*

Sponsor's position

No undue prominence in the PI is required based on the single reported serum sickness. As pointed out by the TGA for this one reported AE of serum sickness in the Riximyo arm, the onset 6 hours after administration of study drug makes it questionable if this is a newly induced classic case of rituximab-induced serum sickness - an onset within 6 hours without pre-existing antibodies would be very unusual. It is well known serum sickness rarely occurs after use of rituximab based on both the literature and its labelling as it is a chimeric mouse-human antibody. In addition, as discussed in *Question to the sponsor* below, upon detailed medical review of grouped signs and symptoms there is no case that plausibly qualifies as serum sickness.

Question 3

> *Considering physicochemical comparisons (including in vitro tests of biological function) and nonclinical and clinical studies, does the ACM consider Riximyo to be sufficiently comparable to MabThera to allow approval as a biosimilar?*

Sponsor's position

Based on the totality-of-data including structural, functional, nonclinical and clinical studies, the sponsor considers that biosimilarity of Riximyo to the reference medicine has been successfully demonstrated.

Riximyo has been developed in a step-wise approach. On the analytical level it was demonstrated that Riximyo has similar physiochemical parameters and biological activity. On the nonclinical level it was demonstrated that Riximyo has similar PK/PD and toxicokinetics, similar toxicology and safety as well as similar efficacy in xenograft tumor disease models. On the clinical level PK bioequivalence and PD equivalence to the reference product was shown. Furthermore, Riximyo and the reference product had a similar efficacy profile in both the oncology and immunology setting, a similar immunogenicity profile and Riximyo was shown to be as safe as the reference medicine.

Question 4

> *Does the ACM have any concerns about extrapolation of indications beyond RA and FL?*

Sponsor's position

The sponsor believes that there are no concerns about extrapolation of indications beyond RA and FL. All the indications for which MabThera is approved are conditions that have

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[22] Vidal L, Gafter-Gvili A, Salles G, eta al (2011) Rituximab maintenance for the treatment of patients with follicular lymphoma: an updated systematic review and meta-analysis of randomized trials. J Natl Cancer Inst, 103: 1799-1806.

the malfunction of CD20 expressing B-cells in common. Notwithstanding the different pathophysiologies of these different conditions, the basic therapeutic effect of rituximab, that is, the depletion of B cells, is the same. Several well-known mechanisms of action (MoA) such as ADCC, CDC and apoptosis contribute to the therapeutic effect although the exact contribution of the different MoAs in various clinical conditions is still not very well understood. Nevertheless, comparability between Riximyo and MabThera was demonstrated in all the well-established MoAs considered to contribute to the therapeutic B-cell depleting effect in various clinical conditions.

The extrapolation of indications beyond RA and FL is based on (a) the same MoA (ADCC, CDC and apoptosis) involved in all indications ultimately leading to B-cell depletion and (b) the totality-of-data provided for Riximyo (that is, physicochemical, nonclinical and clinical data), which includes:

· Robust analytical data showing comparability of biological activity as measured by ADCC, CDC, CD20-binding, C1q binding, apoptosis, FcγR and FcRn binding.

· The results of the nonclinical studies demonstrating comparability of Riximyo and MabThera in terms of PK/PD (B-cell depletion both in vivo and in vitro) and toxicokinetics, in terms similar toxicology and safety, and in terms of anti-tumor activity (murine xenograft models).

· The results of the clinical studies, demonstrating PK bioequivalence, PD equivalence, therapeutic equivalence and a comparable safety and immunogenicity profile between Riximyo and MabThera.

In summary, based on the understanding of rituximab's MoA in the therapeutic areas of immunology and oncology and based on the totality-of-data provided for Riximyo, it is considered scientifically justified to accept that the clinical efficacy and safety of Riximyo and MabThera will be comparable across all approved indications of MabThera.

Question 5

> *Does the ACM have any comments about the proposed PI?*

Sponsor's position

The sponsor generally agrees with the Delegate's advice and updated the PI accordingly. The Delegate's advice regarding addition of outcomes for PFS and OS as well as the advice to delete a statement regarding safety risks from the GP13-302 study was not implemented and the sponsor's rationale was attached.

Delegate's question to the sponsor

> *Related to Study 302: Can other instances of serum sickness be ruled out in this study, based on review of grouped signs and symptoms and investigator diagnoses?*

Sponsor's response

It is well known serum sickness rarely occurs after use of rituximab based on both the literature and its labelling as it is a chimeric mouse-human antibody.

In a review article on rituximab induced serum sickness, in the classical triad of serum sickness the most common clinical presentation was fever, followed by arthralgia and rash. This classical triad occurred in almost half of the patients. Other reported symptoms were myalgia, malaise, fatigue, conjunctival hyperaemia and purpura. In patients with

rheumatoid arthritis (RA) serum sickness may thus mimic exacerbation of RA. The serum sickness occurred usually 7 days following the infusion.[23]

Using the above adverse event (AE) terms (and taking nausea and vomiting into consideration as well), the AE listing for Study GP13-302 (12 week CSR) was medically reviewed for any signs of serum sickness considering grouped signed and symptoms based on investigator diagnosis. Worsening of pre-existing conditions had thus not been considered.

In the Riximyo arm, one case of mild polyarthralgia not suspected to be drug-related was reported 21 days after the last drug exposure. The AE spontaneously resolved within 57 days and the investigator did not consider the AE immunological related. The patient experienced no further AEs. Two further cases had been reported in the Riximyo arm; one of hip pain starting 1 day after administration of the study drug and one of knee pain starting 67 days after study drug administration. These two cases of arthralgia were not suspected to be drug related and were not accompanied by other symptoms. Rash was reported for two patients in the Riximyo group (pustular and eczema) on Days 77 and 70 respectively without further symptoms. Malaise was reported in one patient in the Riximyo group after the first infusion. It resolved spontaneously within 15 days and did not re-occur after the second infusion, this patient did not experience any other AEs. One case of an isolated AE of intermittent nausea starting one day after the exposure to study drug occurred in a patient with a coexisting AE of anaemia.

In the Riximyo/MabThera arm one patient experienced mild fever starting 8 hours after the study drug administration resolving after two days after treatment with paracetamol for 1 day, no other AE was reported concomitantly. One patient developed vomiting 20 hours after study drug administration lasting for one day. One patient developed nausea immediately after starting study drug administration, and resolving within one day.

Exacerbation of RA was reported in two patients in the Riximyo arm (onset 18 days and 50 days) and in two patients in the Riximyo/MabThera arm (onset 11 hours and 89 days). In all cases the RA exacerbation was not accompanied by further symptoms making a case of serum sickness unlikely.

The AEs occurring within one day of studydrug administration should be considered infusion- related reactions and not signs of serum sickness. Also an onset beyond 21 days after last exposure to study drug makes a serum sickness highly unlikely. The polyarthralgia in one patient exposed to Riximyo would from the time to onset fit with a serum sickness reaction however the lack of further symptoms makes this highly unlikely. Further osteoarthritis is also reported in the patient's medical history prior to study commencement. As noted by the Delegate, the one reported AE of serum sickness in the Riximyo arm, the onset 6 hours after administration of study drug makes it questionable whether this is a newly induced classical case of rituximab-induced serum sickness; an onset within 6 hours without pre-existing antibodies would be very unusual.

Based on this detailed medical review of grouped signs and symptoms, no case which plausibly qualifies as rituximab-induced serum sickness could be identified.

Concluding remarks

The sponsor believes that structural and functional similarity as well as comparative safety and efficacy versus the reference medicine has been convincingly demonstrated for Riximyo.

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[23] Karmacharya P, Poudel DR, et al (2015). Rituximab-induced serum sickness: A systematic review. Seminars in Arthritis and Rheumatism; 45: 334-340.

Therapeutic equivalence was established by a sensitive endpoint (ORR), the PFS outcome does not preclude biosimilarity in the totality-of-evidence approach, especially considering that PFS is not a powered endpoint and too immature to allow comparisons to be drawn.

Based on the established biosimilarity and supported by the same mode of action involved in all approved indications leading ultimately to B cell depletion, it is scientifically justified to extrapolate to all approved indications.

Advisory Committee Considerations[24]

The ACM taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Riximyo concentrated injection containing 100 mg/10 mL and 500 mg/50 mL vials of Rituximab to have an overall positive benefit-risk profile for the proposed indications, which are identical to MabThera:

- *Non-Hodgkin's Lymphoma (NHL): Riximyo (rituximab) 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 (CLL): Riximyo (rituximab) is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia in combination with chemotherapy.*

- *Rheumatoid Arthritis (RA): Riximyo (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. Rituximab 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): Riximyo (rituximab) 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 rituximab have not been established.*

In making this recommendation the ACM noted:

- the TGA evaluation framework for the Regulation of Biosimilar Medicines.

- that this was the first Australian submission for a biosimilar medicine of rituximab.

- that some GMP clearances are required before approval may be granted.

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[24] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Specific advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

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

1. *In Study GP13-301 (the FL study), can therapeutic equivalence be concluded, despite the PFS outcomes to date? Should PFS outcomes be included in the PI?*

The ACM considered that therapeutic equivalence for Riximyo can be concluded from the follicular lymphoma study, based on the ORR. The committee considered that the PFS data is early for an indolent lymphoma and because of this should have less weighting in the determination of equivalence. It was recommended that this study, including its PFS outcomes to date, should be included in the PI document with timeframes that allow prescriber interpretation of the data.

2. *Regarding the switching Study GP13-302, what weight should be placed on the single event of serum sickness in a patient switched to Riximyo? This AE is already listed in the proposed PI (Table 24), but should it be more prominent?*

The ACM did not consider that emphasis should be placed on this single event which was noted to have resolved with care. The committee did not believe that this adverse event should be highlighted more prominently than description under the adverse events section of the PI. With serum sickness described in the adverse events section of the PI, this will draw prescriber suspicion if it occurs in clinical practice. If the incidence increases, then this matter may be revisited in the future.

3. *Considering physicochemical comparisons (including in vitro tests of biological function) and non-clinical and clinical studies, does the ACM consider Riximyo to be sufficiently comparable to MabThera to allow approval as a biosimilar?*

The ACM considered that there is sufficient evidence to consider Riximyo to be comparable to MabThera and to approve its registration as a as a biosimilar product.

4. *Does the ACM have any concerns about extrapolation of indications beyond RA and FL?*

The ACM noted that this was the first submission in Australia to register a biosimilar where the extrapolation of therapeutic equivalence from a pivotal study crossed pathophysiological boundaries from malignancy to inflammatory arthritis to vasculitis (granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis). In applying the previously used biosimilar framework principles, the committee considered that it was reasonable to extrapolate equivalence to include vasculitis in the indications for Riximyo.

5. *Does the ACM have any comments about the proposed PI?*

The ACM agreed with the TGA requested changes to the PI and did not recommend additional changes.

6. *The committee was also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.*

The ACM advised that 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 this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Riximyo rituximab (rch) 100 mg/10 mL concentrated injection vial and Riximyo rituximab (rch) 500 mg/50 mL concentrated injection vial, indicated for:

Non-Hodgkin's Lymphoma (NHL)

Riximyo (rituximab) 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 (CLL)

Riximyo (rituximab) is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia in combination with chemotherapy.

Rheumatoid Arthritis (RA)

Riximyo (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.

Rituximab 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)

Riximyo (rituximab) 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 rituximab have not been established.

Specific conditions of registration applying to these goods

1. Implement EU-RMP (version 1.4, date 17 March 2017, data lock point 17 March 2017) with Australian Specific Annex (version 1.1, date 24 June 2017) and any future updates as a condition of registration. Specifically, the ASA must be revised to include the approved educational materials, which the sponsor has committed to providing to the TGA for review prior to marketing the product.

2. Batch Release Testing & Compliance with Certified Product Details (CPD)

    a. It is a condition of registration that all batches of Riximyo rituximab (rch) imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

    b. It is a condition of registration that each batch of Riximyo rituximab (rch) imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

Attachment 1. Product Information

The PI for Riximyo approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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