Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Rituximab

Proprietary Product Name: Ruxience

Sponsor: Pfizer Australia Pty Ltd

April 2021

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

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ACR	American College of Rheumatology
ADA	Anti drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
ANCA	Anti-neutrophil cytoplasmic antibody
ARTG	Australian Register of Therapeutic Goods
ASA	Australian-specific Annex
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero to infinity
AusPAR	Australian Public Assessment Report
BE	Bioequivalent
BSA	Body surface area
C1q	Complement component 1q
CCP	Cyclic citrullinated peptides
CDC	Complement-dependent cytotoxicity
CHO	Chinese hamster ovary
CHOP	Cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone or prednisolone (combination treatment)
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
C_{max}	Maximum plasma concentration
CR	Complete response
CSR	Clinical study report
CVP	Cyclophosphamide, vincristine and prednisone (combination treatment)
DAS	Disease Activity Score

Abbreviation	Meaning
DCA	Data capture aid
DMARD	Disease-modifying antirheumatic drug
DP	Durg product
DS	Drug substance
EMA	European Medicines Agency (European Union)
ESMO	European Society for Medical Oncology
EU	European Union
EULAR	European League Against Rheumatism
Fc	Fragment crystallisable
FDA	Food and Drug Administration (United States)
FLIPI2	Follicular Lymphoma International Prognostic Index 2
GPA	Granulomatosis with polyangiitis
GVP	Good pharmacovigilance practices
Ig	Immunoglobulin
IgGκ	Immunoglobulin G kappa
ITT	Intent to treat
IV	Intravenous
LTB-FL	Low tumour burden, follicular lymphoma
mAb	Monoclonal antibody
MPA	Microscopic polyangiitis
MTX	Methotrexate
n	Number of subjects
Nab	Neutralising antibody
NCCN	National Comprehensive V Cancer Network (United States)
NHL	Non-Hodgkin's lymphoma
NK	Natural killer

Abbreviation	Meaning
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamic(s)
PF-05280586	Drug development code used by sponsor for Ruxience (rituximab)
PI	Product Information
PK	Pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PP	Per protocol
PR	Partial response
Pro	Progenitor
PSUR	Periodic safety update report
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RGA	Reporter gene assay
RMP	Risk management plan
RTX	Rituximab
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SMQ	Standardised MedDRA query
TGA	Therapeutic Goods Administration
TNF	Tumour necrosis factor
US(A)	United States (of America)

I. Introduction to product submission

Submission details

Type of submission:	New biosimilar
Product name:	Ruxience
Active ingredient:	Rituximab
Decision:	Approved
Date of decision:	26 February 2021
Date of entry onto ARTG:	3 March 2021
ARTG numbers:	330537, 330536
, *Black Triangle Scheme:*[1]	No
Sponsor's name and address:	Pfizer Australia Pty Ltd Level 17, 151 Clarence Street Sydney NSW 2000
Dose form:	Concentrated solution for injection
Strengths:	100 mg/10 mL, 500 mg/50 mL
Container:	Vial
Pack size:	One
Approved therapeutic use:	***Non-Hodgkin's Lymphoma*** *Ruxience 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*** *Ruxience is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.*

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Rheumatoid Arthritis

Ruxience 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.

Ruxience 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)

Ruxience 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 Ruxience have not been established.

Route of administration: Intravenous (IV) infusion

Dosage: In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded in the patient dispensing record.

Ruxience intravenous formulation is not intended for subcutaneous (SC) administration.

Ruxience may be administered in an outpatient setting. Ruxience 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.

Dosage of Ruxience depends on multiple factors, including the condition being treated. For further information regarding dosage, refer to the Product Information.

Pregnancy category: C

Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Pfizer Australia Pty Ltd (the sponsor) to register Ruxience (rituximab) 100 mg/10 mL, 500 mg/50 mL, concentrate for solution for injection vial for the following proposed indication:

> ***Non-Hodgkin's Lymphoma***
>
> *Ruxience 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***
>
> *Ruxience is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.*
>
> ***Rheumatoid Arthritis***
>
> *Ruxience 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.*
>
> *Ruxience 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)***
>
> *Ruxience 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 Ruxience have not been established.*

Ruxience (rituximab) is a monoclonal biosimilar antibody of MabThera (rituximab). Rituximab is a genetically engineered chimeric mouse/human monoclonal immunoglobulin G kappa (IgGκ) antibody targeting the transmembrane CD20 antigen. CD20 is a 32-kDa, non-glycosylated transmembrane phosphoprotein, located on the surface of normal precursor B cells, mature B lymphocytes and malignant B cells. The antigen is expressed on > 95% of all B cell non-Hodgkin's lymphomas. It is found on both normal and malignant B cells, but not on haematopoietic stem cells, progenitor B cells, normal plasma cells or other normal tissue. CD20 does not internalise upon antibody binding and is not shed from the cell surface. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding. The natural ligand for CD20 has not been identified, and the biological function of CD20 remains unclear. Rituximab binds to a discontinuous conformational epitope on CD20. Upon binding, rituximab initiates multiple immune effector functions leading to target cell lysis.

The currently approved indications for licensed rituximab (MabThera) are for rheumatoid arthritis (RA), non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL), granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). The mechanism of action of rituximab in NHL, CLL, RA, GPA, and MPA is the result of specific binding to the transmembrane CD20 antigen.

Non-Hodgkin's lymphoma

Lymphoma is a malignant disease of the lymphoid system, for which there are two main clinico-pathological types, Hodgkin's disease (also known as Hodgkin's lymphoma) and non-Hodgkin's lymphoma (NHL). Depending on where it is located in the body NHL can cause different symptoms, but frequent symptoms include painless lymph node enlargement, weight loss and fever with or without infection, pruritus, splenomegaly and fatigue. The overall incidence of NHL in Australia is 22 cases per 100,000 persons (which is higher in males versus females, 26 versus 18 cases per 100,000, respectively). NHL can be classified into indolent (low grade), aggressive (intermediate grade) and very aggressive (high grade) subtypes. Approximately 40% of new cases of indolent lymphoma are follicular lymphoma, which is the second most common type of NHL worldwide accounting for 20-25% of all cases. The majority of patients with follicular lymphoma have advanced disease (Ann Arbor stage III or IV)[2] and 50% have bone marrow involvement at diagnosis.

Treatment for NHL depends on the subtype of lymphoma, stage of disease and the expected rate of disease progression. Current treatment options for NHL in Australia include chemotherapy and radiotherapy, alone or in combination. Alkylator based combination chemotherapy with cyclophosphamide has been the standard first line treatment option for patients with advanced indolent lymphoma for 20 years, but in the last 10 years there is published evidence showing improved overall survival (OS) rates with the addition of rituximab to combination chemotherapy with cyclophosphamide, vincristine and prednisone (CVP) versus CVP alone (4 year OS of 83% versus 77%).[3] Moreover, the introduction of rituximab maintenance treatment after successful induction treatment with chemotherapy has increased progression free survival rates. Therefore, at present, the recommended treatment for advanced follicular lymphoma involves the use of rituximab in combination with chemotherapy for induction treatment followed by rituximab maintenance therapy.

Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is a neoplasm of activated B lymphocytes, which morphologically resemble mature, small lymphocytes of the peripheral blood, accumulate in the bone marrow, blood, lymph nodes and spleen in large numbers. Onset is frequently insidious, and it is not unusual for CLL to be discovered incidentally after a blood cell count is performed for another reason (25 to 50% of patients will be asymptomatic at presentation). Enlarged lymph nodes are the most common presenting symptom, seen in 87% of patients symptomatic at time of diagnosis. Transformation of CLL into an aggressive large B cell lymphoma is seen in approximately 3 to10% of cases. The incidence of CLL increases with age (usually seen after 50 years of age) and the mean age at diagnosis is 70 years.

Treatment for CLL depends on the stage of disease and the expected rate of disease progression. Current treatment options for CLL in Australia include chemotherapy with fludarabine and alkylating agents such as cyclophosphamide. Glucocorticoids are also useful in certain circumstances such as in the treatment of associated Coombs test;[4]

[2] The **Ann Arbor staging system** is a lymphoma staging classification system for both Hodgkin lymphoma and non-Hodgkin lymphoma. Stage III: involvement of lymph node regions or structures on both sides of the diaphragm. Stage IV: diffuse or disseminated involvement of one or more extralymphatic organs, or either: isolated extralymphatic organ involvement without adjacent regional lymph node involvement, but with disease in distant sites involvement of the liver, bone marrow, pleura or cerebrospinal fluid.
[3] Marcus R et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. *J Clin Oncol*. 2008 Oct 1;26(28):4579-86.
[4] **Coombs test**, also known as an antiglobulin test, is an immunology laboratory procedure used to detect the presence of antibodies against circulating red blood cells in the body, which then induce haemolysis.

positive haemolytic anaemia and immune thrombocytopenia. Radiotherapy may occasionally be useful in palliating localised disease or hypersplenism in the aged. Monoclonal antibodies such as rituximab may be one of the treatment options along with chemotherapy in younger patients with poor prognostic factors such as very high lymphocyte cell numbers or rapid doubling time. An autologous stem cell transplant may also be one of the treatment options in selected cases.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterised by polyarticular inflammatory synovitis, which is associated with cartilage breakdown, bony erosion and ultimately loss of function of the affected joints. It is the second most common form of arthritis and the most common autoimmune disease in Australia with a prevalence of 2%.

RA is a heterogeneous condition in terms of clinical presentation, natural history and drug responsiveness. Published evidence and current guidelines for the treatment of RA emphasise the importance of achieving clinical remission, or at least low disease activity, as both of these states are associated with a favourable long term prognosis. In addition to treating the signs and symptoms of RA, an impact on inhibiting the structural bone damage of the condition is highly desirable as this is associated with better long-term patient outcomes, particularly regarding maintenance of physical function and quality of life. Conventional synthetic disease-modifying antirheumatic drug (DMARD) (in particular, methotrexate (MTX)), alone or in combination with each other, are the initial recommended treatments for RA. Observational studies and meta-analyses of DMARD treatment efficacy and tolerability demonstrate highly variable outcomes to single and combination DMARD therapy over time. In 10-year follow up studies, 25% of patients with RA had to discontinue conventional DMARD treatment due to insufficient therapeutic benefit and 20% discontinued treatment due to adverse effects. Biological DMARDs, either as add-on or single drug therapy, is the next recommended line of therapy in active RA after conventional synthetic DMARD failure or intolerability. While anti-TNF drugs and cytokine modulators such as abatacept and tocilizumab have been shown to demonstrate significant efficacy in treating active RA, a substantial proportion of patients are not achieving meaningful American College of Rheumatology (ACR) responses. Based on the current literature for biological therapies, ACR20 response rates range from 50 to 65% and ACR50 response rates are 35 to 50%. So despite the availability of many therapies with various modes of action for the treatment of RA, a significant proportion of individuals either fail to initially respond to treatment, do not tolerate therapy or lose response over time. Rituximab is approved in Australia and around the world for the treatment of active RA in patients who have an inadequate response to at least one anti-TNF therapy.

Granulomatosis with polyangiitis and microscopic polyangiitis

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are types of anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis, a rare, multisystem, autoimmune disease characterised by small to medium sized vessel vasculitis, the production of ANCA, and a high occurrence for causing significant respiratory tract and kidney disease in its severe form.

Patients with GPA and MPA typically have systemic disease at presentation (few have limited disease) and receive induction treatment with high dose IV glucocorticoids together with cyclophosphamide. Rituximab is an approved alternative induction treatment for severely active GPA and MPA. However, the efficacy and safety of re-treatment with rituximab has not been established. After induction of remission treatment, patients with GPA and MPA are recommended to receive maintenance therapy

for at least two years, which may include the drug options of azathioprine, MTX or mycophenolate in conjunction with low dose oral glucocorticoids.

Regulatory status

This product is considered a new biosimilar medicine for Australian regulatory purposes.

Rituximab, as the originator product MabThera, received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 6 October 1998.

At the time the TGA considered this application, similar applications had been approved in the European Union (EU) on 1 April 2020, the United States of America (USA) on 23 July 2019, in Japan on 20 September 2019, in Canada on 4 May 2020, and in Switzerland in 4 August 2020. A similar application was also under consideration in New Zealand.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
EU via Centralised procedure	25 July 2018	Approved on 1 April 2020	*All indications held by the reference product: non-Hodgkins lymphoma, chronic lymphocytic leukemia, rhematoid arthritis, granulamatosis with polyangiitis, microscopic polyangiitis and pemphigus vulgaris*
USA	25 July 2018	Approved on 23 July 2019	*Non-Hodgkins lymphoma, chronic lymphocytic leukemia, granulamatosis with polyangiitis, microscopic polyangiitis*
Japan	21 November 2018	Approved on 20 September 2019	*CD20-positive, B-cell non-Hodgkin's Lymphoma (NHL), CD20-positive, B-cell lymphoproliferative disease under immunosuppression, Granulomatosis with polyangiitis, microscopic polyangiitis*
Canada	6 February 2019	Approved on 4 May 2020	*All indications held by the reference product*
Switzerland	30 March 2020	Approved on 4 August 2020	*All indications held by the reference product*
New Zealand	21 May 2020	Under consideration	Under consideration

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 timeline

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

Table 2: Timeline for Submission PM-2020-00593-1-6

Description	Date
Submission dossier accepted and first round evaluation commenced	6 April 2020
First round evaluation completed	28 August 2020
Sponsor provides responses on questions raised in first round evaluation	2 November 2020
Second round evaluation completed	10 December 2020
Delegate's Overall benefit-risk assessment	22 February 2021
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	26 February 2021
Completion of administrative activities and registration on the ARTG	3 March 2021
Number of working days from submission dossier acceptance to registration decision*	188

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

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

The following guideline documents are considered to be relevant:

- Therapeutic Goods Administration: Regulation of biosimilar medicines (version 2.0; December 2015).
- Clinical investigation of medicinal products other than non-steroidal anti-inflammatory drugs for treatment of rheumatoid arthritis (revision 1). Effective: 29 January 2007. CPMP/EWP/556/95

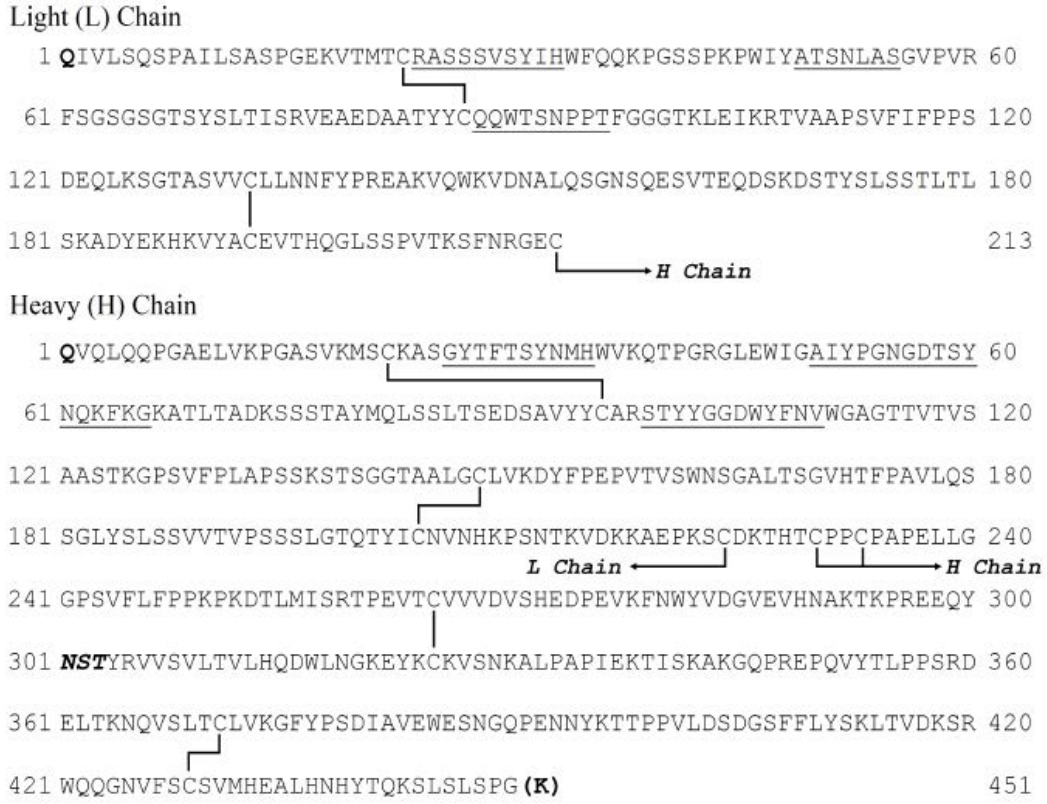
- Guideline on similar biological medicinal products (revision 1). Effective: 25 May 2015. CHMP/437/04
- Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use. Effective: 1 June 2014. EMA/CHMP/BMWP/86289/2010:
- Guideline on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues. Effective: 17 August 2015. EMA/CHMP/BMWP/403543/2010

Quality

Ruxience (rituximab) is a recombinant, chimeric, IgG1κ monoclonal antibody produced from Chinese hamster ovary (CHO) cells and is proposed for registration as a biosimilar to MabThera (rituximab). The drug product is supplied as a 10 mg/mL concentrated solution for intravenous infusion. There are two dosage presentations (10 mL and 50 mL); both are presented single use in clear glass vials sealed with a stopper and an aluminium seal with a flip-off plastic cap.

PF-05280586;[5] is also an IgG1κ monoclonal antibody (mAb) with two identical heavy chains and two identical light chains, covalently linked with four inter-chain disulphide bonds. Each light chain consists of 213 amino acids and each heavy chain 451 amino acids. The complete amino acid sequence of PF-05280586 is shown below in Figure 1.

Figure 1: Amino acid sequence of Ruxience (rituximab)



[5] PF-05280586 is the drug development code used by the sponsor for Ruxience (rituximab).

Comparison studies between Ruxience, EU-sourced rituximab and US-sourced rituximab

55 US-sourced rituximab drug product lots (100 mg/10 mL and 500 mg/50 mL presentations) and 65 EU-sourced drug product lots (100 mg/10 mL and 500 mg/50 mL presentation) were sourced for comparison. These batches represent nearly the full 30 month expiry period (stored at 2 ± 8°C) of the licensed rituximab product; at the start of the individual lot testing they had between 1 and 27 months remaining prior to expiry.

Ten PF-05280586;[5] drug substance batches and 12 drug product lots produced at the commercial scale have been included in the similarity assessment. In addition, 5 PF-05280586;[5] development scale drug substance batches were also included in the similarity assessment.

Comparison studies indicated that PF-05280586, EU-sourced rituximab and US-sourced rituximab:

- have identical primary structure/amino acid sequence and similar post-translational modifications;
- have comparable size distribution and purity is considered comparable;
- have comparable higher order structure;
- have highly similar charge variants/hydrophobic heterogeneity; although differences in charge variants;
- have comparable protein content;
- have comparable total afucosylation and total galactosylation in glycan analysis; and
- have comparable *in vitro* biological activity/potency as in CD20-binding and apoptosis; *in vitro* complement-dependent cytotoxicity (CDC) and complement component 1q (C1q) binding; fragment crystallisable (Fc)ɤRIIIa 158V binding and natural killer (NK) antibody-dependent cell-mediated cytotoxicity (ADCC) (V/V, V/F), FcɤRIIa-binding, FcRn-binding, and a cell based antibody-dependent cellular phagocytosis (ADCP) reporter gene assay (RGA).

Taken all attributes evaluated, PF-05280586, EU-sourced rituximab and US-sourced rituximab are considered highly similar.

Bridging study with Australian-sourced rituximab

The sponsor also sourced four batches of rituximab (MabThera) from the Australian market for further comparison.

The bridge study confirmed that MabThera (Australian-sourced rituximab) is highly similar to Rituxan and MabThera sourced from the US and EU markets respectively.

Overall, it can be concluded that PF-05280586 (Ruxience) is highly similar to US-sourced Rituxan and EU- and Australian-sourced MabThera in terms of protein content, amino acid sequence, physical integrity, secondary and higher order structure, charge and glycan isoforms and bioactivity and functionality.

The quality evaluator has no objections to marketing of Ruxience.

Nonclinical

The nonclinical dossier contained comparative data on pharmacokinetics (from toxicity studies), single- and repeat-dose toxicity and a nucleotide polymorphisms (SNP) analysis of samples from the toxicity studies. The scope of the nonclinical program is adequate

under the relevant EU guideline. The studies were conducted using EU-sourced Mabthera as the reference product. No data were provided in nonclinical module to verify the comparability of the EU-sourced and Australian-sourced Mabthera.

No meaningful differences between Ruxience and Mabthera were observed in the comparative pharmacology, pharmacokinetic and toxicity studies.

There are no nonclinical objections to the registration of Ruxience.

Clinical

Pharmacology

Comparable results of PF-05280586 (Ruxience) with US-sourced rituximab, and EU-sourced rituximab were found in terms of their ability to bind to CD20, for inducing apoptosis and also for binding to C1q and inducing CDC.

Pharmacokinetics

Table 3: Tabular overview of clinical studies conducted for the evaluation of pharmacokinetics, pharmacodynamics, safety, efficacy and immunogenicity

Study ID	Protocol title	Status	Number of Subjects or Patients Treated/PK
Study B3281001	A randomised, double-blind, study comparing the pharmacokinetics and pharmacodynamics, and assessing the safety of PF-05280586 and rituximab in subjects with active rheumatoid arthritis on a background of methotrexate (MTX) who have had an inadequate response to one or more tumour necrosis factor (TNF) antagonist therapies.	Completed, final CSR issued;[a]	220[b]/198[c]
Study B3281004	Extension study evaluating treatment with PF- 05280586 versus rituximab in subjects with active rheumatoid arthritis who have participated in other PF-05280586 clinical trials.	Completed, final CSR issued	183[d]/183
Study B3281006	A Phase III, randomised, double-blind study of PF-05280586 versus rituximab for the first-line treatment of patients with CD20-positive,	Completed; final CSR issued	393/393

Study ID	Protocol title	Status	Number of Subjects or Patients Treated/PK
	low tumour burden, follicular lymphoma.		

CSR = clinical study report; PF-05280586 = drug development code for Ruxience (rituximab); PK = pharmacokinetics.

a) A supplemental CSR (sCSR) reported the post-hoc PK analysis requested by the European Medicines Agency.

b) Intent to treat safety population.

c) Per protocol (PP) population.

d) Modified intent to treat safety population.

e) Following the CSR primary completion date (cutoff date 23 October 2017) at Week 26, data was included in the initial submission. A full CSR (through to Week 52/study completion for all subjects) included data for all primary data endpoints and secondary endpoints.

Study B3281001 (biosimilarity)

Study B3281001 was a randomised, double-blind study comparing the pharmacokinetics (PK) and pharmacodynamics (PD) and assessing the safety of PF-05280586 and rituximab (US- and EU-sourced) in subjects with active RA on a background of MTX who have had an inadequate response to one or more TNF antagonist therapies.

The study was conducted from 20 March 2012 to 7 May 2014 in 60 centres in 10 countries, including Australia.

The primary objective was to demonstrate the PK similarity of PF-05280586, EU-sourced rituximab, and US-sourced rituximab in subjects with active RA on a background of MTX who had an inadequate response to one or more TNF antagonist therapies. Secondary objectives were to use population PK/PD modelling to integrate PK and PD data in order to detect potential differences in PK/PD profiles among PF-05280586, EU-sourced rituximab and US-sourced rituximab. Some clinical response endpoints and overall safety, tolerability and immunogenicity of the three products were also evaluated.

Study subjects were to receive one course of PF-05280586, EU-sourced rituximab and US-sourced rituximab administered by IV infusion at a dose of 1000 mg on Days 1 and 15 of the study.

For the two primary endpoints, the area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) and maximum concentration (C_{max}), there are three co-primary analyses:

- test for bioequivalence of PF-05280586 (Ruxience) to US-sourced rituximab;
- test for bioequivalence of PF-05280586 (Ruxience) to EU-sourced rituximab; and
- test for bioequivalence of US-sourced rituximab to EU-sourced rituximab.

Results

Overall, 220 subjects were randomised; 73 subjects (33%) to US-sourced rituximab, 74 subjects (34%) to EU-sourced rituximab, and 73 subjects (33%) to PF-05280586 (Ruxience). 16 (7.3%) subjects discontinued before completing the study with 6 (2.7%) subjects withdrawing before they received the full course of study treatment (that is withdrew from treatment before completing both doses on Day 1 and Day 15).

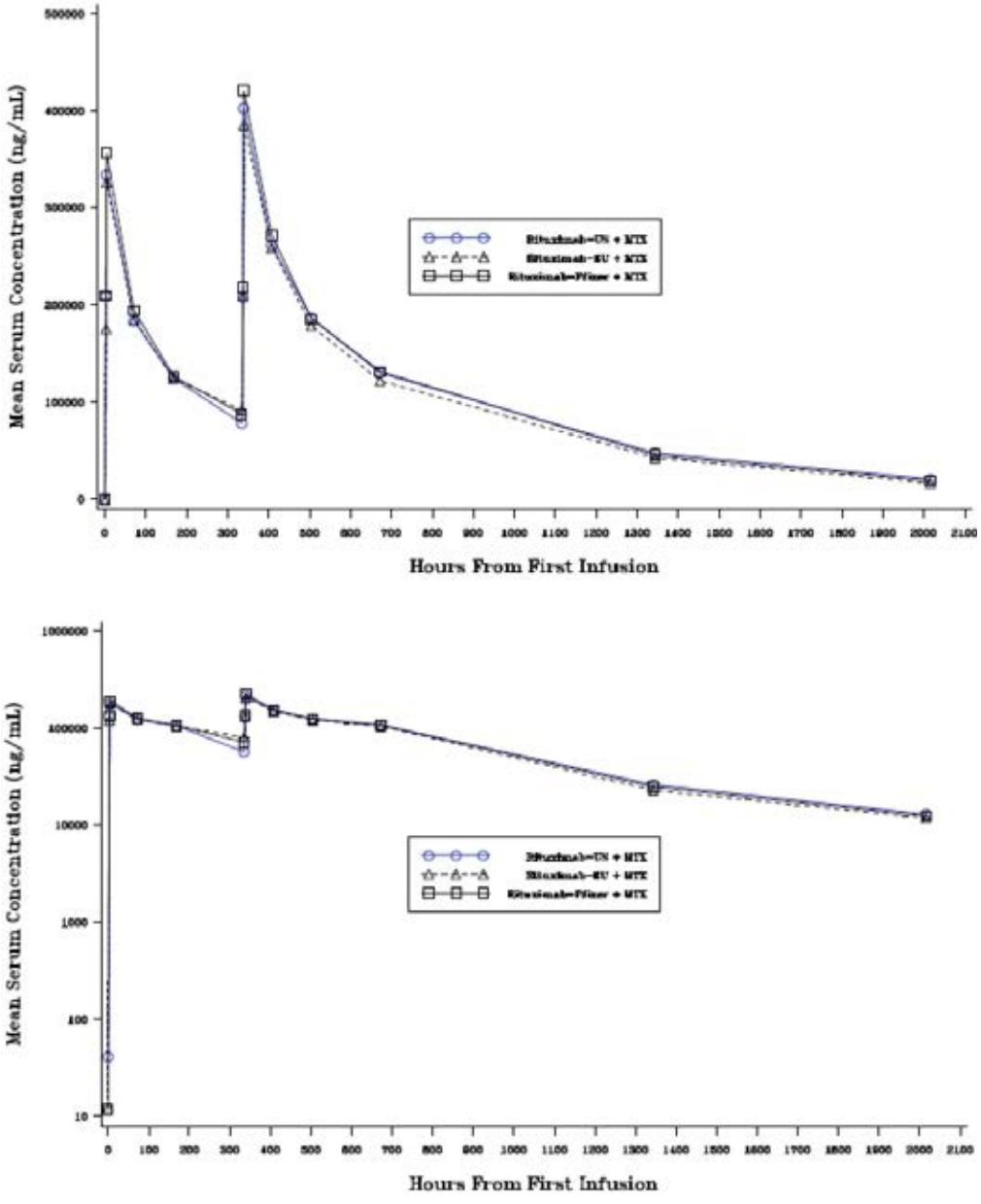
Out of the 220 randomised subjects, 198 were included in the per protocol (PP) population and in the PK analysis.

Table 4: Study B3281001 Per protocol population for pharmacokinetic analysis

	Rituximab-US	Rituximab-EU	Rituximab-Pfizer
Number of subjects, n	63	67	68
Male, n	19	14	13
Female, n	44	53	55
Mean age (±SD), years	53.7 ± 11.64	55.4 ± 10.47	54.8 ± 11.74
Mean weight (±SD), kg	79.9 ± 21.4	82.4 ± 20.4	86.0 ± 22.2

Abbreviations: EU = Europe; n = number of subjects; PK = pharamacokinetics, SD = standard deviation; US = United States

Figure 2: Mean serum concentration-time profiles of PF-05280586 (Ruxience) EU-sourced rituximab and US-sourced rituximab in rheumatoid arthritis patients (n = 198) receiving two intravenous doses of 1000 mg on Day 1 and Day 15



Upper and lower panels are linear and semi-logarithmic scales, respectively. Abbreviations: EU = Europe; US = United States; RA = rheumatoid arthritis; n = number of subjects

Table 5: Summary of statistical comparisons of pharmacokinetic exposure parameters between PF-05280586 (Rituxience) and reference products (EU- and US-sourced rituximab)

Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Test	Reference		
Rituximab-Pfizer (Test) vs. Rituximab-EU (Reference)				
C_{max} (µg/mL)	432	409	105.67	(96.91, 115.21)
AUC_{0-T} (µg.hr/mL)	184000	178000	103.36	(92.81, 115.12)
$AUC_{0-\infty}$ (µg.hr/mL)	196000	188000	104.19	(92.75, 117.06)
AUC_{0-2wk} (µg.hr/mL)	49500	47700	103.74	(95.10, 113.15)
Rituximab-Pfizer (Test) vs. Rituximab-US (Reference)				
C_{max} (µg/mL)	432	405	106.62	(97.65, 116.41)
AUC_{0-T} (µg.hr/mL)	184000	181000	101.33	(90.82, 113.04)
$AUC_{0-\infty}$ (µg.hr/mL)	196000	195000	100.45	(89.20, 113.11)
AUC_{0-2wk} (µg.hr/mL)	49500	46900	105.56	(96.64, 115.30)
Rituximab-EU (Test) vs. Rituximab-US (Reference)				
C_{max} (µg/mL)	409	405	100.90	(92.38, 110.20)
AUC_{0-T} (µg.hr/mL)	178000	181000	98.03	(87.83, 109.40)
$AUC_{0-\infty}$ (µg.hr/mL)	188000	195000	96.40	(85.57, 108.60)
AUC_{0-2wk} (µg.hr/mL)	47700	46900	101.76	(93.13, 111.18)

Abbreviations: CI = confidence interval; SD = standard deviation; EU = Europe; US = United States

a) The ratios (and 90% Cis) are expressed as percentages.

Conclusions

The standard requirements for demonstration of similarity in PK have been convincingly demonstrated for C_{max} and $AUC_{0-\infty}$ in Study B3281001. The ratios were contained within the pre-specified acceptance boundaries of 80.00% to 125.00% for all the pair-wise comparisons among the three study drugs, demonstrating PK similarity among US-sourced rituximab, EU-sourced rituximab, and PF-05280586 (Ruxience).

In the pivotal biosimilarity Study B3281001, US-sourced rituximab, EU-sourced rituximab, and PF-05280586 exhibited similar PK profiles. More importantly, the 90% CIs for test to reference ratios of C_{max} and $AUC_{0-\infty}$ were contained within the pre-specified acceptance boundaries of 80% to 125% for all of the pair-wise comparisons among the three study drugs, demonstrating PK similarity among US-sourced rituximab, EU-sourced rituximab, and PF-05280586 (Ruxience).

Pharmacodynamics

These evaluations have shown a consistently similar effect of the rituximab formulations on timing and extent of reduction in $CD19^+$ cells. The effect is rapid, being apparent within the first day of treatment commencement in patients with RA. Similar effects on $CD19^+$ cells were also demonstrated for PF-05280586 (Ruxience) versus the EU-sourced rituximab (reference) comparison in Study B3281006. Secondary PD effects on IgG, IgM, rheumatoid factor (RF), and cyclic citrullinated peptides (CCP) antibody levels were also consistent between the three products.

A consistent relationship between mean area under the plasma concentration time curve and clinical response was also demonstrated for the three products.

Immunogenicity with neutralising antibodies (Nab) does not appear to be of concern in the treatment durations seen in the bioequivalence study and its continuation study in patients with RA.

Biosimilarity with the EU reference product MabThera has been demonstrated, based on the clinical pharmacology data.

Efficacy

Study B3281006

Study B3281006 was the pivotal study for evaluating efficacy of PF-05280586 (Ruxience).

Study design

This study was a Phase III, randomised, double-blind study of PF-05280586 (Ruxience) versus EU-sourced rituximab for the first-line treatment of patients with $CD20^+$, low tumour burden, follicular lymphoma.

The study was performed in patients with $CD20^+$, low tumour burden, follicular lymphoma. Additional comparative efficacy data were available from Studies B3281001, the bioequivalence study in patients with rheumatoid arthritis and its extension, Study B32881004.

The first subject visit was in September 2014 and the last subject visit was in April 2018. This is the final report, an interim analysis was performed on data to Week 26 of the study.

The primary objective was to compare the efficacy of PF-05280586 (Ruxience) to EU-sourced rituximab when administered as a first-line treatment to subjects with $CD20^+$, low tumour burden, follicular lymphoma (LTB FL).

Secondary objectives were:

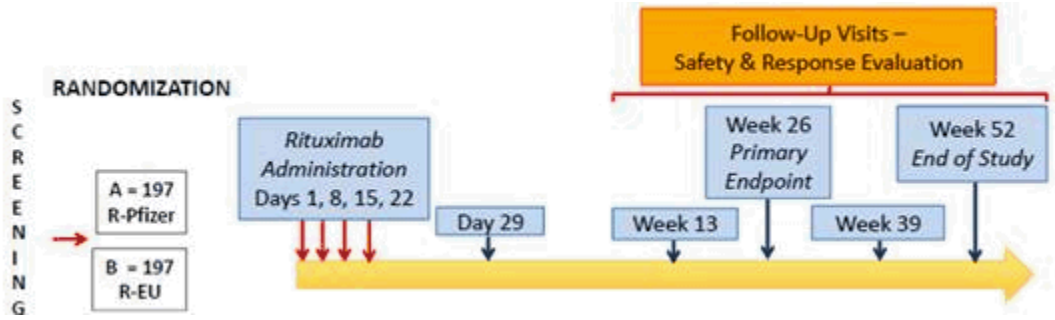
- to evaluate the safety of PF-05280586 (Ruxience) and EU-sourced rituximab;
- to evaluate the population PK of PF-05280586 (Ruxience) and EU-sourced rituximab;
- to evaluate the immunogenicity of PF-05280586 (Ruxience) and EU-sourced rituximab; and
- to characterise CD19-positive B cell depletion and recovery in subjects receiving PF 05280586 (Ruxience) and EU-sourced rituximab.

Subjects were randomised in a 1:1 ratio to receive PF-05280586 (Ruxience) or EU-sourced rituximab. Randomisation was stratified by low, medium and high risk subjects using the Follicular Lymphoma International Prognostic Index 2 (FLIPI2) crieteria.[6] During the study, subjects received four-weekly doses of PF-05280586 (Ruxience) or EU-sourced rituximab administered via IV infusion. The dose of PF-05280586 (Ruxience) or EU-sourced rituximab was 375 mg/m^2 of body surface area (BSA).

The maximum dose that could be infused in one day was 1125 mg. The primary assessment point was at Week 26 and follow-up continued to Week 52. The study schematic is below in Figure 3.

[6] **The Follicular Lymphoma International Prognostic Index 2** is a simple prognostic index based on available clinical data and represent a promising new tool for the identification of patients with FL at different risk in the era of immunochemotherapy. Stage I: disease is located in a single region, usually one lymph node and the surrounding area. Stage II: disease is located in two separate regions, an affected lymph node or organ and a second affected area. Both affected areas are confined to one side of the diaphragm.
Stage III: disease involves both sides of the diaphragm, including one organ or area near the lymph nodes or the spleen. Stage IV: diffuse or disseminated involvement of one or more extranodal organs, with or without associated lymph node involvement

Figure 3: Study B3281006 Study schematic



R-Pfizer = rituximab-Pfizer (Ruxience); R-EU = rituximab sourced from Europe

Results for the primary efficacy outcome

Statistical equivalence between the two treatment groups was demonstrated. The overall response at Week 26 was 140 (70.7%) in the EU-sourced rituximab group and 148 (75.5%) in the PF-05280586 (Ruxience) group. The estimated difference in overall response rate, (ORR) was 4.66% (PF-05280586 (Ruxience) minus EU-sourced rituximab), with 95% CIs of -4.16% to 13.47%, which fell within the -16.0% to 16.0% pre-specified equivalence margin agreed to by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), and also within the -14.9% to 14.9% margin agreed to by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan. Summary statistics of response by treatment at Week 26 are shown below in Table 26.

Table 6: Study B3281006 Summary statistics of response by treatment at Week 26 based on observed data intent to treat population

	rituximab-EU (N=198)	PF-05280586 (N=196)
Number of observed responses at Week 26		
Overall response rate		
n (%)	140 (76.1)	148 (85.1)
SE, %	3.14	2.70
Complete response		
n (%)	57 (31.0)	51 (29.3)
SE, %	3.41	3.45
Partial response		
n (%)	83 (45.1)	97 (55.7)
SE, %	3.67	3.77
Stable disease		
n (%)	36 (19.6)	20 (11.5)
SE, %	2.92	2.42
Progressive disease		
n (%)	8 (4.3)	6 (3.4)
SE, %	1.50	1.38

ORR was defined as the proportion of subjects who achieved either CR or PR at the specific time point.
Abbreviations: CR = complete response; EU = European Union; ITT = intent to treat; n = number of subjects with the specified response; N = number of subjects in the analysis population; ORR = overall response rate; PR = partial response; SE = standard error.

[a] Based on updates to the central review assessments as of the database lock on 18 May 2018.

Subject selection for this study was not consistent with the approved NHL indications for the innovator product, MabThera. Study subjects were required to have previously untreated, low tumour burden, Stage II, III or IV follicular NHL. The indications for MabThera most similar to this patient group are:

- CD20-positive, previously untreated, Stage III/IV follicular, B cell non-Hodgkin's lymphoma; and

- CD20-positive, relapsed or refractory low grade or follicular, B cell non-Hodgkin's lymphoma.

Similarly the indications in the USA and EU are not consistent with the patient group and dose regimen used in this study. Rituximab as monotherapy as treatment for symptomatic Stage II/III/IV follicular lymphoma for histological Grades 1 to 3a is listed in European Society for Medical Oncology (ESMO) treatment guidelines, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline in Oncology. The patient group and dose regimen are considered acceptable.

The monotherapy rituximab dose regimen given in this study was the same as is recommended for relapsed or refractory low grade or follicular NHL. Monotherapy rituximab is not recommended for previously untreated follicular NHL. The recommended dose regimen for previously untreated NHL requires combination treatment with cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone or prednisolone (CHOP).

While it is not unacceptable to conduct a clinical comparability study with a novel dose regimen of a product it is not the usual practice. The patient selection and dose regimen does give a clearer comparison of efficacy and safety of the two products than if one of the indications and its recommended dose regimen had been selected. Patients in this study had not received a range of treatments prior to exposure to one of the rituximab products. Ensuring the patients in the two groups had similar histories of prior treatment would have been extremely difficult. The inclusion of other treatments, such as CHOP which is recommended in combination with rituximab for previously untreated Stage III/IV follicular NHL would also have potentially obscured differences due to rituximab alone.

The selection of ORR as primary efficacy measure is acceptable and consistent with the primary efficacy measure used in the initial pivotal study for approval of rituximab to treat relapsed/refractory low grade or follicular NHL with monotherapy rituximab. Selection of the 95% CIs for the between treatment difference in ORR of ± 16% was generous as the 95% CIs difference between rituximab and watchful waiting was 20% that is. ± 10%. If the ± 10% margin had been applied to this study then the criteria for equivalence would not have been met at the upper bound that is the ORR for PF-05280586 (Ruxience) would have been higher than the upper bound for ORR to conclude equivalence.

Other efficacy studies

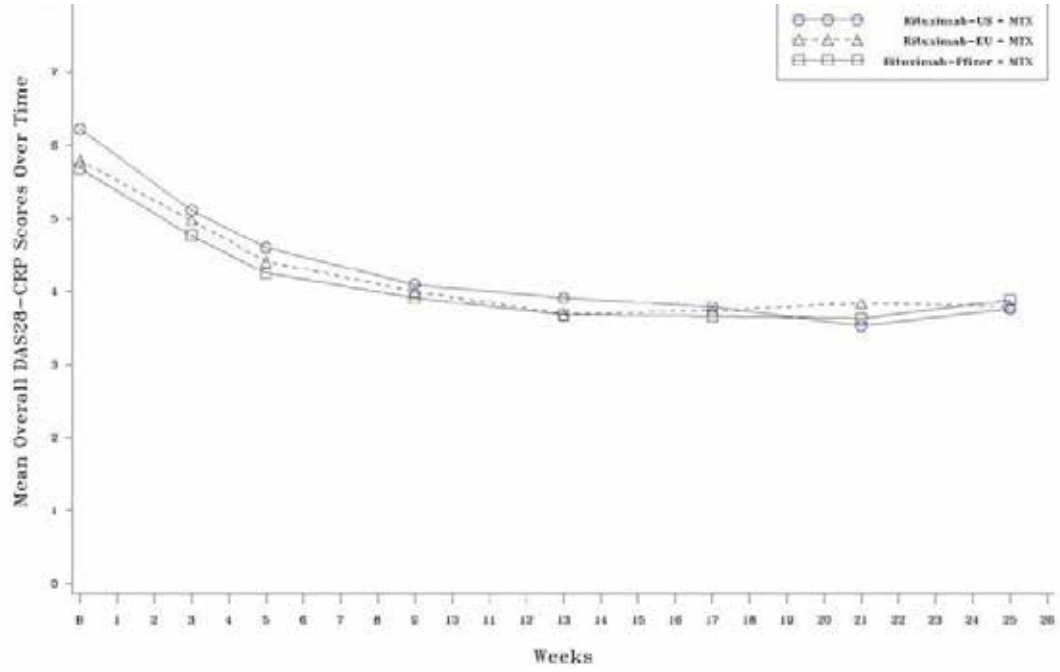
Study B3281001

This study was a randomised, double-blind, study comparing the pharmacokinetics and pharmacodynamics, and assessing the safety of PF-05280586 (Ruxience) and comparator rituximab in subjects with active rheumatoid arthritis on a background of MTX who have had an inadequate response to one or more TNF antagonist therapies.

This was primarily a PK study. It was conducted over 26 weeks.

Efficacy was assessed using the Disease Activity Score (DAS), ACR responses and European League Against Rheumatism (EULAR) response (see Figure 4 below).

Figure 4: Study B3281001 Overall DAS28-CRP scores over time



Abbreviations: DAS28-CRP = Disease Activity Score in 28 joints – C reactive protein; EU = European Union; mITT = modified intent to treat; MTX = methotrexate; US = United States

Study B3281004

This study was an extension to Study B3281001. First subject first visit 16 August 2012, last subject last visit 14 March 2016. There were 48 study centres in 10 countries. This study evaluated the safety (including immunogenicity) of treatment with PF-05280586 (Ruxience), as well as the safety and immunogenicity occurring after transitioning from US-sourced rituximab or EU-sourced rituximab to PF-05280586 (Ruxience). The objectives were:

- too provide continued treatment access to subjects with active RA who have participated for at least 16 weeks in other protocols in the PF-05280586 program;
- to evaluate the overall safety, tolerability and immunogenicity of PF-05280586 occurring after transition from a licensed rituximab product to PF-05280586; and
- to continue follow-up of biomarker and efficacy endpoints of interest in Study B3281001.

The supportive efficacy studies in patients with RA while not designed to demonstrate equivalence of efficacy have shown similar efficacy for the EU and USA rituximab products and the proposed PF-05280586 (Ruxience) product. The switching study also provided reassurance that no clinically significant changes in efficacy are likely to occur on switching between different rituximab products.

Conclusion on efficacy

Assessment of the similarity of efficacy between Ruxience and the innovator product has been comprehensive. It included assessments in both therapeutic areas (oncology and rheumatology), a demonstration of therapeutic comparability, and a lack of clinically significant changes in efficacy outcomes on switching between innovator and the proposed Ruxience product.

Whether the 95% CIs for determination of clinical equivalence was sufficiently narrow to be considered not of clinical concern is the main efficacy issue, however taken together with the other efficacy data, particularly the longer term efficacy comparisons in

Study B3281004, the evaluator considers that similarity of efficacy has been adequately demonstrated.

Safety

There was no integrated safety assessment which is appropriate given there were two distinct patient groups in the in studies. Safety data from the two studies in the same RA patient population (Study B3281001 and its extension, Study B3281004) were not pooled due to differences in the number of doses administered in the two studies, and the re-randomisation and transition from EU-sourced rituximab or US-sourced rituximab treatments to PF-05280586 (Ruxience) treatment in Study B3281004.

The safety population was defined as subjects who received at least one dose of study drug (PF-05280586 (Ruxience), EU-sourced rituximab, or US-sourced rituximab).

Conclusion

Quite extensive comparisons of the safety of rituximab products when used as proposed have been performed. There was no evidence that there were clinically significant differences in the safety profiles of EU-sourced rituximab, US-sourced rituximab or PF-05280586 (Ruxience). Switching between these products did not result in changes to the frequency of immunogenicity-related adverse events.

Immunogenicity and immunological events

Possible immunogenicity effects on switching were examined in Study B3281004. Anti-drug antibody (ADA) and clinical outcomes associated with immunogenicity for each treatment course. The clinical outcomes associated with immunogenicity were those from the Standardised MedDRA query (SMQ) for anaphylaxis or hypersensitivity.

There was no evidence of changes in immunogenicity as a result of switching between the rituximab products.

Risk management plan

The sponsor has submitted EU-risk management plan (RMP) version 0.4 (date 18 December 2019; data lock point (DLP) (18 May2018) and Australian-specific Annex (ASA) version 1.0 (date 3 February 2020) in support of this application. In response to TGA questions, the sponsor provided an updated ASA version 2.0 (date 1 October 2020). During evaluation of submitted RMP, the sponsor submitted EU-RMP version 1.0 (date 18 December 2019; DLP 18 May 2018) associated with ASA version 2.0 (date 1 October 2020). In response to further TGA questions, sponsor submitted ASA version 3.0 (11 January 2021) related to EU-RMP version 1.0 (date 18 December 2019; DLP 18 May2018) to address outstanding recommendations from RMP evaluation.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 7.[7]

[7] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Table 7: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Infusion related reactions (All Indications)	ü	–	ü	-
	Infections including serious infections (All Indications)	ü	–	ü	ü‡
	Progressive multifocal leukoencephalopathy (All Indications)	ü†	–	ü	ü‡
	Hepatitis B reactivation (All Indications)	ü	–	ü	–
	Hypogammaglobulinaemia (Non-oncology indications)	ü	–	ü	-
Important potential risks	Malignant events (Non-oncology indications)	ü†	–	ü	–
	Impact on cardiovascular disease (Non-oncology indications)	ü	–	ü	–
	Relapses (GPA/MPA only)	ü	–	ü	–
	Off-label use in paediatric patients (All Indications)	ü†	–	ü	–
	Administration route error (NHL/CLL)	ü	–	ü	ü§
Missing information	Use in pregnancy and lactation (All Indications)	ü	–	ü	–
	Long-term use in GPA/MPA patients (GPA/MPA only)	ü	–	ü	–

† Adverse event follow up form/data capture aid (DCA)

‡ Guide for healthcare professionals, Patient Alert Card, Patient Information Pack, (Non-oncology indications only)

§ Guide for healthcare professionals

The summary of safety concerns aligns with the summary of safety concerns for the reference product, apart from the safety concerns relating to the subcutaneous presentation, as Ruxience does not have a subcutaneous presentation. The summary of safety concerns is acceptable from an RMP perspective.

Routine pharmacovigilance is proposed for all safety concerns and missing information including adverse reaction follow-up forms for the safety concerns indicated above. No additional pharmacovigilance activities have been proposed by the sponsor. The proposed pharmacovigilance plan is acceptable.

Routine risk minimisation is proposed for all safety concerns and missing information, including used enhanced routine risk minimisation for risks progressive multifocal leukoencephalopathy (PML) (Product Information/Consumer Medicines Information, boxed warning and data capture aid (DCA)), malignant events (DCA) and off-label use in paediatric patients (DCA).

Additional risk minimisation activities are proposed for specific safety concerns (Table 7), and consist of healthcare professional and patient educational materials and a Patient Alert Card (PAC). The proposed risk minimisation plan is acceptable.

Wording for conditions of registration

The suggested wording is:

> *The Ruxience EU-Risk Management Plan (RMP) (version 1.0, dated 18 December 2019, data lock point 18 May 2018), with Australian Specific Annex (version 3.0, dated 11 January 2021), included with submission PM-2020-00593-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*
>
> The following wording is recommended for the PSUR requirement:
>
> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).*
>
> *Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.*
>
> *The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.*

Risk-benefit analysis

Delegate's considerations

The risk benefit balance for Ruxience (rituximab) is favourable.

Proposed action

It is recommended that Ruxience (rituximab) be approved for the same indications that are approved for MabThera, the comparator product.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Ruxience (rituximab) 100 mg/10 mL, 500 mg/50 mL concentrate for solution for infusion vial, indicated for:

> ***Non-Hodgkin's Lymphoma***
>
> *Ruxience 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

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

Rheumatoid Arthritis

Ruxience 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.

Ruxience 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)

Ruxience 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 Ruxience have not been established.

Specific conditions of registration applying to these goods

- The Ruxience EU-RMP (version 1.0, dated 18 December 2019, data lock point 18 May 2018), with ASA (version 3.0, dated 11 January 2021), included with submission PM-2020-00593-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.
- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Ruxience 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>.

Therapeutic Goods Administration

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