יוני 2024

RIXATHON®
rituximab

רופא/ה נכבד/ה,

רוקח/ת נכבד/ה,

חברת סנדוז פרמצבטיקה ישראל בע"מ מבקשת להודיעכם על עדכון העלון של התכשיר עודכן:

שם תכשיר	מספר רישום
Rixathon	162-10-35741-00

המרכיב הפעיל הינו: rituximab 10mg/ml

<u>תוספת התוויה rheumatoid arthritis כמפורט מטה:</u>

<u>Rheumatoid arthritis</u>

Rixathon is indicated, in combination with methotrexate, to reduce signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who had an inadequate response or intolerance to one or more TNF antagonist therapies.

<u>ההתוויות הרשומות לתכשיר בישראל הינן:</u>

Rixathon is indicated for the following indications:

<u>* Non-Hodgkin’s lymphoma (NHL):</u>

Rixathon is indicated for the treatment of patients with relapsed or refractory low-grade or follicular, B-cell nonhodgkin’s lymphoma.

Rixathon is indicated for the treatment of previously untreated patients with low-grade or follicular lymphoma in combination with chemotherapy.

Rixathon is indicated for the treatment of patients with CD20 positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP chemotherapy.

Rixathon maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.

<u>* Chronic lymphocytic leukaemia (CLL):</u>

Rixathon in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including Rixathon or patients refractory to previous Rixathon plus chemotherapy.

<u>* Granulomatosis with polyangiitis and Microscopic polyangiitis:</u>

Rixathon, in combination with glucocorticoids, is indicated for the treatment of adult patients with

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

*Pemphigus vulgaris (PV):

Rixathon is indicated for the treatment of adult patients with moderate to severe pemphigus vulgaris (PV)

בהודעה זו מצויינים רק הסעיפים בהם בוצעו שינויים מהותיים ועדכוני בטיחות בעלונים לרופא ולצרכן. החמרות הודגשו בצהוב, עדכונים שאינם החמרות סומנו בצבע שונה, ומידע שהוסר סומן עם קו חוצה.

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות:

https://data.health.gov.il/drugs/index.html#/byDrug

לעדכונכם בברכה,

מגר' דפנה סנדובסקי

רוקחת ממונה

סנדוז פרמצבטיקה ישראל בע"מ

השינויים בעלון לרופא:

4 . CLINICAL PARTICULARS

4.1 Therapeutic indications

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Rheumatoid arthritis

Rixathon is indicated, in combination with methotrexate, to reduce signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who had an inadequate response or intolerance to one or more TNF antagonist therapies.

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4.2 Posology and method of administration

...In patients with rheumatoid arthritis or pemphigus vulgaris, premedication with 100 mg intravenous methylprednisolone should be completed 30 minutes prior to Rixathon infusions to decrease the incidence and severity of infusion related reactions (IRRs).

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Posology

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Rheumatoid arthritis
A course of Rixathon consists of two 1000 mg intravenous infusions. The recommended dosage of

Rixathon is 1000 mg by intravenous infusion followed by a second 1000 mg intravenous infusion two weeks later.

Subsequent courses should be administrated every 24 weeks or based on clinical evaluation, but not
sooner than every 16 weeks.

Available data suggest that clinical response is usually achieved within 16 - 24 weeks of an initial treatment course. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.
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Subsequent infusions

All indications

Subsequent doses of Rixathon can be infused at an initial rate of 100 mg/h, and increased by 100 mg/h increments at 30 minute intervals, to a maximum of 400 mg/h.

Rheumatoid arthritis only

Alternative subsequent, faster, infusion schedule

If patients did not experience a serious infusion related reaction with their first or subsequent infusions of a dose of 1000 mg Rixathon administered over the standard infusion schedule, a more rapid infusion can be administered for second and subsequent infusions using the same concentration as in previous infusions (4 mg/mL in a 250 mL volume). Initiate at a rate of 250mg/hour for the first 30 minutes and then 600 mg/hour for the next 90 minutes. If the more rapid infusion is tolerated, this infusion schedule can be used when administering subsequent infusions.

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

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4.3 Contraindications

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Contraindications for use in rheumatoid arthritis, granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and pemphigus vulgaris

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4.4 Special warnings and precautions for use

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Rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis and pemphigus vulgaris

Methotrexate (MTX) naïve populations with rheumatoid arthritis

The use of Rituximab is not recommended in MTX-naïve patients since a favourable benefit risk

relationship has not been established.

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Severe IRRs with fatal outcome have been reported in rheumatoid arthritis patients ~~(indication currently not registered in Israel)~~ in the post-marketing setting. In rheumatoid arthritis most infusion-related events reported in clinical trials were mild to moderate in severity.~~In this patient population, infusion-related events reported in clinical trials were mild to moderate in severity~~. The most common symptoms were allergic reactions like headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia. In general, the proportion of patients experiencing any infusion reaction was higher following the first infusion than following the second infusion of any treatment course. The incidence of IRR decreased with subsequent courses (see section 4.8). The reactions reported were usually reversible with a reduction in rate, or interruption, of rituximab infusion and administration of an anti-pyretic, an antihistamine, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required. Closely monitor patients with pre-existing cardiac conditions and those who experienced prior cardiopulmonary adverse reactions. Depending on the severity of the IRR and the required interventions, temporarily or permanently discontinue Rixathon. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved.

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IRRs in patients with GPA, MPA and pemphigus vulgaris were consistent with those seen for rheumatoid arthritis patients in clinical trials and in the post-marketing setting (see section 4.8).

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Hepatitis B Infections

Cases of hepatitis B reactivation, including those with a fatal outcome, have been reported in rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis and other patients receiving rituximab.

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Patients treated with Rixathon may receive non-live vaccinations. However, response rates to non-live vaccines may be reduced. In a randomised trial, patients with rheumatoid arthritis treated with rituximab and methotrexate had comparable response rates to tetanus recall antigen (39% vs. 42%), reduced rates to pneumococcal polysaccharide vaccine (43% vs. 82% to at least 2 pneumococcal antibody serotypes), and KLH neoantigen (47% vs. 93%), when given 6 months after rituximab as compared to patients only receiving methotrexate. Should non-live vaccinations be required whilst receiving rituximab therapy, these should be completed at least 4 weeks prior to commencing the next course of rituximab. ~~Should non-live vaccinations be required whilst receiving rituximab therapy, these should be completed at least 4 weeks prior to commencing the next course of rituximab.~~

In the overall experience of rituximab repeat treatment over one year in rheumatoid arthritis, the proportions of patients with positive antibody titers against S. pneumoniae, influenza, mumps, rubella, varicella and tetanus toxoid were generally similar to the proportions at baseline.

Concomitant/sequential use of other DMARDs in rheumatoid arthritis
The concomitant use of Rixathon and anti-rheumatic therapies other than those specified under the rheumatoid arthritis indication and posology is not recommended.
There are limited data from clinical trials to fully assess the safety of the sequential use of other DMARDs (including TNF inhibitors and other biologics) following rituximab (see section 4.5). The available data indicate that the rate of clinically relevant infection is unchanged when such therapies are used in patients previously treated with rituximab, however patients should be closely observed for signs of infection if biologic agents and/or DMARDs are used following rituximab therapy.

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4.5 Interaction with other medicinal products and other forms of interaction

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Co-administration with methotrexate had no effect on the pharmacokinetics of rituximab in rheumatoid arthritis patients.

Patients with human anti-mouse antibody (HAMA) or anti-drug antibody (ADA) titres may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.

In patients with rheumatoid arthritis, 283 patients received subsequent therapy with a biologic DMARD following rituximab. In these patients the rate of clinically relevant infection while on rituximab was 6.01 per 100 patient years compared to 4.97 per 100 patient years following treatment with the biologic DMARD.

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4.8 Undesirable effects

...Experience from rheumatoid arthritis

Summary of the safety profile

The overall safety profile of rituximab in rheumatoid arthritis is based on data from patients from clinical trials and from post-marketing surveillance.

The safety profile of rituximab in patients with moderate to severe rheumatoid arthritis (RA) is summarised in the sections below. In clinical trials more than 3100 patients received at least one treatment course and were followed for periods ranging from 6 months to over 5 years; approximately 2400 patients received two or more courses of treatment with over 1000 having received 5 or more courses. The safety information collected during post marketing experience reflects the expected adverse reaction profile as seen in clinical trials for rituximab(see section 4.4).

Patients received 2 x 1000 mg of rituximab separated by an interval of two weeks; in addition to methotrexate (10-25 mg/week). Rituximab infusions were administered after an intravenous infusion of 100 mg methylprednisolone; patients also received treatment with oral prednisone for 15 days.

Tabulated list of adverse reactions

Adverse reactions are listed in Table 2. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥ 1/10,000 to < 1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The most frequent adverse reactions considered due to receipt of rituximab were IRRs. The overall incidence of IRRs in clinical trials was 23% with the first infusion and decreased with subsequent infusions. Serious IRRs were uncommon (0.5% of patients) and were predominantly seen during the initial course. In addition to adverse reactions seen in RA clinical trials for rituximab, progressive multifocal leukoencephalopathy (PML) (see section

4.4) and serum sickness-like reaction have been reported during post marketing experience.

Table 2 Summary of adverse reactions reported in clinical trials or during postmarketing surveillance occurring in patients with rheumatoid arthritis receiving rituximab

MedDRA System Organ Class	Very Common	Common	Uncommon	Rare	Very rare	Not known
Infections and Infestations	upper respiratory tract infection, urinary tract infections	Bronchitis, sinusitis, gastroenteritis, tinea pedis			PML, reactivation of hepatitis B	serious viral infection[1] enterovirai[1] meningoencephalitis[2]
Blood and lymphatic system disorders		neutropenia[2]		late neutropenia[3]	Serum sickness-like reaction	
Immune System Disorders	[4]Infusion related reactions (hypertension, nausea, rash, pyrexia, pruritus, urticaria, throat irritation, hot flush, hypotension, rhinitis, rigors, tachycardia, fatigue, oropharyngeal pain, peripheral oedema, erythema)		[4]Infusion related reactions (generalized oedema, bronchospasm, wheezing, laryngeal oedema, angioneurotic oedema, generalized pruritus, anaphylaxis, anaphylactoid reaction)			
General disorders and administration site conditions						
Metabolism and nutrition Disorders		hypercholesterolemia				
Psychiatric disorders		depression, anxiety				
Nervous System disorders	headache	paraesthesia, migraine, dizziness, sciatica				

MedDRA System Organ Class	Very Common	Common	Uncommon	Rare	Very rare	Not known
Cardiac disorders				angina pectoris, atrial fibrillation, heart failure, myocardial infarction	atrial flutter	
Gastrointestinal Disorders		Dyspepsia, diarrhoea, gastro-oesophageal reflux, mouth ulceration, upper abdominal pain				
Skin and Subcutaneous Tissue Disorders		alopecia			Toxic Epidermal Necrolysis (Lyell's syndrome), Stevens-Johnson syndrome[6]	
Musculo skeletal disorders and connective tissue disorders		arthralgia / musculoskeletal pain, osteoarthritis, bursitis				
Investigations	decreased IgM levels[5]	decreased IgG levels[5]				

[1] See also section infections below.
[2] Frequency category derived from laboratory values collected as part of routine laboratory monitoring in clinical trials
[3] Frequency category derived from post-marketing data.
[4]Reactions occurring during or within 24 hours of infusion. See also infusion-related reactions below. IRRs may occur as a result of hypersensitivity and/or to the mechanism of action.
[5]Includes observations collected as part of routine laboratory monitoring.
[6]Includes fatal cases

Multiple courses

Multiple courses of treatment are associated with a similar ADR profile to that observed following first exposure. The rate of all ADRs following first rituximab exposure was highest during the first 6 months and declined thereafter. This is mostly accounted for by IRRs (most frequent during the first treatment course), RA exacerbation and infections, all of which were more frequent in the first 6 months of treatment.

Description of selected adverse reactions Infusion-related reactions

The most frequent ADRs following receipt of rituximab in clinical studies were IRRs (refer to Table 2). Among the 3189 patients treated with rituximab, 1135 (36%) experienced at least one IRR with 733/3189 (23%) of patients experiencing an IRR following first infusion of the first exposure to rituximab. The incidence of IRRs declined with subsequent infusions. In clinical trials fewer than 1% (17/3189) of patients experienced a serious IRR. There were no CTC Grade 4 IRRs and no deaths due to IRRs in the clinical trials. The proportion of CTC Grade 3 events and of IRRs leading to withdrawal decreased by course and were rare from course 3 onwards. Premedication with intravenous glucocorticoid significantly reduced the incidence and severity of IRRs (see sections 4.2 and 4.4).
Severe IRRs with fatal outcome have been reported in the post-marketing setting.

In a trial designed to evaluate the safety of a more rapid rituximab infusion in patients with rheumatoid arthritis, patients with moderate-to-severe active RA who did not experience a serious IRR during or within 24 hours of their first studied infusion were allowed to receive a 2-hour intravenous infusion of rituximab. Patients with a history of a serious infusion reaction to a biologic therapy for RA were excluded from entry. The incidence, types and severity of IRRs were consistent with that observed historically. No serious IRRs were observed.

Infections

The overall rate of infection reported from clinical trials was approximately 94 per 100 patient years in rituximab treated patients. The infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections and urinary tract infections. The incidence of infections that were serious or required IV antibiotics was approximately 4 per 100 patient years. The rate of serious infections did not show any significant increase following multiple courses of rituximab. Lower respiratory tract infections (including pneumonia) have been reported during clinical trials, at a similar incidence in the rituximab arms compared to control arms.

In the post marketing setting, serious viral infections have been reported in RA patients treated with rituximab.

Cases of progressive multifocal leukoencephalopathy with fatal outcome have been reported following use of rituximab for the treatment of autoimmune diseases. This includes rheumatoid arthritis and off- label autoimmune diseases, including Systemic Lupus Erythematosus (SLE) and vasculitis.

In patients with non-Hodgkin's lymphoma receiving rituximab in combination with cytotoxic chemotherapy, cases of hepatitis B reactivation have been reported (see non-Hodgkin's lymphoma). Reactivation of hepatitis B infection has also been very rarely reported in RA patients receiving rituximab (see Section 4.4).

Cardiovascular adverse reactions

Serious cardiac reactions were reported at a rate of 1.3 per 100 patient years in the rituximab treated patients compared to 1.3 per 100 patient years in placebo treated patients. The proportions of patients experiencing cardiac reactions (all or serious) did not increase over multiple courses.

Neurologic events

Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognised risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.

Neutropenia

Events of neutropenia were observed with rituximab treatment, the majority of which were transient and mild or moderate in severity. Neutropenia can occur several months after the administration of rituximab (see section 4.4).

In placebo-controlled periods of clinical trials, 0.94% (13/1382) of rituximab treated patients and 0.27% (2/731) of placebo patients developed severe neutropenia.

Neutropenic events, including severe late onset and persistent neutropenia, have been rarely reported in the post-marketing setting, some of which were associated with fatal infections.

Skin and subcutaneous tissue disorders

Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported very rarely.

Laboratory abnormalities
Hypogammaglobulinaemia (IgG or IgM below the lower limit of normal) has been observed in RA patients treated with rituximab. There was no increased rate in overall infections or serious infections after the development of low IgG or IgM (see section 4.4).

A small number of spontaneous and literature cases of hypogammaglobulinaemia have been observed in paediatric patients treated with rituximab, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in paediatric patients are unknown.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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Peripheral B cell counts declined below normal following completion of the first dose of rituximab. In patients treated for haematological malignancies, B cell recovery began within 6 months of treatment and generally returned to normal levels within 12 months after completion of therapy, although in some patients this may take longer (up to a median recovery time of 23 months post-induction therapy). In rheumatoid arthritis patients, immediate depletion of B cells in the peripheral blood was observed following two infusions of 1000 mg rituximab separated by a 14 day interval. Peripheral blood B cell counts begin to increase from week 24 and evidence for repopulation is observed in the majority of patients by week 40, whether rituximab was administered as monotherapy or in combination with methotrexate. A small proportion of patients had prolonged peripheral B cell depletion lasting 2 years or more after their last dose of rituximab. In patients with granulomatosis with polyangiitis or microscopic polyangiitis, the number of peripheral blood B cells decreased to <10 cells/µL after two weekly infusions of rituximab 375 mg/m2, and remained at that level in most patients up to the 6 month timepoint. The majority of patients (81%) showed signs of B cell return, with counts >10 cells/µL by month 12, increasing to 87% of patients by month 18.
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Clinical experience in rheumatoid arthritis

The efficacy and safety of rituximab in alleviating the symptoms and signs of rheumatoid arthritis in patients with an inadequate response to TNF-inhibitors was demonstrated in a pivotal randomised, controlled, double-blind, multicenter trial (Trial 1).

Trial 1 evaluated 517 patients that had experienced an inadequate response or intolerance to one or more TNF inhibitor therapies. Eligible patients had active rheumatoid arthritis, diagnosed according to the criteria of the American College of Rheumatology (ACR). Rituximab was administered as two IV infusions separated by an interval of 15 days. Patients received 2 x 1000 mg intravenous infusions of rituximab or placebo in combination with

MTX. All patients received concomitant 60 mg oral prednisone on days 2-7 and 30 mg on days 8-14 following the first infusion. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24. Patients were followed beyond week 24 for long term endpoints, including radiographic assessment at 56 weeks and at 104 weeks. During this time, 81% of patients, from the original placebo group received rituximab between weeks 24 and 56, under an open label extension study protocol.

Trials of rituximab in patients with early arthritis (patients without prior methotrexate treatment and patients with an inadequate response to methotrexate, but not yet treated with TNF-alpha inhibitors) have met their primary endpoints. Rituximab is not indicated for these patients, since the safety data about long-term rituximab treatment are insufficient, in particular concerning the risk of development of malignancies and PML.

Disease activity outcomes

Rituximab in combination with methotrexate significantly increased the proportion of patients achieving at least a 20 % improvement in ACR score compared with patients treated with methotrexate alone (Table 12). Across all development studies the treatment benefit was similar in patients independent of age, gender, body surface area, race, number of prior treatments or disease status.

Clinically and statistically significant improvement was also noted on all individual components of the ACR response (tender and swollen joint counts, patient and physician global assessment, disability index scores (HAQ), pain assessment and C-Reactive Proteins (mg/dL).

Table 12 Clinical response outcomes at primary endpoint in Trial 1(ITT population)

	Outcome†	Placebo+MTX	rituximab+MTX (2 x 1000 mg)
Trial 1		N= 201	N= 298
	ACR20 ACR50 ACR70	36 (18%) 11 (5%) 3 (1%)	153 (51%)*** 80 (27%)*** 37 (12%)***
	EULAR Response (Good/Moderate)	44 (22%)	193 (65%)***
	Mean Change in DAS	-0.34	-1.83***

† Outcome at 24 weeks

Significant difference from placebo + MTX at the primary timepoint: ***p ≤ 0.0001

Patients treated with rituximab in combination with methotrexate had a significantly greater reduction in disease activity score (DAS28) than patients treated with methotrexate alone (Table 11). Similarly, a good to moderate European League Against Rheumatism (EULAR) response was achieved by significantly more rituximab treated patients treated with rituximab and methotrexate compared to patients treated with methotrexate alone (Table 12).

Radiographic response

Structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (mTSS) and its components, the erosion score and joint space narrowing score.

In Trial 1, conducted in patients with inadequate response or intolerance to one or more TNF

inhibitor therapies, receiving rituximab in combination with methotrexate demonstrated significantly less radiographic progression than patients originally receiving methotrexate alone at 56 weeks. Of the patients originally receiving methotrexate alone, 81 % received rituximab either as rescue between weeks 16-24 or in the extension trial, before week 56. A higher proportion of patients receiving the original rituximab /MTX treatment also had no erosive progression over 56 weeks (Table 13).

Table 13 Radiographic outcomes at 1 year (mITT population)

	Placebo+MTX	rituximab+MTX 2 × 1000 mg
Trial 1	(n = 184)	(n = 273)
Mean Change from Baseline:		
Modified Total Sharp score	2.30	1.01*
Erosion Score	1.32	0.60*
Joint Space narrowing score	0.98	0.41**
Proportion of patients with no radiographic change	46%	53%, NS
Proportion of patients with no erosive change	52%	60%, NS

150 patients originally randomised to placebo + MTX in Trial 1 received at least one course of RTX + MTX by one year

* p <0.05, ** p < 0.001. Abbreviation: NS, non significant

Inhibition of the rate of progressive joint damage was also observed long term. Radiographic analysis at 2 years in Trial 1 demonstrated significantly reduced progression of structural joint damage in patients receiving rituximab in combination with methotrexate compared to methotrexate alone as well as a significantly higher proportion of patients with no progression of joint damage over the 2 year period.

Physical function and quality of life outcomes

Significant reductions in disability index (HAQ-DI) and fatigue (FACIT-Fatigue) scores were observed in patients treated with rituximab compared to patients treated with methotrexate alone. The proportions of rituximab treated patients showing a minimal clinically important difference (MCID) in HAQ-DI (defined as an individual total score decrease of >0.22) was also higher than among patients receiving methotrexate alone (Table 14).

Significant improvement in health related quality of life was also demonstrated with significant improvement in both the physical health score (PHS) and mental health score (MHS) of the SF-36. Further, a significantly higher proportion of patients achieved MCIDs for these scores (Table 14).

Table 14 Physical function and quality of life outcomes at week 24 in Trial 1

Outcome†	Placebo+MTX	rituximab+MTX *(2 x 1000 mg)*
	n=201	n=298
Mean change in HAQ-DI	0.1	-0.4***

% HAQ-DI MCID	20%	51%
Mean change in FACIT-T	-0.5 n=197	-9.1*** n=294
Mean Change in SF-36 PHS	0.9	5.8***
% SF-36 PHS MCID	13%	48%***
Mean Change in SF-36 MHS	1.3	4.7**
% SF-36 MHS MCID	20%	38%*

† Outcome at 24 weeks

Significant difference from placebo at the primary time point: * p < 0.05, **p < 0.001 ***p ≤ 0.0001 MCID HAQ-DI ≥0.22, MCID SF-36 PHS >5.42, MCID SF-36 MHS >6.33

Efficacy in autoantibody (RF and or anti-CCP) seropositive patients

Patients seropositive to Rheumatoid Factor (RF) and/or anti- Cyclic Citrullinated Peptide (anti-CCP) who were treated with rituximab in combination with methotrexate showed an enhanced response compared to patients negative to both.

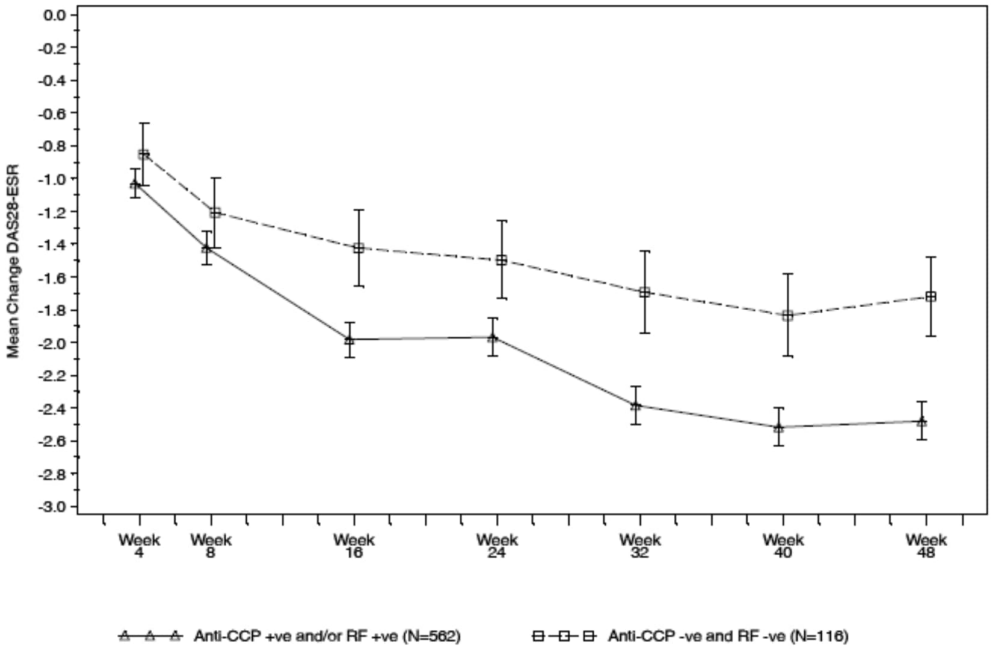
Efficacy outcomes in rituximab treated patients were analysed based on autoantibody status prior to commencing treatment. At Week 24, patients who were seropositive to RF and/or anti-CCP at baseline had a significantly increased probability of achieving ACR20 and 50 responses compared to seronegative patients (p=0.0312 and p=0.0096) (Table 15). These findings were replicated at Week 48, where autoantibody seropositivity also significantly increased the probability of achieving ACR70. At week 48 seropositive patients were 2-3 times more likely to achieve ACR responses compared to seronegative patients. Seropositive patients also had a significantly greater decrease in DAS28-ESR compared to seronegative patients (Figure 1).

Table 15 Summary of efficacy by baseline autoantibody status

	Week 24		**Week 48**	
	Seropositive (n=514)	**Seronegative (n=106)**	**Seropositive (n=506)**	**Seronegative (n=101)**
ACR20 (%)	62.3*	50.9	71. 1*	51.5
ACR50 (%)	32.7*	19.8	44.9**	22.8
ACR70 (%)	12.1	5.7	20.9*	6.9
EULAR Response (%)	74.8*	62.9	84.3*	72.3
Mean change DAS28-ESR	-1.97**	-1.50	-2.48***	-1.72

Significance levels were defined as * *p<0.05, **p<0.001, ***p<0.0001.*

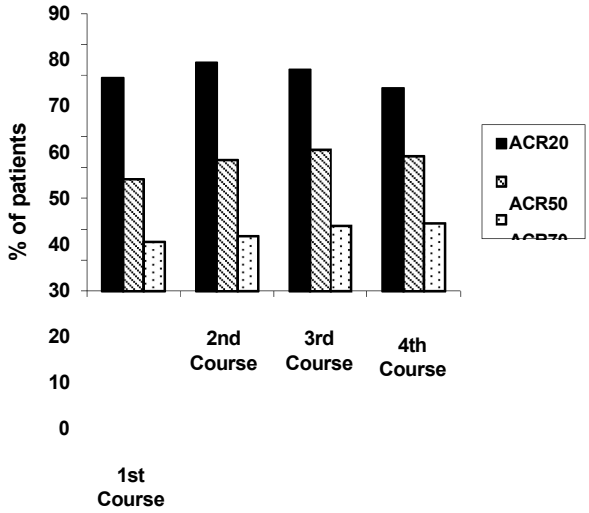
Figure 1: Change from baseline of DAS28-ESR by baseline autoantibody status



Long-term efficacy with multiple course therapy

Treatment with rituximab in combination with methotrexate over multiple courses resulted in sustained improvements in the clinical signs and symptoms of RA, as indicated by ACR, DAS28-ESR and EULAR responses which was evident in all patient populations studied (Figure 2). Sustained improvement in physical function as indicated by the HAQ-DI score and the proportion of patients achieving MCID for HAQ-DI were observed.

Figure 2: ACR responses for 4 treatment courses (24 weeks after each course (within patient, within visit) in patients with an inadequate response to TNF-inhibitors (n=146)



Clinical laboratory findings

A total of 392/3095 (12.7%) patients with rheumatoid arthritis tested positive for ADA in clinical studies following therapy with rituximab. The emergence of ADA was not associated with clinical deterioration or with an increased risk of reactions to subsequent infusions in the majority of patients. The presence of ADA may be associated with worsening of infusion or allergic reactions after the second infusion of subsequent courses.

Paediatric population

See Section 4.2 for information on paediatric use.

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Rheumatoid arthritis

Following two intravenous infusions of MabThera at a dose of 1000 mg, two weeks apart, the mean terminal half-life was 20.8 days (range, 8.58 to 35.9 days), mean systemic clearance was 0.23 L/day (range, 0.091 to 0.67 L/day), and mean steady-state distribution volume was 4.6 l (range, 1.7 to 7.51 L). Population pharmacokinetic analysis of the same data gave similar mean values for systemic clearance and half-life, 0.26 L/day and 20.4 days, respectively. Population pharmacokinetic analysis revealed that BSA and gender were the most significant covariates to explain inter-individual variability in pharmacokinetic parameters. After adjusting for BSA, male subjects had a larger volume of distribution and a faster clearance than female subjects. The gender- related pharmacokinetic differences are not considered to be clinically relevant and dose adjustment is not required. No pharmacokinetic data are available in patients with hepatic or renal impairment.

The pharmacokinetics of rituximab were assessed following two intravenous (IV) doses of 500 mg and 1000 mg on Days 1 and 15 in four studies. In all these studies, rituximab pharmacokinetics were dose proportional over the limited dose range studied. Mean Cmax for serum rituximab following first infusion ranged from 157 to 171 µg/mL for 2 x 500 mg dose and ranged from 298 to 341 µg/mL for 2x 1000 mg dose. Following second infusion, mean Cmax ranged from 183 to 198 µg/mL for the 2 × 500 mg dose and ranged from 355 to 404 µg/mL for the 2 × 1000 mg dose. Mean terminal elimination half-life ranged from 15 to 16 days for the 2 x 500 mg dose group and 17 to 21 days for the 2 × 1000 mg dose group. Mean Cmax was 16 to 19% higher following second infusion compared to the first infusion for both doses.

The pharmacokinetics of rituximab were assessed following two IV doses of 500 mg and 1000 mg upon re-treatment in the second course. Mean Cmax for serum rituximab following first infusion was 170 to 175 µg/mL for 2 x 500 mg dose and 317 to 370 µg/mL for 2 x 1000 mg dose. Cmax following second infusion, was 207 µg/mL for the 2 x 500 mg dose and ranged from 377 to 386 µg/mL for the 2x 1000 mg dose. Mean terminal elimination half-life after the second infusion, following the second course, was 19 days for 2 x 500 mg dose and ranged from 21 to 22 days for the 2 x 1000 mg dose.

PK parameters for rituximab were comparable over the two treatment courses. The pharmacokinetic (PK) parameters in the anti-TNF inadequate responder population, following the same dosage regimen (2 x 1000 mg, IV, 2 weeks apart), were similar with a mean maximum serum concentration of 369 µg/mL and a mean terminal half-life of 19.2 days.

Granulomatosis with polyangiitis and microscopic polyangiitis

Adult population

Based on the population pharmacokinetic analysis of data in 97 patients with granulomatosis with polyangiitis and microscopic polyangiitis who received 375 mg/m2 rituximab once weekly for four

doses, the estimated median terminal elimination half-life was 23 days (range, 9 to 49 days).

Rituximab mean clearance and volume of distribution were 0.313 L/day (range, 0.116 to 0.726 L/day)

and 4.50 L (range 2.25 to 7.39 L) respectively. Maximum concentration during the first 180 days

(Cmax), minimum concentration at Day 180 (C180) and Cumulative area under the curve over 180 days (AUC180) were (median [range]) 372.6 (252.3-533.5) µg/mL, 2.1 (0-29.3) µg/mL and 10302 (3653- 21874) µg/mL*days, respectively.

The PK parameters of rituximab in adult GPA and MPA patients appear similar to what has been observed in rheumatoid arthritis patients.

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