ינואר 2022

רופא/ה נכבד/ה,

רוקח/ת נכבד/ה,

חברת נוברטיס ישראל בע"מ מבקשת להודיעכם כי העלון לרופא של התכשיר Rixathon עודכן באופן הבא:.

- תוספת התוויה – Pemphigus Vulgaris:

*Pemphigus vulgaris (PV):

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

- שינוי בחיי המדף לאחר הוצאת התכשיר מהמקרר – ניתן לאחסן בטמפרטורה שאינה עולה על 30ºC למשך עד 7 ימים.

המרכיב הפעיל הינו: rituximab 10mg/ml

ההתוויות הרשומות לתכשיר בישראל הינן:

Rixathon is indicated for the following indications:

* Non-Hodgkin's lymphoma (NHL):

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.

* Chronic lymphocytic leukaemia (CLL):

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.

* Granulomatosis with polyangiitis and Microscopic polyangiitis:

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).

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 חטיבת סנדוז

נוברטיס ישראל בע"מ

השינויים בעלון לרופא:

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pemphigus vulgaris (PV)

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

4.2 Posology and method of administration

Premedication and prophylactic medications

Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome. For CLL patients whose lymphocyte counts are > 25 x 10^9/L it is recommended to administer prednisone/prednisolone 100 mg intravenous shortly before infusion with Rixathon to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

In patients with 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).

Pneumocystis jirovecii pneumonia (PJP) prophylaxis is recommended for patients with GPA/MPA or PV during and following Rixathon treatment, as appropriate according to local clinical practice guidelines.

Posology

Pemphigus vulgaris

The recommended dosage of Rixathon for the treatment of pemphigus vulgaris is 1000 mg

administered as an IV infusion followed two weeks later by a second 1000 mg IV infusion in combination with a tapering course of glucocorticoids.

Maintenance treatment

A maintenance infusion of 500 mg IV should be administered at month 12 and then every 6 months thereafter based on clinical evaluation.

Treatment of relapse

In the event of relapse, patients may receive 1000 mg IV. The healthcare provider should also consider resuming or increasing the patient's glucocorticoid dose based on clinical evaluation. Subsequent infusions may be administered no sooner than 16 weeks following the previous infusion

4.4 Special warnings and precautions for use

Malignancy

~~Immunomodulatory drugs may increase the risk of malignancy. On the basis of limited experience with rituximab in patients in the granulomatosis with polyangiitis and microscopic polyangiitis (see section 4.8) the present data do not seem to suggest any increased risk of malignancy. However, the possible risk for the development of solid tumours cannot be excluded at this time.~~

Immunomodulatory medicinal products may increase the risk of malignancy. However, available data do not suggest an increased risk of malignancy for rituximab used in autoimmune indications beyond the malignancy risk already associated with the underlying autoimmune condition.

4.6 Fertility, pregnancy and lactation

Breast-feeding

~~Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, and rituximab was detectable in milk from lactating monkeys, women should not breastfeed while treated with Rixathon and for 12 months following Rixathon treatment.~~

Limited data on rituximab excretion into breast milk suggest very low milk levels (relative infant dose less than 0.4%). Few cases of follow-up of breastfed infants describe normal growth and development up to 1.5 years. However, as these data are limited and the long-term outcomes of breastfed infants remain unknown, breastfeeding is not recommended while being treated with rituximab and optimally for 12 months following rituximab treatment.

4.7 Effects on ability to drive and use machines

~~Rituximab may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of rituximab (see section 4.8).~~

No studies on the effects of Rixathon on the ability to drive and use machines have been performed, although the pharmacological activity and adverse reactions reported to date suggest that Rixathon would have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Experience from granulomatosis (GPA) with polyangiitis and microscopic polyangiitis (MPA)

~~*Induction of remission*~~

~~Ninety-nine patients were treated for induction of remission of GPA and MPA in a clinical trial with rituximab (375 mg/m2, once weekly for 4 weeks) and glucocorticoids (see section 5.1).~~

Experience from granulomatosis (GPA) with polyangiitis and microscopic polyangiitis (MPA)
In the GPA/MPA study, 99 patients were treated with rituximab(375 mg/m2, once weekly for 4 weeks) and glucocorticoids (see section 5.1).

Description of selected adverse drug reactions

~~*Infusion related reactions*~~

~~In the clinical trial studying induction of remission with severe active GPA and MPA, IRRs were defined as any adverse event occurring within 24 hours of an infusion and considered to be infusion-related by investigators in the safety population. Of the ninety nine patients treated with rituximab, 12 (12%) experienced at least one IRR. All IRRs were CTC Grade 1 or 2. The most common IRRs included cytokine release syndrome, flushing, throat irritation, and tremor. Rituximab was given in combination with intravenous glucocorticoids which may reduce the incidence and severity of these events.~~

IRRs in the GPA and MPA clinical trial were defined as any adverse event occurring within 24 hours of an infusion and considered to be infusion-related by investigators in the safety population. Of the 99 patients treated with rituximab and 12% experienced at least one IRR. All IRRs were CTC Grade 1 or 2. The most common IRRs included cytokine release syndrome, flushing, throat irritation, and tremor. Rituximab was given in combination with intravenous glucocorticoids which may reduce the incidence and severity of these events.

Hypogammaglobulinaemia

~~Hypogammaglobulinaemia (IgA, IgG or IgM below the lower limit of normal) has been observed in granulomatosis with polyangiitis and microscopic polyangiitis patients treated with rituximab. The rate of overall infections and serious infections was not increased after the development of low IgA, IgG or IgM.~~

~~In the induction of remission clinical trial, at 6 months, in the rituximab group, 27%, 58% and 51% of patients with normal immunoglobulin levels at baseline, had low IgA, IgG and IgM levels, respectively compared to 25%, 50% and 46% in the cyclophosphamide group.~~

Hypogammaglobulinaemia (IgA, IgG or IgM below the lower limit of normal) has been observed in GPA and MPA patients treated with rituximab.
In GPA/MPA Study, at 6 months, in the rituximab group, 27%, 58% and 51% of patients with normal immunoglobulin levels at baseline, had low IgA, IgG and IgM levels, respectively compared to 25%, 50% and 46% in the cyclophosphamide group. The rate of overall infections and serious infections was not increased after the development of low IgA, IgG or IgM.

Neutropenia

~~In the induction of remission clinical trial, 24% of patients in the rituximab group (single course) and 23% of patients in the cyclophosphamide group developed CTC grade 3 or greater neutropenia. Neutropenia was not associated with an observed increase in serious infection in rituximab-treated patients.~~

In GPA/MPA Study, 24% of patients in the rituximab group (single course) and 23% of patients in the cyclophosphamide group developed CTC grade 3 or greater neutropenia. Neutropenia was not associated with an observed increase in serious infection in rituximab-treated patients. The effect of multiple rituximab courses on the development of neutropenia in GPA and MPA patients has not been studied in clinical trials.

Experience from pemphigus vulgaris

Summary of the safety profile in PV Study 1 (Study ML22196) and PV Study 2 (Study WA29330)

The safety profile of rituximab in combination with short-term, low-dose glucocorticoids in the treatment of patients with pemphigus vulgaris was studied in a Phase 3, randomised, controlled, multicenter, open-label study in pemphigus patients that included 38 pemphigus vulgaris (PV) patients randomised to the rituximab group (PV Study 1). Patients randomised to the rituximab group received an initial 1000 mg IV on Study Day 1 and a second 1000 mg IV on Study Day 15. Maintenance doses of 500 mg IV were administered at months 12 and 18. Patients could receive 1000 mg IV at the time of relapse (see section 5.1).

In PV Study 2, a randomized, double-blind, double-dummy, active-comparator, multicenter study evaluating the efficacy and safety of rituximab compared with mycophenolate mofetil (MMF) in patients with moderate-to-severe PV requiring oral corticosteroids, 67 PV patients received treatment with rituximab (initial 1000 mg IV on Study Day 1 and a second 1000 mg IV on Study Day 15 repeated at Weeks 24 and 26) for up to 52 weeks (see section 5.1).

The safety profile of rituximab in PV was consistent with the established safety profile in other approved autoimmune indications.

Tabulated list of adverse reactions for PV Studies 1 and 2

Adverse reactions from PV Studies 1 and 2 are presented in Table 3. In PV Study 1, ADRs were defined as adverse events which occurred at a rate of ≥ 5% among rituximab-treated PV patients, with a ≥ 2% absolute difference in incidence between the rituximab-treated group and the standard-dose prednisone group up to month 24. No patients were withdrawn due to ADRs in Study 1. In PV Study 2, ADRs were defined as adverse events occurring in ≥ 5% of patients in the rituximab arm and assessed as related.

Table 3 Adverse reactions in rituximab-treated pemphigus vulgaris patients in PV Study 1 (up to month 24) and PV Study 2 (up to Week 52)

MedDRA System Organ Class	Very Common	Common
Infections and infestations	Upper respiratory tract infection	Herpes virus infection Herpes zoster Oral herpes Conjunctivitis Nasopharyngitis Oral candidiasis Urinary tract infection
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)		Skin papilloma
Psychiatric disorders	Persistent depressive disorder	Major depression Irritability
Nervous system disorders	Headache	Dizziness
Cardiac disorders		Tachycardia
Gastrointestinal disorders		Abdominal pain upper
Skin and subcutaneous tissue disorders	Alopecia	Pruritus Urticaria Skin disorder
Musculoskeletal, connective tissue and bone disorders		Musculoskeletal pain Arthralgia Back pain

General disorders and administration site conditions		Fatigue Asthenia Pyrexia
Injury, Poisoning and Procedural Complications	Infusion-related reactions*	

*Infusion-related reactions for PV Study 1 included symptoms collected on the next scheduled visit after each infusion and adverse events occurring on the day of or one day after the infusion. The most common infusion-related reaction symptoms/Preferred Terms for PV Study 1 included headaches, chills, high blood pressure, nausea, asthenia and pain.

The most common infusion-related reaction symptoms/Preferred Terms for PV Study 2 were dyspnoea, erythema, hyperhidrosis, flushing/hot flush, hypotension/low blood pressure and rash/rash pruritic.

Description of selected adverse reactions

Infusion-related reactions

In PV Study 1, infusion-related reactions were common (58%). Nearly all infusion-related reactions were mild to moderate. The proportion of patients experiencing an infusion- related reaction was 29% (11 patients), 40% (15 patients), 13% (5 patients), and 10% (4 patients) following the first, second, third, and fourth infusions, respectively. No patients were withdrawn from treatment due to infusion-related reactions. Symptoms of infusion-related reactions were similar in type and severity to those seen in RA and GPA/MPA patients.

In PV Study 2, IRRs occurred primarily at the first infusion and the frequency of IRRs decreased with subsequent infusions: 17.9%, 4.5%, 3% and 3% of patients experienced IRRs at the first, second, third, and fourth infusions, respectively. In 11/15 patients who experienced at least one IRR, the IRRs were Grade 1 or 2. In 4/15 patients, Grade ≥ 3 IRRs were reported and led to discontinuation of rituximab treatment; three of the four patients experienced serious (life-threatening) IRRs. Serious IRRs occurred at the first (2 patients) or second (1 patient) infusion and resolved with symptomatic treatment.

Infections

In PV Study 1, 14 (37%) in the rituximab group experienced treatment-related infections compared to 15 patients (42%) in the standard-dose prednisone group. The most common infections in the rituximab group were herpes simplex and zoster infections, bronchitis, urinary tract infection, fungal infection and conjunctivitis. Three patients (8%) in the rituximab group experienced a total of 5 serious infections (Pneumocystis jirovecii pneumonia, infective thrombosis, intervertebral discitis, lung infection, Staphylococcal sepsis) and one patient (3%) in the standard-dose prednisone group experienced a serious infection (Pneumocystis jirovecii pneumonia).

In PV Study 2, 42 patients (62.7%) in the rituximab arm experienced infections. The most common infections in the rituximab group were upper respiratory tract infection, nasopharyngitis, oral candidiasis and urinary tract infection. Six patients (9%) in the rituximab arm experienced serious infections.

Laboratory abnormalities

In PV Study 2, in the rituximab arm, transient decreases in lymphocyte count, driven by decreases in the peripheral T-cell populations, as well as a transient decrease in phosphorus level were very commonly observed post-infusion. These were considered to be induced by IV methylprednisolone premedication infusion.

In PV Study 2, low IgG levels were commonly observed and low IgM levels were very commonly observed; however, there was no evidence of an increased risk of serious infections after the

development of low IgG or IgM.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Clinical experience in pemphigus vulgaris

PV Study 1 (Study ML22196)
The efficacy and safety of rituximab in combination with short-term, low-dose glucocorticoid (prednisone) therapy were evaluated in newly diagnosed patients with moderate to severe pemphigus (74 pemphigus vulgaris [PV] and 16 pemphigus foliaceus [PF]) in this randomised, open-label, controlled, multicenter study. Patients were between 19 and 79 years of age and had not received prior
therapies for pemphigus. In the PV population, 5 (13%) patients in the rituximab group and 3 (8%) patients in the standard prednisone group had moderate disease and 33 (87%) patients in the rituximab group and 33 (92%) patients in the standard-dose prednisone group had severe disease according to disease severity defined by Harman's criteria.

Patients were stratified by baseline disease severity (moderate or severe) and randomised 1:1 to receive either rituximab and low-dose prednisone or standard-dose prednisone. Patients randomised to the rituximab group received an initial intravenous infusion of 1000 mg rituximab on Study Day 1 in combination with 0.5 mg/kg/day oral prednisone tapered off over 3 months if they had moderate disease or 1 mg/kg/day oral prednisone tapered off over 6 months if they had severe disease, and a second intravenous infusion of 1000 mg on Study Day 15. Maintenance infusions of rituximab 500 mg were administered at months 12 and 18. Patients randomised to the standard-dose prednisone group received an initial 1 mg/kg/day oral prednisone tapered off over 12 months if they had moderate disease or 1.5 mg/kg/day oral prednisone tapered off over 18 months if they had severe disease. Patients in the rituximab group who relapsed could receive an additional infusion of rituximab 1000 mg in combination with reintroduced or escalated prednisone dose. Maintenance and relapse infusions were administered no sooner than 16 weeks following the previous infusion.

The primary objective for the study was complete remission (complete epithelialisation and absence of new and/or established lesions) at month 24 without the use of prednisone therapy for two months or more (CRoff for ≥2 months).

PV Study 1 Results
The study showed statistically significant results of rituximab and low-dose prednisone over standard-dose prednisone in achieving CRoff ≥2 months at month 24 in PV patients (see Table 12).

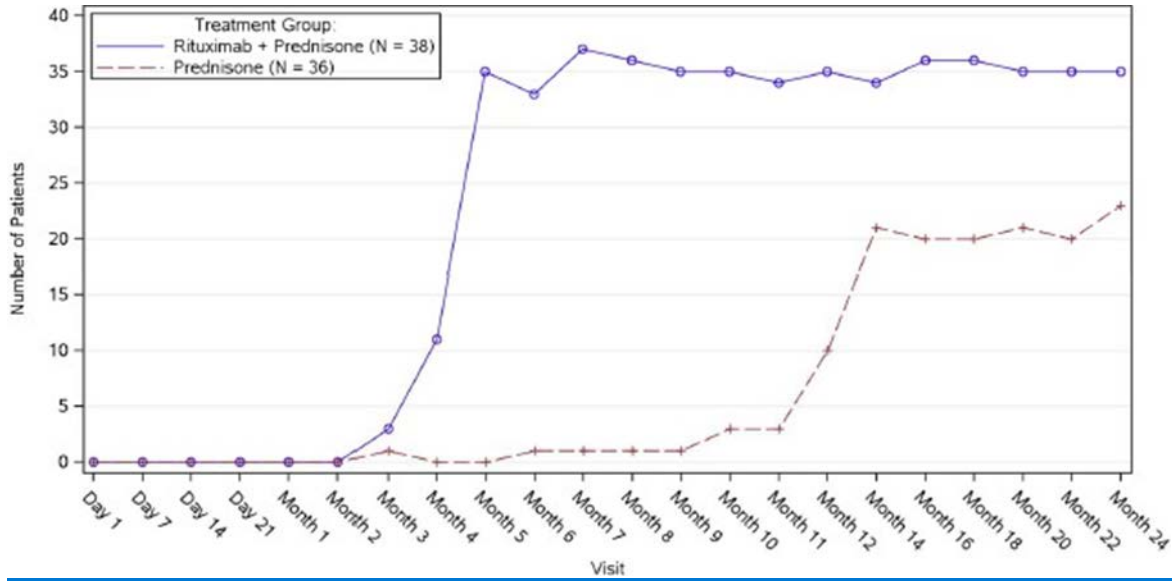
Table 12 Percentage of PV patients who achieved complete remission off corticosteroid therapy for two months or more at month 24 (Intent-to-Treat Population - PV)

	Rituximab + Prednisone N=38	Prednisone N=36	p-value [a]	95% CI [b]
Number of responders (response rate [%])	34 (89.5%)	10 (27.8%)	<0.0001	61.7% (38.4, 76.5)

[a] p-value is from Fisher's exact test with mid-p correction
[b] 95% confidence interval is corrected Newcombe interval

The number of rituximab plus low-dose prednisone patients off prednisone therapy or on minimal therapy (prednisone dose of 10 mg or less per day) compared to standard-dose prednisone patients over the 24-month treatment period shows a steroid-sparing effect of rituximab (Figure 4).

Figure 4: Number of patients who were off or on minimal corticosteroid (≤10mg/day) therapy over time



Post-hoc retrospective laboratory evaluation

A total of 19/34 (56%) patients with PV, who were treated with rituximab, tested positive for ADA antibodies by 18 months. The clinical relevance of ADA formation in rituximab -treated PV patients is unclear.

PV Study 2 (StudyWA29330)

In a randomized, double-blind, double-dummy, active-comparator, multicenter study, the efficacy and safety of rituximab compared with mycophenolate mofetil (MMF) were evaluated in patients with moderate-to-severe PV receiving 60-120 mg/day oral prednisone or equivalent (1.0-1.5 mg/kg/day) at study entry and tapered to reach a dose of 60 or 80 mg/day by Day 1. Patients had a confirmed diagnosis of PV within the previous 24 months and evidence of moderate-to-severe disease (defined as a total Pemphigus Disease Area Index, PDAI, activity score of ≥ 15).

One hundred and thirty-five patients were randomized to treatment with rituximab 1000 mg administered on Day 1, Day 15, Week 24 and Week 26 or oral MMF 2 g/day for 52 weeks in combination with 60 or 80 mg oral prednisone with the aim of tapering to 0 mg/day prednisone by Week 24.

The primary efficacy objective for this study was to evaluate at week 52, the efficacy of rituximab compared with MMF in achieving sustained complete remission defined as achieving healing of lesions with no new active lesions (i.e., PDAI activity score of 0) while on 0 mg/day prednisone or equivalent, and maintaining this response for at least 16 consecutive weeks, during the 52-week treatment period.

PV Study 2 Results

The study demonstrated the superiority of rituximab over MMF in combination with a tapering course of oral corticosteroids in achieving CRoff corticosteroid ≥ 16 weeks at Week 52 in PV patients (Table 13).The majority of patients in the mITT population were newly diagnosed (74%) and 26% of patients had established disease (duration of illness ≥ 6 months and received prior treatment for PV).

Table 13 Percentage of PV Patients Who Achieved Sustained Complete Remission Off Corticosteroid Therapy for 16 Weeks or More at Week 52 (Modified Intent-to-Treat Population)

	Rituximab (N=62)	MMF (N=63)	Difference (95% CI)	p-value
Number of responders (response rate [%])	25 (40.3%)	6 (9.5%)	30.80% (14.70%, 45.15%)	<0.0001
Newly diagnosed patients	19 (39.6%)	4 (9.1%)		
Patients with established disease	6 (42.9%)	2 (10.5%)		

MMF = Mycophenolate mofetil. CI = Confidence Interval.
Newly diagnosed patients = duration of illness < 6 months or no prior treatment for PV.
Patients with established disease = duration of illness ≥ 6 months and received prior treatment for PV.
Cochran-Mantel-Haenszel test is used for p-value.

The analysis of all secondary parameters (including cumulative oral corticosteroid dose, the total number of disease flares, and change in health-related quality of life, as measured by the Dermatology Life Quality Index) verified the statistically significant results of rituximab compared to MMF. Testing of secondary endpoints were controlled for multiplicity.

Glucocorticoid exposure
The cumulative oral corticosteroid dose was significantly lower in patients treated with rituximab. The median (min, max) cumulative prednisone dose at Week 52 was 2775 mg (450, 22180) in the rituximab group compared to 4005 mg (900, 19920) in the MMF group (p=0.0005).

Disease flare
The total number of disease flares was significantly lower in patients treated with rituximab compared to MMF (6 vs. 44, p<0.0001) and there were fewer patients who had at least one disease flare (8.1% vs. 41.3%).

Laboratory evaluations
By week 52, a total of 20/63 (31.7%) (19 treatment-induced and 1 treatment-enhanced) rituximab - treated PV patients tested positive for ADA. There was no apparent negative impact of the presence of ADA on safety or efficacy in PV Study 2.

5.2 Pharmacokinetic properties

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.

Pemphigus vulgaris
The PK parameters in adult PV patients receiving rixathon 1000 mg at Days 1, 15, 168, and 182 are summarized in Table 14.

Table 14 Population PK in adult PV patients from PV Study 2

Parameter	Infusion Cycle	
	1st cycle of 1000 mg Day 1 and Day 15 N=67	2nd cycle of 1000 mg Day 168 and Day 182 N=67
Terminal Half-life (days)		
Median	21.0	26.5
(Range)	(9.3-36.2)	(16.4-42.8)
Clearance (L/day)		
Mean	391	247
(Range)	(159-1510)	(128-454)
Central Volume of Distribution (L)		
Mean	3.52	3.52
(Range)	(2.48-5.22)	(2.48-5.22)

Following the first two rituximab administrations (at day 1 and 15, corresponding to cycle 1), the PK parameters of rituximab in patients with PV were similar to those in patients with GPA/MPA and patients with RA. Following the last two administrations (at day 168 and 182, corresponding to cycle 2), rituximab clearance decreased while the central volume of distribution remained unchanged.

~~Based on the population pharmacokinetic analysis of data in 97 patients with granulomatosis with polyangiitis and microscopic polyangiitis who received 375 mg/m^2 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.~~

6. PHARMACEUTICAL PARTICULARS

6.3 Shelf life

Rixathon may be stored at temperatures up to a maximum of 30°C for a single period of up to 7 days, but not exceeding the original expiry date. The new expiry date must be written on the carton. Upon removal from refrigerated storage, Rixathon must not be returned to refrigerated storage.