נובמבר 2022

RIXATHON®
rituximab

רופא/ה נכבד/ה,

רוקח/ת נכבד/ה,

חברת נוברטיס 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>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).

<u>*Pemphigus vulgaris (PV):</u>

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 חטיבת סנדוז

נוברטיס ישראל בע"מ

השינויים בעלון לרופא:

4.6 Fertility, pregnancy and lactation

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Breast-feeding

Limited data on rituximab excretion into breast milk suggest very low rituximab concentration in milk~~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~~2 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~~ 6 ~~months following rituximab treatment.~~

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4.8 Undesirable effects

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

Induction of remission (GPA/MPA Study 1)

In the GPA/MPA study 1, 99 patients were treated for induction of remission of GPA and MPA with rituximab (375 mg/m2, once weekly for 4 weeks) and glucocorticoids (see section 5.1).

The ADRs listed in Table 2 were all adverse events which occurred at an incidence of ≥ 5% in the rituximab group and at a higher frequency than the comparator group.

Table 2 Adverse reactions occurring at 6- months in ≥ 5% of patients receiving rituximab ~~for induction of remission of~~ in GPA ~~and~~ / MPA Study 1 (Rituximab n=99 ~~, and~~ at a higher frequency than the comparator group), or during postmarketing surveillance.

MedDRA System organ class ~~Body System~~ **Adverse reaction**	~~Rituximab~~ **Frequency~~(n=99)~~**
Infections and infestations	
Urinary tract infection	7%
Bronchitis	5%
Herpes zoster	5%
Nasopharyngitis	5%
Serious viral infection[1]	not known
Blood and lymphatic system disorders	
Thrombocytopenia	7%

MedDRA System organ class ~~Body System~~ **Adverse reaction**	~~Rituximab~~ **Frequency~~(n=99)~~**
Immune system disorders	
Cytokine release syndrome	5%
Metabolism and nutrition disorders	
Hyperkalaemia	5%
Psychiatric disorders	
Insomnia	14%
Nervous system disorders	
Dizziness	10%
Tremor	10%
Vascular disorders	
Hypertension	12%
Flushing	5%
Respiratory, thoracic and mediastinal disorders	
Cough	12%
Dyspnoea	11%
Epistaxis	11%
Nasal congestion	6%
Gastrointestinal disorders	
Diarrhoea	18%
Dyspepsia	6%
Constipation	5%
Skin and subcutaneous tissue disorders	
Acne	7%
Musculoskeletal and connective tissue disorders	
Muscle spasms	18%
Arthralgia	15%
Back pain	10%
Muscle weakness	5%
Musculoskeletal pain	5%
Pain in extremities	5%
General disorders and administration site conditions	
Peripheral oedema	16%
Investigations	
Decreased haemoglobin	6%

[1] Observed during post-marketing surveillance. See also section infections below.

Maintenance treatment (GPA/PA Study2)

In GPA/MPA Study 2 ~~a further clinical study~~, a total of 57 severe, active GPA and MPA ~~patients in disease remission~~ were treated with rituximab for the maintenance of remission (see section 5.1).

Table 3 Adverse ~~drug~~ reactions occurring in ≥ 5% of patients receiving rituximab ~~for maintenance treatment of GPA and MPA~~ in GPA/MPA Study 2 (Rituximab n=57), and at a higher frequency than the comparator group, or during postmarketing surveillance.

MedDRA System Organ Class Adverse ~~drug~~ reaction	~~Rituximab~~ ~~(n=57)~~Frequency
Infections and infestations	
Bronchitis	14%
Rhinitis	5%
Serious viral infection[1]	not known
General disorders and administration site conditions	
Pyrexia	9%
Influenza-like illness	5%
Oedema peripheral	5%
Gastrointestinal disorders	
Diarrhoea	7%
Respiratory, thoracic and mediastinal disorders	
Dyspnoea	9%
Injury, poisoning and procedural complications	
Infusion-related ~~reactions~~[1]reactions[2]	12%
[1]Observed during post-marketing surveillance. See also section infections below. [2]Details on infusion related reactions are provided in the description of selected adverse drug reactions section.	

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Long-term follow-up (GPA/MPA Study 3)

In a long-term observational safety study, 97 GPA and ~~/~~MPA patients received treatment with rituximab (mean of 8 infusions [range 1-28]) for up to 4 years, according to their physician's standard practice and discretion. The overall safety profile was consistent with the well-established safety profile of rituximab in GPA~~/~~ and MPA and no new adverse drug reactions were reported.

Description of selected adverse drug reactions

Infusion related reactions

In GPA/MPA Study 1 (adult induction of remission study), 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 (~~-~~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.

In GPA/MPA Study 2 (adult maintenance study),~~In the maintenance therapy clinical trial,~~ 7/57 (12%) patients in the rituximab arm experienced at least one infusion-related reaction. The incidence of IRR symptoms was highest during or after the first infusion (9%) and decreased with subsequent infusions (<4%). All IRR symptoms were mild or moderate and most of them were reported from the SOCs Respiratory, Thoracic and Mediastinal Disorders and Skin and Subcutaneous Tissue disorders.

Infections

In GPA/MPA Study 1,~~In the 99 rituximab patients,~~ the overall rate of infection was approximately 237 per 100 patient years (95% CI 197 - 285) at the 6-month primary endpoint. Infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections, herpes zoster and urinary tract infections.

The rate of serious infections was approximately 25 per 100 patient years. The most frequently reported serious infection in the rituximab group was pneumonia at a frequency of 4%.

In GPA/MPA Study 2, 30/57 (53%) patients in the rituximab arm experienced infections. The incidence of all grade infections was similar between the arms. Infections were predominately mild to moderate. The most common infections in the rituximab arm included upper respiratory tract infections, gastroenteritis, urinary tract infections and herpes zoster. The incidence of serious infections was similar in both arms (approximately 12%). The most commonly reported serious infection in the rituximab group was mild or moderate bronchitis.

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

~~In the maintenance therapy clinical trial, 30/57 (53%) patients in the rituximab arm experienced infections. The incidence of all grade infections was similar between the arms. Infections were predominately mild to moderate. The most common infections in the rituximab arm included upper respiratory tract infections, gastroenteritis, urinary tract infections and herpes zoster. The incidence of serious infections was similar in both arms (approximately 12%). The most commonly reported serious infection in the rituximab group was mild or moderate bronchitis.~~

Malignancies

In GPA/MPA Study 1, ~~T~~the incidence of malignancy in rituximab treated patients in the granulomatosis with polyangiitis and microscopic polyangiitis clinical study was 2.00 per 100 patient years at the study common closing date (when the final patient had completed the follow-up period). On the basis of standardized incidence ratios, the incidence of malignancies appears to be similar to that previously reported in patients with ANCA-associated vasculitis.

Cardiovascular adverse reactions

In GPA/MPA Study 1, ~~In the clinical trial on induction of remission,~~ cardiac events occurred at a rate of approximately 273 per 100 patient years (95% CI 149 - 470) at the 6-month primary endpoint. The rate of serious cardiac events was 2.1 per 100 patient years (95% CI 3 - 15). The most frequently reported events were tachycardia (4%) and atrial fibrillation (3%) (see section 4.4).

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Hypogammaglobulinaemia

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In GPA/MPA Study 2, ~~In the maintenance therapy clinical trial,~~ no clinically meaningful differences between the two treatment arms or decreases in total immunoglobulin, IgG, IgM or IgA levels were observed throughout the trial.

Neutropenia

In GPA/MPA Study 1, 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.~~

In GPA/MPA Study 2, ~~In the maintenance therapy clinical trial,~~ the incidence of all-grade neutropenia was 0% for rituximab- treated patients vs 5% for azathioprine treated patients.

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Tabulated list of adverse reactions for PV Studies 1 and 2

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Table 4 Adverse reactions in rituximab-treated pemphigus vulgaris patients in PV Study 1 (up to month 24) and PV Study 2 (up to Week 52), or during post-marketing surveillance

MedDRA System Organ Class	Very Common	Common	Not known
Infections and infestations	Upper respiratory tract infection	Herpes virus infection Herpes zoster Oral herpes Conjunctivitis Nasopharyngitis Oral candidiasis Urinary tract infection	serious viral infection[1]
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*[2]		

*[1] Observed during post-marketing surveillance. See also section infections below.

[2] 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.

Description of selected adverse reactions

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Infections

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

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