אפריל 2020

RIXATHON®
rituximab

רופא/ה נכבד/ה,

רוקח/ת נכבד/ה,

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

מדובר בעדכוני בטיחות ועדכוני עריכה. כמו כן, ישנו שינוי בחיי המדף לאחר מיהול בתמיסת NaCl 0.9% בטמפרטורת החדר (≤ 25°C) ל – 24 שעות.

המרכיב הפעיל הינו: rituximab

<u>ההתוויה הרשומה לתכשיר בישראל הינה:</u>

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.

העלונים לרופא ולצרכן נשלחו 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:

4.8 Undesirable effects

Experience from granulomatosis with polyangiitis and microscopic polyangiitis

~~In the clinical trial in granulomatosis with polyangiitis and microscopic polyangitis, 99 patients were treated with rituximab (375 mg/m^2, once weekly for 4 weeks) and glucocorticoids (*see section 5.1*).~~

~~*Tabulated list of adverse reactions*~~

~~The ADRs listed in Table 2 were all adverse events which occurred at an incidence of ≥5% in the rituximab group.~~

Induction of remission

Ninety-nine patients were treated for induction of remission of GPA and MPA in a clinical trial with rituximab (375 mg/m^2, 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 Drug Reactions occurring at 6 months in ≥5% of patients receiving rituximab, and at a higher frequency than the comparator group, in the pivotal clinical study**

Body System **Adverse event**	**rituximab** **(n=99)**
Blood and lymphatic system disorders	
Thrombocytopenia	7%
Gastrointestinal disorders	
Diarrhoea	18%
Dyspepsia	6%
Constipation	5%
General disorders and administration site conditions	
Peripheral oedema	16%
Immune system disorders	
Cytokine release syndrome	5%
Infections and infestations	
Urinary tract infection	7%
Bronchitis	5%
Herpes zoster	5%
Nasopharyngitis	5%
Investigations	
Decreased haemoglobin	6%
Metabolism and nutrition disorders	
Hyperkalaemia	5%
Musculoskeletal and connective tissue disorders	
Muscle spasms	18%
Arthralgia	15%
Back pain	10%
Muscle weakness	5%
Musculoskeletal pain	5%
Pain in extremities	5%
Nervous system disorders	
Dizziness	10%
Tremor	10%
Psychiatric disorders	
Insomnia	14%
Respiratory, thoracic and mediastinal disorders	
Cough	12%
Dyspnoea	11%
Epistaxis	11%
Nasal congestion	6%

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~~Body System~~ ~~Adverse event~~	~~rituximab~~ ~~(n=99)~~
~~Skin and subcutaneous tissue disorders~~	
~~Acne~~	~~7%~~
~~Vascular disorders~~	
~~Hypertension~~	~~12%~~
~~Flushing~~	~~5%~~

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Adverse drug reactions occurring at 6-months in ≥ 5% of patients receiving rituximab for induction of remission of GPA and MPA, and at a higher frequency than the comparator group.

Body System **Adverse reaction**	**Rituximab** **(n=99)**
Infections and infestations	
Urinary tract infection	7%
Bronchitis	5%
Herpes zoster	5%
Nasopharyngitis	5%
Blood and lymphatic system disorders	
Thrombocytopenia	7%
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	

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Body System Adverse reaction	Rituximab (n=99)
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%

Maintenance treatment

In 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, and at a higher frequency than the comparator group

System Organ Class Adverse drug reaction[1]	Rituximab (n=57)
Infections and infestations	
Bronchitis	14%
Rhinitis	5%
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[2]	12%

[1] Events were considered ADRs only after thorough assessment and where a causal relationship between the medicinal product and the adverse event was at least a reasonable possibility.

[2]Details on infusion related reactions are provided in the description of selected adverse drug reactions section.

The overall safety profile was consistent with the well-established safety profile for rituximab in approved autoimmune indications, including GPA/MPA. Overall, 4% of patients in the rituximab arm experienced adverse events leading to discontinuation. Most adverse events in the rituximab arm were mild or moderate in intensity. No patients in the rituximab arm had fatal adverse events.

The most commonly reported events considered as ADRs were infusion-related reactions and infections.

In a long-term observational safety study, 97 GPA/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 ~~RA and~~ GPA/MPA and no new adverse drug reactions were reported.

Description of s~~S~~elected adverse drug reactions

~~*Infusion related reactions*~~

~~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. Ninety nine patients were 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.~~

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.

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 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 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

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

~~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).~~

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).

Neurologic events

Cases of posterior reversible encephalopathy syndrome (PRES)/reversible posterior leukoencephalopathy syndrome (RPLS) have been reported in autoimmune conditions. 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.

Hepatitis-B reactivation

A small number of cases of hepatitis-B reactivation, some with fatal outcome, have been reported in granulomatosis with polyangiitis and microscopic polyangiitis patients receiving rituximab in the post-marketing setting.

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. At 6 months, in the active-controlled, randomised, double-blind, multicenter, non-inferiority trial, 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. There was no increased rate in overall infections or serious infections in patients with low IgA, IgG or IgM.~~

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.

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 the active-controlled, randomised, double-blind, multicenter, non-inferiority trial of rituximab in granulomatosis with polyangiitis and microscopic polyangiitis, 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 granulomatosis with polyangiitis and microscopic polyangiitis patients has not been studied in clinical trials.~~

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 the maintenance therapy clinical trial, the incidence of all-grade neutropenia was 0% for rituximab-treated patients vs 5% for azathioprine treated patients.

6.3 Shelf life

Diluted solution

• After aseptic dilution in sodium chloride solution:

Chemical and physical stability of Rixathon diluted in 0.9% sodium chloride solution has been demonstrated for 30 days at 2°C - 8°C and subsequently ~~12~~ 24 hours at room temperature (≤ 25°C).