פברואר 2024

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:

Granulomatosis with polyangiitis and microscopic polyangiitis

The recommended dosage of Rixathon for induction of remission therapy of granulomatosis with polyangiitis and microscopic polyangiitis is 375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for 4 weeks (four infusions in total).

~~Pneumocystis jiroveci pneumonia (PCP) prophylaxis is recommended for patients with granulomatosis with polyangiitis or microscopic polyangiitis during and following Rixathon treatment, as appropriate.~~

…

4.4 Special warnings and precautions for use

…

Infections

…

Cases of enteroviral meningoencephalitis including fatalities have been reported following use of rituximab.

False negative serologic testing of infections

Due to the risk of false negative serologic testing of infections, alternative diagnostic tools should be considered in case of patients presenting with symptoms indicative of rare infectious disease e.g. West Nile virus and neuroborreliosis.

…

Granulomatosis with polyangiitis, microscopic polyangiitis and pemphigus vulgaris

Infusion related reactions

Rituximab is associated with infusion related reactions (IRRs), which may be related to release of cytokines and/or other chemical mediators. ~~Premedication consisting of an analgesic/anti-pyretic drug and an anti-histaminic drug, should always be administered before each infusion of Rixathon.~~

...

Immunisation

Physicians should review the patient's vaccination status and patients should, if possible, be brought up-to-date with all immunisations in agreement with current immunisation guidelines prior to initiating Rixathon therapy. Vaccination should be completed at least 4 weeks prior to first administration of Rixathon.

~~Physicians should review the patient's vaccination status and follow current immunisation guidelines prior to Rixathon therapy. Vaccination should be completed at least 4 weeks prior to first administration of Rixathon.~~

…

4.8 Undesirable effects

Table 1 ADRs reported in clinical trials or during post-marketing surveillance in patients with NHL and CLL disease treated with rituximab monotherapy/maintenance or in combination with chemotherapy

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations	bacterial infections, viral infections, +bronchitis	sepsis, +pneumonia, +febrile infection, +herpes zoster, +respiratory tract infection, fungal infections, infections of unknown aetiology, +acute bronchitis, +sinusitis, hepatitis B[1]		serious viral infection[2] Pneumocystis jirovecii	PML	enteroviral meningoencephalitis[2, 3]
Blood and lymphatic system disorders	neutropenia, leucopenia, +febrile neutropenia, +thrombocytopenia	anaemia, +pancytopenia, +granulocytopenia	coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy		transient increase in serum IgM levels[3]	late neutropenia[3]
Immune system disorders	infusion related reactions[4], angioedema	hypersensitivity		anaphylaxis	tumour lysis syndrome, cytokine release syndrome[4], serum sickness	infusion-related acute reversible thrombocytopenia[4]
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia				
Psychiatric disorders			depression, nervousness			
Nervous system disorders		paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	Dysgeusia		peripheral neuropathy, facial nerve palsy[5]	cranial neuropathy, loss of other senses[5]
Eye disorders		lacrimation disorder, conjunctivitis			severe vision loss[5]	
Ear and labyrinth disorders		tinnitus, ear pain				hearing loss[5]
Cardiac disorders		+myocardial infarction[4 and 6], arrhythmia, +atrial fibrillation, tachycardia, +cardiac disorder	+left ventricular failure, +supraventricular tachycardia, +ventricular tachycardia, +angina, +myocardial ischaemia, bradycardia	severe cardiac disorders[4 and 6]	heart failure[4 and 6]	

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Vascular disorders		hypertension, orthostatic hypotension, hypotension			vasculitis (predominately cutaneous), leukocytoclastic vasculitis	
Respiratory, thoracic and mediastinal disorders		Bronchospasm[4], respiratory disease, chest pain, dyspnoea, increased cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia	interstitial lung disease[7]	respiratory failure[4]	lung infiltration
Gastrointestinal disorders	nausea	vomiting, diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation	abdominal enlargement		gastro-intestinal perforation[7]	
Skin and subcutaneous tissue disorders	pruritus, rash, [+]alopecia	urticaria, sweating, night sweats, [+]skin disorder			severe bullous skin reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) [7]	
Musculoskeletal, connective tissue and bone disorders		hypertonia, myalgia, arthralgia, back pain, neck pain, pain				
Renal and urinary disorders					renal failure[4]	
General disorders and administration site conditions	fever, chills, asthenia, headache	tumour pain, flushing, malaise, cold syndrome, [+]fatigue, [+]shivering, [+]multi-organ failure[4]	infusion site pain			
Investigations	decreased IgG levels					

For each term, the frequency count was based on reactions of all grades (from mild to severe), except for terms marked with "+" where the frequency count was based only on severe (≥grade 3 NCI common toxicity criteria) reactions. Only the highest frequency observed in the trials is reported

[1] includes reactivation and primary infections; frequency based on R-FC regimen in relapsed/refractory CLL

[2] see also section infection below

[3] observed during post-marketing surveillance

[34] see also section haematologic adverse reactions below

[5] see also section infusion related reactions below. Rarely fatal cases reported

[6] signs and symptoms of cranial neuropathy. Occurred at various times up to several months after completion of rituximab therapy

[7] observed mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and were mostly associated with infusion-related reactions

[8] includes fatal cases

…

Description of selected adverse reactions

Infections

Rituximab induces B-cell depletion in about 70-80% of patients but was associated with decreased serum immunoglobulins only in a minority of patients.

Localized candida infections as well as Herpes zoster were reported at a higher incidence in the

rituximab-containing arm of randomised studies. Severe infections were reported in about 4% of patients treated with rituximab monotherapy. Higher frequencies of infections overall, including grade 3 or 4 infections, were observed during rituximab maintenance treatment up to 2 years when compared to observation. There was no cumulative toxicity in terms of infections reported over a 2-year treatment period. In addition, other serious viral infections either new, reactivated or exacerbated, some of which were fatal, have been reported with rituximab treatment. The majority of patients had received rituximab in combination with chemotherapy or as part of a haematopoetic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (Cytomegalovirus, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (progressive multifocal leukoencephalopathy (PML))~~-~~, enterovirus (meningoencephalitis) and hepatitis C virus (see section 4.4). Cases of fatal PML that occurred after disease progression and retreatment have also been reported in clinical trials. Cases of hepatitis B reactivation, have been reported, the majority of which were in patients receiving rituximab in combination with cytotoxic chemotherapy. In patients with relapsed/refractory CLL, the incidence of grade 3/4 hepatitis B infection (reactivation and primary infection) was 2% in R-FC vs 0% FC. Progression of Kaposi's sarcoma has been observed in rituximab-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive.

…

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/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 reactions occurring at 6 months in ≥ 5% of patients receiving rituximab in GPA / MPA Study 1 (Rituximab n=99 at a higher frequency than the comparator group), or during post-marketing surveillance

MedDRA System organ class **Adverse reaction**	**Frequency**
Infections and infestations	
Urinary tract infection	7%
Bronchitis	5%
Herpes zoster	5%
Nasopharyngitis	5%
Serious viral infection[1]	not known
Enteroviral meningoencephalitis[1,2]	not known
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%

MedDRA System organ class **Adverse reaction**	**Frequency**
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.

2 See also infections below

Tabulated list of adverse reactions for PV Studies 1 and 2

Adverse reactions from PV Studies 1 and 2 are presented in Table 4. 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 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[1,2], Enteroviral meningoencephalitis[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[3,2]		

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

[2] see also section infections below

[3,2] 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.

...