מאי 2019

MabThera (rituximab) 10mg/ml IV

Concentrate for solution for intravenous infusion

רופא/ה יקר/ה, רוקח/ת יקר/ה,

חברת רוש פרמצבטיקה (ישראל) בע"מ מבקשת להודיעכם על רישום התוויה נוספת לתכשיר מבטרה 10מ"ג/מ"ל IV, לטיפול במבוגרים עם פמפיגוס וולגריס בדרגת מחלה בינונית או חמורה. נוסח ההתוויות המלא של התכשיר הינו כדלקמן:

ההתוויות הרשומות לתכשיר בישראל:

Non-Hodgkin's lymphoma (NHL)
MabThera is indicated for the treatment of patients with relapsed or refractory low-grade or follicular, B-cell non-hodgkin's lymphoma.
MabThera is indicated for the treatment of previously untreated patients with low-grade or follicular lymphoma in combination with chemotherapy
MabThera is indicated for the treatment of patients with CD20 positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP chemotherapy.
MabThera maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.

Chronic lymphocytic leukaemia (CLL)
MabThera 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 MabThera or patients refractory to previous MabThera plus chemotherapy.

Rheumatoid arthritis
MabThera 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.

Granulomatosis with polyangiitis and Microscopic polyangiitis
MabThera, 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

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

כפועל יוצא של עדכון ההתוויה נעשה עדכון בסעיפים שונים בעלון לרופא ובעלון לצרכן.
בהודעה זו מצוינים רק עדכונים מהותיים ועדכונים אשר מהווים החמרה.

הסבר:

טקסט עם קו תחתי מציין טקסט שהוסף לעלון.
~~טקסט עם קו חוצה~~ מציין טקסט שהוסר מן העלון.

למידע נוסף יש לעיין בעלון לרופא כפי שאושר ע"י משרד הבריאות.

העלון המעודכן נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלו מודפס על-ידי פנייה לבעל הרישום: רוש פרמצבטיקה (ישראל) בע"מ, ת.ד 6391 , הוד השרון 4524079 טלפון 09-9737777. כתובתנו באינטרנט: www.roche.co.il.

ב ב ר כ ה,

בתאור צפרי-חגג
מחלקת רישום

לילי אדר
רוקחת ממונה

עדכונים מהותיים בעלון לרופא

בסעיף 4.1 Therapeutic indications עודכן המידע הבא:

[…]
Pemphigus vulgaris

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

[…]

בסעיף .4.2 Posology and method of administration עודכן המידע הבא:

Premedication and prophylactic medications

[…]

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

[…]

Pneumocystis jirovecii pneumonia (PCP) prophylaxis is recommended for patients ~~with granulomatosis with polyangiitis or microscopic polyangiitis~~ with GPA/MPA or PV during and following MabThera treatment, as appropriate according to local clinical practice guidelines.

[…]

Pemphigus vulgaris

The recommended dosage of MabThera 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.

[…]

בסעיף 4.4 Special warnings and precautions for use עודכן המידע הבא:

Infusion related reactions
IRRs for patients with granulomatosis with polyangiitis ~~and~~ microscopic polyangiitis and pemphigus vulgaris were consistent with ~~similar to~~ those seen for rheumatoid arthritis patients in clinical trials

בסעיף 4.8 Undesirable effects עודכן המידע הבא:

Experience from pemphigus vulgaris

Summary of the safety profile

The safety profile of MabThera 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 MabThera group. Patients randomised to the MabThera 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).

The safety profile of MabThera in patients with PV was consistent with that observed in RA and GPA/MPA patients.

Tabulated list of adverse reactions

Adverse drug reactions presented in Table 4 were adverse events which occurred at a rate of ≥ 5% among MabThera-treated PV patients, with a ≥ 2% absolute difference in incidence between the MabThera-treated group and the standard-dose prednisone group up to month 24. No patients were withdrawn due to ADRs.

Table 4 Adverse drugs reactions for MabThera-treated pemphigus vulgaris patients in the clinical study up to month 24

System Organ Class Adverse drug reaction	**MabThera + low-dose prednisone (n = 38)**
Injury, Poisoning and Procedural Complications	
Infusion-related reactions*	58%
Skin and Subcutaneous Tissue Disorders	
Alopecia	13%
Pruritus	5%
Urticaria	5%
Skin disorder	5%
Psychiatric Disorders	
Persistent depressive disorder	13%
Major depression	5%
Irritability	5%
Infections and Infestations	
Herpes virus infection	8%
Herpes zoster	5%
Oral herpes	5%
Conjunctivitis	5%
General Disorders and Administration Site Conditions	
Fatigue	8%
Pyrexia	5%
Nervous System Disorders	
Headache	5%
Dizziness	5%
Gastrointestinal Disorders	
Abdominal pain upper	5%
Cardiac Disorders	
Tachycardia	5%
Musculoskeletal and Connective Tissue Disorders	
Musculoskeletal pain	5%
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	
Skin papilloma	5%

* Infusion-related reactions 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 included headaches, chills, high blood pressure, nausea, asthenia and pain.

Description of selected adverse reactions

Infusion-related reactions
Infusion-related reactions in the pemphigus vulgaris clinical study 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.

Infections
Fourteen patients (37%) in the MabThera group experienced treatment-related infections compared to 15 patients (42%) in the standard-dose prednisone group. The most common infections in the MabThera group were herpes simplex and zoster infections, bronchitis, urinary tract infection, fungal infection and conjunctivitis. Three patients (8%) in the MabThera 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).

בסעיף 5.1 Pharmacodynamic properties עודכן המידע הבא:

Clinical experience in pemphigus vulgaris

The efficacy and safety of MabThera 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 MabThera group and 3 (8%) patients in the standard prednisone group had moderate disease and 33 (87%) patients in the MabThera 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 MabThera and low-dose prednisone or standard-dose prednisone. Patients randomised to the MabThera group received an initial intravenous infusion of 1000 mg MabThera 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 MabThera 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 MabThera group who relapsed could receive an additional infusion of MabThera 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).

Results
The study showed statistically significant results of MabThera and low-dose prednisone over standard-dose prednisone in achieving CRoff ≥ 2 months at month 24 in PV patients (see Table 17).

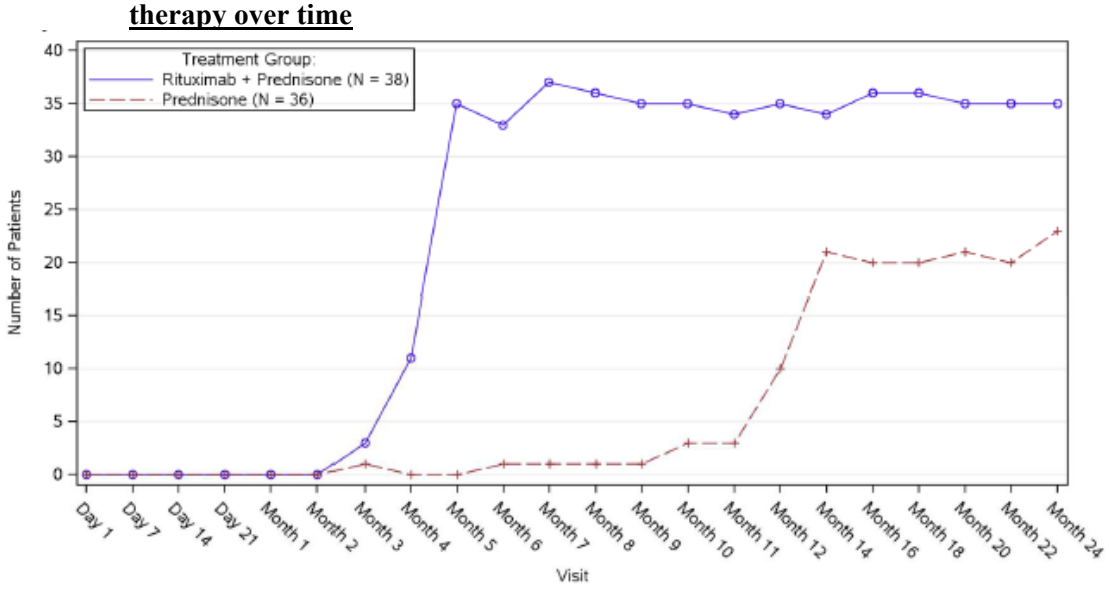
Table 17 Percentage of PV patients who achieved complete remission off corticosteroid therapy for two months or more at month 24 (Intent-to-Treat Population - PV)

	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 MabThera (Figure 3).

Figure 3: 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 MabThera, tested positive for ADA antibodies by 18 months. The clinical relevance of ADA formation in MabThera-treated PV patients is unclear.