דצמבר 2020

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 עדכון בעלון לרופא של התכשיר מבטרה 10מ"ג/מ"ל IV. בהודעה זו מצוינים רק עדכונים מהותיים ועדכונים אשר מהווים החמרה.

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).

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,

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4.4 Special warnings and precautions for use

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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 ~~follow~~ current immunisation guidelines prior to initiating MabThera therapy. Vaccination should be completed at least 4 weeks prior to first administration of MabThera.

Excipients

This medicinal product contains 2.3 mmol (or 52.6 mg) sodium per 10 mL vial and 11.5 mmol (or 263.2 mg) sodium per 50 mL vial, equivalent to 2.6% (for 10ml vial) and 13.2% (for 50ml vial) of the WHO recommended maximum daily intake of 2 g sodium for an adult. ~~To be taken into consideration by patients on a controlled sodium diet.~~

4.8 Undesirable effects

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Experience from pemphigus vulgaris

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

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In PV Study 2, a randomized, double-blind, double-dummy, active-comparator, multicenter study evaluating the efficacy and safety of MabThera compared with mycophenolate mofetil (MMF) in patients with moderate-to-severe PV requiring oral corticosteroids, 67 PV patients received treatment with MabThera (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).

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 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 in Study 1. In PV Study 2, ADRs were defined as adverse events occurring in ≥5% of patients in the MabThera arm and assessed as related.

Table 4 Adverse reactions in MabThera-treated pemphigus vulgaris patients in ~~the clinical study~~ PV Study 1 (up to month 24) and PV Study 2 (up to Week 52)

~~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.~~

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.		

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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 MabThera 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.

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

Laboratory abnormalities

PV Study 2, in the MabThera 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

Clinical Experience in granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)

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Laboratory Evaluations

A total of 23/99 (23%) MabThera-treated patients from the trial tested positive for ~~HACA~~ ADA by 18 months. None of the 99 MabThera-treated patients were ADA positive at screening. There was no apparent trend or negative impact of the presence of ADA on safety or efficacy in the induction of remission trial. ~~The clinical relevance of ADA formation in MabThera-treated patients is unclear.~~

Clinical experience in pemphigus vulgaris

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PV Study 2 (Study WA29330)

In a randomized, double-blind, double-dummy, active-comparator, multicenter study, the efficacy and safety of MabThera 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 MabThera 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 MabThera 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 MabThera over MMF in combination with a tapering course of oral corticosteroids in achieving CRoff corticosteroid ≥ 16 weeks at Week 52 in PV patients (Table 18).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 18 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)

	MabThera (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 MabThera 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 MabThera. The median (min, max) cumulative prednisone dose at Week 52 was 2775 mg (450, 22180) in the MabThera 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 MabThera 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) MabThera -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

Pemphigus vulgaris

The PK parameters in adult PV patients receiving MabThera 1000 mg at Days 1, 15, 168, and 182 are summarized in Table 19.

Table 19 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 (Range)	21.0 (9.3-36.2)	26.5 (16.4-42.8)
Clearance (L/day) Mean (Range)	391 (159-1510)	247 (128-454)
Central Volume of Distribution (L) Mean (Range)	3.52 (2.48-5.22)	3.52 (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.