# הודעה על החמרה (מידע בטיחות)

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| **תאריך:** | **08/04/2013** |
| **שם התכשיר באנגלית:** | **MabThera®**  |
| **מספרי רישום:** | **112.51.29472.00** |
| **שם בעל הרישום:** | **רוש פרמצבטיקה (ישראל) בע"מ** |

ההחמרות בעלון מסומנות על רקע צהוב

בעלון לרופא

| **פרטים על השינוי/ים המבוקש/ים** |
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| **פרק בעלון** | **טקסט נוכחי** | **טקסט חדש** |
| **4.2 Posology and method of administration** | ANCA-Associated Vasculitis (AAV) | Granulomatosis with polyangiitis and Microscopic polyangiitisPremedication consisting of an analgesic/anti-pyretic (e.g. paracetamol) and an anti-histaminic drug (e.g. diphenhydramine) should always be administered before each MabThera infusion. |
| **4.4 Special warnings and precautions for use** |  | In order to improve traceability of biological medicinal products, the tradename of the administered product should be clearly recorded (or stated) in the patient file. |
| **4.4 Special warnings and precautions for use** | Use of MabThera maybe associated with an increased risk of PML. | Very rare cases of fatal PML have been reported following use of MabThera. |
| **4.4 Special warnings and precautions for use** | *Non-Hodgkin’s lymphoma and chronic lymphocytic leukaemia**Infections*Hepatitis B virus (HBV) screening should be considered for high risk patients before initiation of treatment with MabThera. | *Non-Hodgkin’s lymphoma and chronic lymphocytic leukaemia**Infections*Hepatitis B virus (HBV) screening should always be performed in patients at risk of infection with HBV before initiation of treatment with MabThera.*Skin reactions:*Severe skin reactions such as Toxic Epidermal Necrolysis (Lyell’s Syndrome) and Stevens-Johnson Syndrome, some with fatal outcome, have been reported(see section 4.8).In case of such an event, treatment should be permanently discontinued.  |
| **4.4 Special warnings and precautions for use** | Rheumatoid arthritis and ANCA-Associated Vasculitis (AAV) Patients | Rheumatoid arthritis,Granulomatosis with polyangiitis and Microscopic polyangiitisCardiac disordersAngina pectoris, cardiac arrhythmiassuch as atrial flutter and fibrillation, heart failure and/or myocardial infarction have occurred in patients treated with MabThera. Therefore patients with a history of cardiac disease should be monitored closely (see Infusion related reactions, above).InfectionsBased on the mechanism of action of MabThera and the knowledge that B cells play an important role in maintaining normal immune response, patients have an increased risk of infection following MabThera therapy (see section 5.1).Hepatitis B virus (HBV) screening should always be performed in patients at risk of infection with HBV before initiation of treatment with MabThera. Carriers of hepatitis B and patients with a history of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection during, and for several months following, MabThera therapy.*Late neutropenia*Measure blood neutrophils prior to each course of MabThera, and regularly up to 6-months after cessation of treatment, and upon signs or symptoms of infection (see section 4.8). *Skin reactions:*Severe skin reactions such as Toxic Epidermal Necrolysis (Lyell’s Syndrome) and Stevens-Johnson Syndrome, some with fatal outcome, have been reported(see section 4.8).In case of such an event, treatment should be permanently discontinued.  |
| **4.6 Fertility, pregnancy and lactation** |  | FertilityThere are no data currently available on the effects of MabThera on fertility.  |
| **4.8 Undesirable effects** | *Experience from non-Hodgkin’s lymphoma and chronic lymphocytic leukaemia*Very rare- anaphylaxis, necrolysis | *Experience from non-Hodgkin’s lymphoma and chronic lymphocytic leukaemia*Rare- Pneumocystis jirovecii, anaphylaxisVery rare- PML, Stevens-Johnson Syndrome, necrolysis (Lyell’s Syndrome)Studies in previously untreated and relapsed/refractory CLL have established that in up to 25% of patients treated with R-FC neutropenia was prolonged (defined as neutrophil count remaining below 1x109/L between day 24 and 42 after the last dose) or occurred with a late onset (defined as neutrophil count below 1x109/L later than 42 days after last dose in patients with no previous prolonged neutropenia or who recovered prior to day 42) following treatment with MabThera plus FC.A small number of spontaneous and literature cases of hypogammaglobulinaemia have been observed in pediatric patients treated with MabThera, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in paediatric patients are unknown.*Skin and subcutaneous tissue disorders:*Toxic Epidermal Necrolysis (Lyell Syndrome) and Stevens-Johnson Syndrome, some with fatal outcome, have been reported very rarely. |
| **4.8 Undesirable effects** |  | *Experience from rheumatoid arthritis* Very common- decreased IgM levelscommon-neutropenia, decreased IgG levelsRare- late neutropenia, Angina pectoris, atrial fibrillation, heart failure, myocardial infarctionVery rare- Atrial flutter, Toxic Epidermal Necrolysis (Lyell’s Syndrome), Stevens-Johnson Syndrome*Neutropenia*Events of neutropenia were observed with MabThera treatment, the majority of which were transient and mild or moderate in severity. Neutropenia can occur several months after the administration of MabThera (see section 4.4).In placebo-controlled periods of clinical trials, 0.94% (13/1382) of rituximab treated patients and 0.27% (2/731) of placebo patients developed severe neutropenia.Neutropenic events, including severe late onset and persistent neutropenia, have been rarely reported in the post-marketing setting, some of which were associated with fatal infections*Skin and subcutaneous tissue disorders:*Toxic Epidermal Necrolysis (Lyell’s Syndrome) and Stevens-Johnson Syndrome, some with fatal outcome, have been reported very rarely.Laboratory abnormalitiesHypogammaglobulinaemia (IgG or IgM below the lower limit of normal) has been observed in RA patients treated with MabThera. There was no increased rate in overall infections or serious infections after the development of low IgG or IgM (see section 4.4). A small number of spontaneous and literature cases of hypogammaglobulinaemia have been observed in pediatric patients treated with MabThera, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in paediatric patients are unknown. |
| **4.8 Undesirable effects** | *Experience from ANCA-Associated Vasculitis (AAV)* | *Experience from Granulomatosis with polyangiitis and Microscopic polyangiitis*Thrombocytopenia, Dyspepsia, Constipation, Hyperkalaemia, Back pain, Muscle weakness, Musculoskeletal pain, Pain in extremities, Dizziness, Acne*Cardiovascular*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).*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 MabThera in the postmarketing 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 MabThera. At 6 months, in the active‑controlled, randomized, double-blind, multicenter, non-inferiority study, in the MabThera 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.*Neutropenia*In the active‑controlled, randomized, double-blind, multicenter, non-inferiority study of MabThera in Granulomatosis with polyangiitis and Microscopic polyangiitis, 24% of patients in the MabThera 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 MabThera-treated patients. The effect of multiple MabThera courses on the development of neutropenia in Granulomatosis with polyangiitis and Microscopic polyangiitis patients has not been studied in clinical trials.*Skin and subcutaneous tissue disorders:*Toxic Epidermal Necrolysis (Lyell’s Syndrome) and Stevens-Johnson Syndrome, some with fatal outcome, have been reported very rarely. |

בעלון לצרכן

אין עלון לצרכן לתכשיר MabThera®.