Further information

Consult the Product Information before prescribing, preparing or administering MabThera
If you have any questions or problems: Call: +44 (0)800 328 1629 or email: Medinfo.uk@roche.com

References

1. MabThera (rituximab) Summary of Product Characteristics.
2. Calabrese LH, Molloy ES, Huang D & Ransohoff RM. Progressive multifocal leukoencephalopathy in rheumatic diseases: evolving clinical and pathologic patterns of disease. Arthritis Rheum 2007;56:2116–2128.
3. Egli A, Infanti L, Dumoulin A, Buser A, Samaridis J, Stebler C, et al. Prevalence of polyomavirus BK and JC infection and replication in 400 healthy blood donors. J Infect Dis 2009;199:837–846.

Product information for MabThera is available on the EMC web site:
http://www.medicines.org.uk/emc

Call for reporting

Suspected adverse reactions associated with the use of MabThera should be reported to:
Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gzira GZR 1368, or at:
http://www.medicinesauthority.gov.mt/adrportal
Suspected adverse events should also be reported to Roche by phone on +44 (0)1707 367554,
fax on +44 (0)1707 367582 or e-mail at welwyn.uk_dsc@roche.com

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Important information about MabThera® (rituximab)

Information to assist healthcare professionals in caring for patients receiving MabThera therapy*

This material is provided as a licence requirement for this medicine, as part of the Risk Management Plan

* For non-oncology indications

RXUKMABR00465c/June 2013

About this guide

This guide is intended to present important safety information including the risk for infections, and progressive multifocal leukoencephalopathy (PML) associated with the use of MabThera in non-oncology diseases and to provide important patient counselling information to assist healthcare professionals in caring for patients receiving MabThera therapy. It does not contain all information about this product. You should always consult the Product Information before prescribing, preparing or administering MabThera

MabThera in rheumatoid arthritis: Indications and usage

MabThera in combination with methotrexate (MTX) is indicated for the treatment of adult patients with severe active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARDs), including one or more tumour necrosis factor (TNF) inhibitor therapies.

MabThera has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with MTX.

The efficacy and safety of MabThera in alleviating the symptoms and signs of RA in patients with an inadequate response to TNF inhibitors was demonstrated in a pivotal randomised, controlled, double-blind, multicentre study. Eligible patients had active RA, diagnosed according to the criteria of the American College of Rheumatology (ACR). Structural joint damage was assessed radiographically and expressed as change in modified total Sharp score and its components, the erosion score and joint space narrowing score.

MabThera in Granulomatosis with polyangiitis or Microscopic polyangiitis: Indications and usage

MabThera , in combination with glucocorticoids, is indicated for the induction of remission in adult patients with severe, active Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA).

The efficacy and safety of MabThera in GPA and MPA was determined in a Phase II/III, randomized, active controlled, double blind study in patients with severe, active GPA or MPA. The primary objective of the study was to determine if MabThera plus glucocorticoids are non inferior to conventional therapy in the induction of complete remission, defined as a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) of 0 and off glucocorticoid therapy at 6 months.

Please note that a positive benefit-risk balance for MabThera within the area of non-oncology diseases has currently only been established and approved by the European Medicines Agency for:

- the treatment of adult patients with severe active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARDs), including one or more tumour necrosis factor (TNF) inhibitor therapies
- the induction of remission in adult patients with severe, active Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA), in combination with glucocorticoids.

Prior to administering MabThera therapy

Before you administer MabThera ask and/or check if the patient:

- Is allergic to MabThera or to any of the excipients or to murine proteins
- Has an active, severe infection or has a severely decreased immune system function
- Has had or now has viral hepatitis or any other hepatic disease
- Is taking or has previously taken medicines which may affect the immune system, such as chemotherapy or immunosuppressive agents
- Has signs of an infection, such as a fever, cough or headache, or is feeling unwell
- Has an infection, is being treated for an infection or has a history of recurring, chronic or severe infections
- Has recently received a vaccination or is scheduled for any vaccination
- Is taking or has recently taken any other medicines (including those they have bought from a pharmacy, supermarket or health store)
- Is pregnant or wants to become pregnant, or is breastfeeding
- Is taking treatment for high blood pressure
- Has a history of cardiac disease and/or cardiotoxic chemotherapy or a history of breathing problems.

During or after administration of MabThera therapy

- Patients should be closely monitored during administration of MabThera in an environment where full resuscitation facilities are immediately available.
- Medicinal products for the treatment of hypersensitivity reactions, e.g., epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of MabThera.
- Use of MabThera may be associated with an increased risk for infections.
- Patients reporting signs and symptoms of infection following MabThera therapy should be promptly evaluated and treated appropriately. Before giving a subsequent course of MabThera treatment, patients should be re-evaluated for any potential risk for infections.
- Use of MabThera may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML). Patients must be monitored regularly for any new or worsening of neurological symptoms or signs suggestive of PML.
  - Cases of PML with fatal outcome have been reported following use of MabThera for the treatment of autoimmune diseases (see following pages).

Inform patients of the importance of seeking medical attention immediately if they experience any of these symptoms after their MabThera treatment:

- Symptoms of an infection, for example fever, persistent cough, weight loss or listlessness
- Confusion, memory loss or problems thinking
- Loss of balance or a change in the way they walk or talk
- Decreased strength or weakness on one side of the body
- Blurred vision or loss of vision.

Progressive Multifocal Leukoencephalopathy

As described in the Product Information[1], use of MabThera may be associated with an increased risk of PML.

About PML

PML is a rare, progressive, demyelinating disease of the central nervous system that can lead to death or severe disability.[2] PML is caused by activation of the JC (John Cunningham) virus, a polyomavirus that resides in latent form in up to 70% of healthy adults.[3] JC virus typically only causes PML in immunocompromised patients.[2] The factors leading to activation of latent infection are not fully understood.

MabThera and PML in non-oncology diseases

A small number of confirmed cases of PML have been reported worldwide in patients who have been treated with MabThera for the indications of RA and GPA/MPA in addition to some other diseases. The patients had received prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their last infusion of MabThera.

While the potential role of MabThera in the development of PML is unclear, the information to-date suggests that some patients who receive MabThera have an increased risk of PML.

PML: Patient counselling information

- Patients should be advised of the potential benefits and risks of treatment with MabThera
- Inform patients that very rarely, some patients taking MabThera have had a serious brain infection, which in many cases has been fatal.
- Instruct the patient to contact their doctor or nurse immediately if they experience memory loss, trouble thinking, difficulty with walking and/or loss of vision.

All patients treated with MabThera for RA, GPA or MPA must be given the MabThera Patient Alert Card with each infusion. The Alert Card contains important safety information regarding potential increased risk of infections, including PML.

Inform the patient of the importance of keeping the Alert Card with them at all times and of telling their partner or caregiver about their treatment, since they may notice symptoms that the patient is not aware of.

PML: Patient monitoring

Patients must be monitored at regular intervals for any new or worsening of neurological symptoms or signs that may be suggestive of PML. The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice – for example, cognitive, neurological or psychiatric symptoms.

The physician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction and, if so, whether these symptoms are possibly suggestive of PML.

If PML is suspected, further dosing must be suspended until PML has been excluded.

If any doubt exists, consultation with a neurologist is recommended and further evaluation, including an MRI scan (preferably with contrast), cerebrospinal fluid testing for JC viral DNA and repeat neurological assessments, should be considered.

If a patient develops PML, the dosing of MabThera must be permanently discontinued.

Following reconstitution of the immune system in immunocompromised patients with PML, stabilisation or improved outcome has been seen. It remains unknown if early detection of PML and suspension of MabThera therapy may lead to similar stabilisation or improved outcome.

Other infections

Serious infections, including fatalities, can occur during therapy with MabThera. MabThera should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis, hepatitis or opportunistic infections) or severely immunocompromised patients (e.g. where levels of CD4 or CD8 are very low). Physicians should exercise caution when considering the use of MabThera in patients with a history of recurring or chronic infections (e.g. hepatitis B) or with underlying conditions which may further predispose patients to serious infection (e.g. hypogammaglobulinaemia). It is recommended that immunoglobulin levels are determined prior to initiating treatment with MabThera