Important information about MabThera® (rituximab)

Information to assist healthcare professionals in:

- communicating risk of PML and Infections to patients receiving MabThera therapy*
- caring for patients receiving MabThera therapy*.

This educational material is provided by Roche Products (Ireland) Limited and is mandatory as a condition of the Marketing Authorisation in order to further minimise important selected risks.

* For non-oncology indications

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About this brochure

This brochure is intended to summarise important safety information about MabThera when it is used in non-oncology diseases.

This information is intended to assist healthcare professionals in communicating key safety messages to patients receiving MabThera therapy and in caring for patients receiving MabThera therapy.

It does not contain all the information about this product. You should always consult the Summary of Products Characteristics (SmPC) before prescribing, preparing or administering MabThera.

MabThera is indicated for:

- **Severe, active Rheumatoid Arthritis (RA)** – to treat adults with severe, active RA, who have had an inadequate response or intolerance to other Disease-Modifying Anti-Rheumatic Drugs (DMARDs) including one or more Anti-TNF therapies. For this indication it is given with methotrexate.
- **Severe, active Granulomatosis with Polyangiitis (GPA or Wegener's) or Microscopic Polyangiitis (MPA)** – to treat adults with severe, active GPA (Wegener's), or MPA. For this indication it is given with glucocorticoids.
- **Pemphigus vulgaris** – to treat patients with moderate to severe pemphigus vulgaris (PV).

Use of MabThera in RA

MabThera given with methotrexate has been shown to reduce the rate of progression of joint damage (measured by X-ray) and to improve physical function. The safety and efficacy of MabThera has been demonstrated in a 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 measured by X-ray and expressed as a change in the modified total Sharp score and its components (the erosion score and joint space narrowing score).

Use of MabThera in GPA (Wegener's) or MPA

The efficacy and safety of MabThera in GPA and MPA has been demonstrated in a Phase II/III, randomised, active-controlled, double-blind study in patients with severe, active GPA (Wegener's) or MPA. The aim of the study was to determine if MabThera with glucocorticoids was as effective as conventional therapy in the induction of complete remission.

Complete remission was defined as a "Birmingham Vasculitis Activity Score for Wegener's Granulomatosis" (BVAS/WG) score of 0 in addition to discontinuation of glucocorticoid therapy 6 months after treatment.

Use of MabThera in Pemphigus Vulgaris

The efficacy and safety of MabThera in PV has been demonstrated in a Phase III, investigator sponsored, multicentre, randomised, open-label study. This study evaluated the benefit of rituximab in combination with short-term and low-dose prednisone compared with long-term, standard dose prednisone in patients with newly diagnosed, treatment-naïve, moderate to severe pemphigus.

Complete remission was defined as complete epithelialisation and absence of new and/or established lesions at Month 24 without prednisone therapy and for at least two months ("complete remission off therapy" according to the "Consensus Treatment Definitions of Disease Endpoints and Therapeutic Responses for Pemphigus").

During or after administration of MabThera therapy

Patients should be advised of the potential benefits and risks of treatment with MabThera.

Patients should be closely monitored during administration of MabThera in an environment where full resuscitation facilities are immediately available.

Use of MabThera may be associated with an increased risk of infections or Progressive Multifocal Leukoencephalopathy (PML).

All patients treated with MabThera for RA, GPA/MPA and PV 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.

PML

About PML

PML is a rare, progressive, demyelinating disease of the central nervous system that can lead to severe disability or be fatal. PML is caused by activation of the JC (John Cunningham) virus, a polyomavirus that is latent in up to 70% of healthy adults[1]. The JC virus usually only causes PML in immunocompromised patients[2].The factors leading to activation of a latent infection are not fully understood.

MabThera and PML in non-oncology diseases

A small number of confirmed cases of PML, some of which were fatal, have been reported worldwide in patients who have been treated with MabThera for non-oncology diseases. These patients had received immunosuppressant therapy before or during their MabThera treatment. Most cases of PML were diagnosed within 1 year of their last infusion of MabThera, however patients should be monitored for up to 2 years after treatment.

It is not clear how MabThera affects the development of PML, however evidence suggests that some patients who receive MabThera may develop PML.

What to tell your patient

- Some patients treated with MabThera for the treatment of RA, GPA or MPA have developed a serious brain infection called PML, which in some cases has been fatal.
- To carry the MabThera Patient Alert Card with them at all times. The Patient Alert Card will be given to them at each infusion.
- To tell carers or relatives about the symptoms to look out for.
- **To contact their doctor, pharmacist or nurse immediately if they experience any of the following signs or symptoms suggestive of PML:**
  - 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.

Patient monitoring

Monitor patients for any new or worsening neurological symptoms or signs suggestive of PML during treatment with MabThera and for up to 2 years after treatment. In particular, look out for those symptoms and signs the patients themselves may not notice such as cognitive, neurological or psychiatric symptoms.

Assess the patient promptly to determine if the symptoms are indicative of neurological dysfunction and if they are suggestive of PML.

Suspected PML

Suspend further dosing of MabThera until PML has been excluded.

To confirm diagnosis, consultation with a neurologist and further evaluation including an MRI scan (preferably with contrast), cerebrospinal fluid testing for JC viral DNA and repeat neurological assessments are recommended.

Diagnosed PML

MabThera must be permanently discontinued.

Stabilisation or improved outcome has been seen following reconstitution of the immune system in immunocompromised patients with PML.

It is unknown if early detection of PML and suspension of MabThera therapy may lead to similar stabilisation or improved outcome in patients treated with MabThera.

Infections

Tell patients to contact their doctor, pharmacist or nurse immediately if they experience any of the following signs of possible infection:

- fever
- persistent cough
- weight loss
- pain when they have not hurt themselves
- feeling generally unwell, tired or low in energy
- burning pain when passing urine.

Patients reporting signs of infection following MabThera therapy should be promptly evaluated and treated appropriately. Before giving further MabThera treatment, patients should be re-evaluated for any potential risk of infections as indicated under **"Do not give MabThera to patients who"** and **"Take special care before you give MabThera to patients who"** headings.

Do not give MabThera to patients who:

- are allergic to rituximab or to any of the other ingredients
- are allergic to murine proteins
- have an active severe infection such as tuberculosis, sepsis, hepatitis or an opportunistic infection
- are severely immunocompromised, e.g. levels of CD4 or CD8 are very low.

Take special care before you give MabThera to patients who:

- have signs of an infection – signs may include fever, cough, headache or feeling generally unwell
- have an active infection or are being treated for an infection
- have a history of recurring, chronic or severe infections
- have, or have ever had, viral hepatitis or any other hepatic disease
- are taking, or have ever taken, medicines which may affect their immune system, such as chemotherapy or immunosuppressants
- are taking, or have recently taken, any other medicines (including those they have bought from a pharmacy, supermarket or health store)
- have recently received a vaccination or are planning to have one
- are taking medicines for high blood pressure
- are pregnant, trying to become pregnant or are breastfeeding
- have heart disease or have received cardiotoxic chemotherapy
- have breathing problems
- have an underlying condition which may further predispose them to a serious infection (such as hypogammaglobulinaemia).

Further information

Consult the SmPC before prescribing, preparing or administering MabThera. If you have any questions or problems: Call: [00 353 (0)1 4690700], or email: [Ireland.druginfo@roche.com].

References

1. 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.

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.

Product information for MabThera is available at www.medicines.ie

Reporting of suspected adverse events or reactions

Reporting suspected adverse events or reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse events or reactions (see details below).

Where possible, healthcare professionals should report adverse events or reactions by brand name and batch number.

In the event of a suspected adverse event, please report it to:
The Drug Surveillance Centre, Roche Products (Ireland) Limited,
3004 Lake Drive, Citywest, Naas Road, Dublin 24, Ireland.
Telephone: 00 353 (0)1 4690700
Fax: 00 353 (0)1 4690793
Email: ireland.drug_surveillance_centre@roche.com

Alternatively, suspected adverse reactions should be reported to:
Pharmacovigilance Section at Post-Licensing Directorate,
Medicines Authority, Sir Temi Żammit Buildings,
Malta Life Sciences Park, San Ġwann SĠN 3000, Malta.
Reporting forms and information can be found at
www.medicinesauthority.gov.mt/adrportal

Further Information

For additional copies of this risk minimisation material, refer to the Malta Medicines Authority website [http://www.medicinesauthority.gov.mt/rmm] and download the required material or alternatively if you would like hard copies, please contact Roche Products (Ireland) Limited, 3004 Lake Drive, Citywest, Naas Road, Dublin 24 by mail, telephone [00 353 (0)1 4690700], fax [00 353 (0)1 4690793] or email [ireland.drug_surveillance_centre@roche.com].

For further information about this medicine please contact Medical Information at Roche Products (Ireland) Limited by telephone [00 353 (0)1 4690700], fax [00 353 (0)1 4690793] or email [Ireland.druginfo@roche.com].

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