Important information about MabThera®

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

*For non-oncology indications

About this guide

This guide is intended to review key facts and important safety information about 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.

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

Prior to administering MabThera® therapy

Before you administer MabThera®, ask the patient if he or she:

- 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

- 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 in patients who have been treated with MabThera® for the indication of RA worldwide. 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 patients with RA 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 some 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 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 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®.

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

Visit

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.

Important safety information

PRESCRIBING INFORMATION MabThera® (rituximab) in Rheumatoid Arthritis: Please refer to MabThera SPC for full prescribing information
Indication: MabThera, in combination with methotrexate, for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other DMARDs including one or more 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 methotrexate.
Dosage and Administration: Patients must be given the patient alert card with each infusion. A course of MabThera is: 2x1000 mg iv infusions given 2 weeks apart. Administer through a dedicated line, with full resuscitation facilities immediately available in case of severe infusion related reactions. Premedication with 100mg methylprednisolone should be completed 30 minutes prior to each infusion. Premedication with an analgesic/anti-pyretic and anti-histamine should be administered before each infusion. Monitor for cytokine release syndrome. Interrupt infusion if severe reactions occur. First Infusion: Initial infusion rate 50mg/hr. Second Infusion: Initial rate 100mg/hr.
Contraindications: Hypersensitivity to the active substance, excipients or murine proteins. Active, severe infections. Patients in a severely immunocompromised state. Severe heart failure (NYHA Class IV) or severe, uncontrolled cardiac disease.
Precautions: To improve traceability of biological medicinal products, the tradename of the administered product should be clearly recorded in the patient file. *PML:* Use of MabThera may be associated with an increased risk of PML. Patients must be monitored regularly for any new or worsening neurological symptoms or signs suggestive of PML. *Infusion reactions:* Fatal infusion reactions have been reported in the post-marketing setting. *Hypotension:* Hypotension may occur, consider withholding antihypertensive medications. *Cardiac disorders:* Closely monitor patients with a history of cardiac disease. *Infections:* Serious infections including fatalities can occur during therapy. Do not give to patients with an active and/or severe infection, or severely immunocompromised patients. Caution in patients with recurring/chronic infections. Determining immunoglobulin levels is recommended prior to initiating treatment. *Hepatitis B:* Always screen patients at risk of Hepatitis B infection before initiation of treatment. *Immunisation:* The safety of immunization with live viral vaccines following MabThera Therapy has not been studied. *Concomitant/sequential use of other DMARDs:* Concomitant use of MabThera and antirheumatic therapies other than those specified not recommended. Limited data available suggest the rate of clinically relevant infection is unchanged. *Malignancy:* Limited experience in RA patients, cannot exclude a possible risk for the development of solid tumours. *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.
Pregnancy and Lactation: Patients should not get pregnant or breastfeed during and for 12 months following treatment.
Undesirable effects: Prescribers should consult SPC for full details of ADRs. *Very common:* infusion related reactions (hypertension, nausea, rash, pyrexia, pruritus, urticaria, rhinitis, throat irritation, hot flush, hypotension, rigors, tachycardia, fatigue, oropharyngeal pain, peripheral oedema, erythema), respiratory tract infection, urinary tract infections, headache, decreased IgM levels. *Common:* Bronchitis, sinusitis, gastroenteritis, tinea pedis, hypercholesterolemia, paraesthesia, migraine, dizziness, sciatica, alopecia, depression, anxiety, dyspepsia, diarrhoea, gastro-oesophageal reflux, mouth ulceration, upper abdominal pain, arthralgia / musculoskeletal pain, osteoarthritis, bursitis, neutropenia, decreased IgG levels. *Uncommon:* infusion related reactions (generalised oedema, bronchospasm, wheezing, laryngeal oedema, angioneurotic oedema, generalised pruritus, anaphylaxis, anaphylactoid reaction.) *Rare:* Angina pectoris, atrial fibrillation, heart failure, myocardial infarction, late neutropenia. *Very rare:* PML, reactivation of hepatitis B, serum sickness-like reaction, atrial flutter.
Legal category: POM
Presentations and Basic NHS Costs: 100mg of MabThera in 10ml (10mg/ml) pack of 2 vials: £349.25, 500mg of MabThera in 50ml (10mg/ml) pack of 1 vial: £873.15
Marketing Authorisation Numbers: EU/1/98/067/001 (100mg), EU/1/98/067/002 (500mg)
Marketing Authorisation Holder: Roche Registration Limited, 6 Falcon Way, Welwyn Garden City, Herts AL7 1TW. MabThera is a Registered trademark.

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Please contact the Drug Safety Centre, Roche Products Limted,
6 Falcon Way, Shire Park, Welwyn Garden City, Hertfordshire, England
Telephone number +44 1707 367554.
Adverse events may otherwise be reported via the national Adverse Drug Reactions (ADRs) reporting system.
Reporting forms and information can be found at:
http://medicinesauthority.gov.mt/phvigilance.htm

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