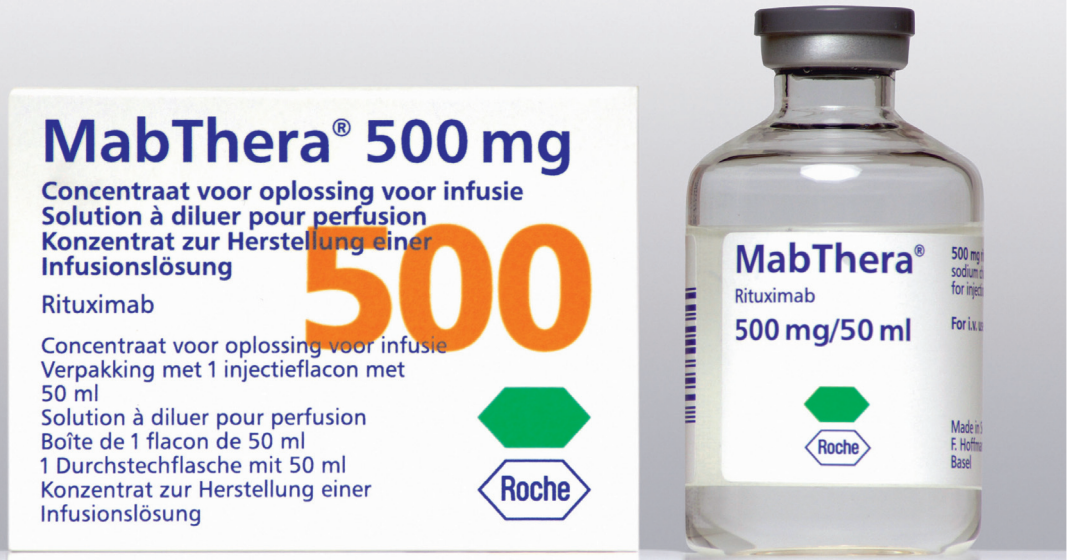
MabThera® dosage and administration



MABTHERA® RITUXIMAB

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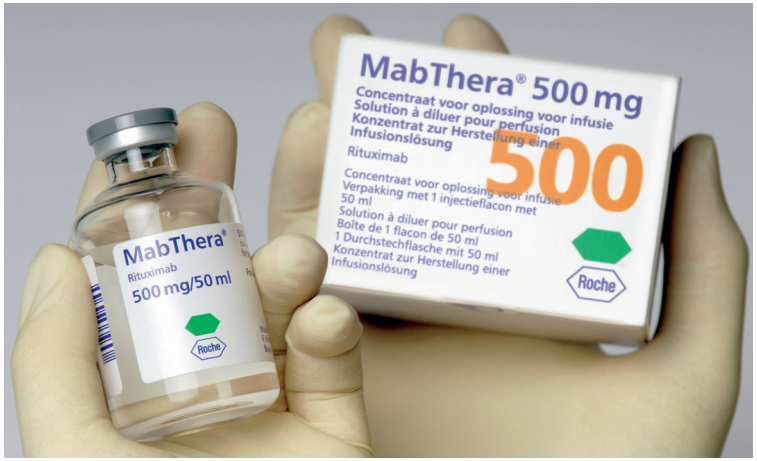
Contents

Introduction to MabThera®

This guide is intended to review key practical facts about the dosage and administration of MabThera®. It does not contain all information about this product. Consult the accompanying full prescribing information before prescribing, preparing, or administering MabThera®.

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



How is MabThera® supplied?

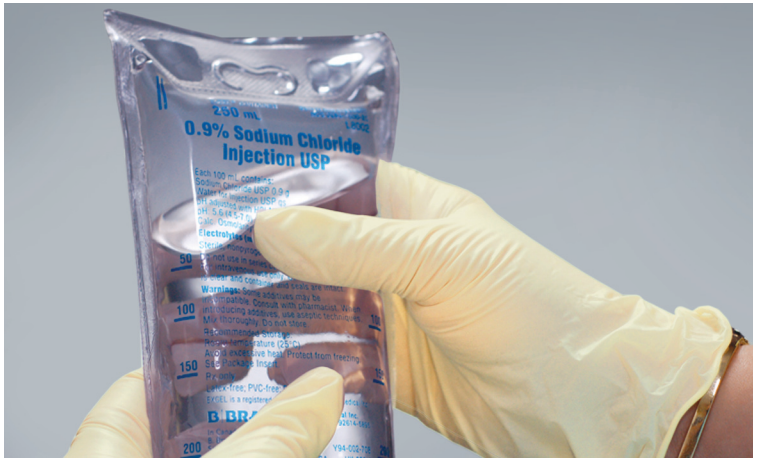
MabThera® is a sterile, clear, colourless, preservative-free liquid concentrate for intravenous (IV) administration after dilution. It is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. MabThera® is formulated in sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid and water for injection.

Storing MabThera®

MabThera® vials are stable at 2 °C to 8 °C. Protect MabThera® vials from direct sunlight. Do not freeze or shake. Do not use MabThera® after the expiration date on the carton.

Dosage and administration of MabThera®

MabThera® is administered to RA patients by IV infusion at a dose of 1000 mg. Patients receive two infusions: a 1000 mg dose on day 1 and a 1000 mg dose on day 15. Glucocorticoids administered as methylprednisolone 100 mg IV or its equivalent 30 minutes prior to each infusion are recommended to reduce the incidence and severity of infusion reactions. MabThera® should not be administered as an IV push or bolus.



Scheduling the patient

Prior to scheduling the patient for the first infusion, a physical examination and review of medical history should be conducted to exclude a contra-indication. These include:

- Known hypersensitivity to any component of the product or to murine proteins.
- Active, severe infection.
- Severe heart failure (NYHA class IV) or severe uncontrolled cardiac disease.

When scheduling the patient, for the first infusion, ensure the patient is aware of the following:

- The length of time anticipated for the infusion.
- The need to arrange for someone else to drive home after the infusion.

Preparing the patient

Before each infusion, inform patients about potential infusion reactions and instruct them to alert attending medical personnel immediately should they feel any side effects coming on. Administration of methylprednisolone (100 mg IV or its equivalent) 30 minutes before each infusion is recommended. Premedication with IV corticosteroids reduces both the incidence and severity of infusion reactions.

Oral premedication with acetaminophen/paracetamol (1g) and diphenhydramine (50mg or equivalent dose of similar agent) should always be administered prior to each MabThera® infusion.

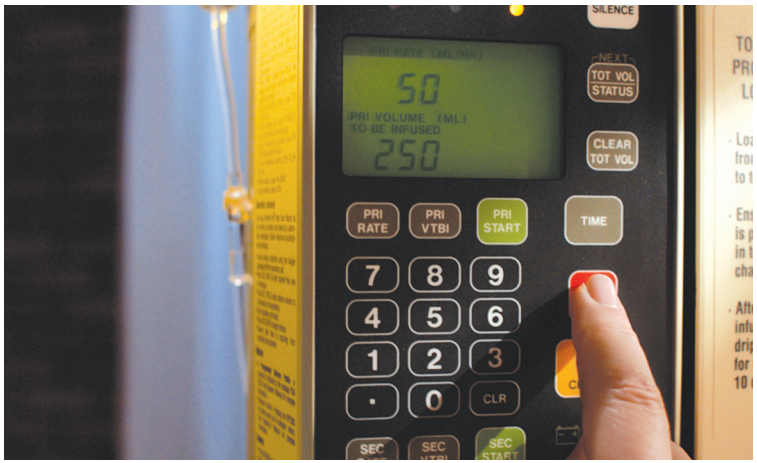
The physician may also consider withholding antihypertensive medications 12 hours before MabThera® infusion (Hypotension may occur during MabThera® infusion).

MabThera® should be administered in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced physician. In patients with known cardiac history, the risk of cardiovascular complication resulting from an infusion reaction should be considered before treatment and patients closely monitored.

Standard equipment for infusion

Assemble the equipment for infusion. Though not mandatory for IV infusion, use of an IV pump may help regulate the administration and dosage of the drug.

Medications and supportive care measures — including, but not limited to, epinephrine, antihistamines, glucocorticoids, intravenous fluids, vasopressors, oxygen, bronchodilators, and acetaminophen/paracetamol — should be available and instituted as medically indicated for use in the event of a reaction during administration.



Preparing MabThera® for infusion

Use aseptic technique throughout the preparation of MabThera® solution.

1. Withdraw appropriate amount of 0.9% Sodium Chloride, or 5% Dextrose in Water and discard.
2. Withdraw the necessary amount of MabThera® to yield 1000 mg.
3. Dilute an infusion bag containing 0.9% Sodium Chloride or 5% Dextrose in Water to yield a final concentration of 1 to 4 mg/mL. (Do not mix or dilute MabThera® with other drugs).
4. Gently invert the bag to mix the solution. Do not shake.
5. Discard any unused portion left in the vial.
6. Inspect solution for particulate matter and discolouration.

Once the infusion solution is mixed, it may be stored at 2 °C to 8 °C for 24 hours. Protect from direct sunlight. Do not freeze.

Prior to administration

- If recommended by the attending physician, ensure that the patient has not taken antihypertensive medications in the 12 hours before infusion.
- Premedication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine, should be considered.
- Treatment with 100 mg IV methylprednisolone (or equivalent) should be given 30 minutes prior to MabThera® to decrease the rate and severity of acute infusion reactions.

Recommended dosage

- MabThera® is administered to RA patients by IV infusion at a dose of 1000 mg. Each course of MabThera® consists of two infusions: a 1000 mg dose on day 1 and a 1000 mg dose on day 15.

Administering MabThera®

- Administer through a dedicated IV line.
- Do not administer as an IV push or bolus.
- Use an aseptic technique.

First infusion (day 1)

- Begin infusion at a rate of 50 mg/h.
- If no infusion reactions occur after 30 minutes, increase rate to 100 mg/h.
- If no infusion reactions occur, continue to escalate the infusion rate in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h.

Second infusion (day 15)

- If the patient did not tolerate the first infusion well, start at the same rate as the first infusion (50 mg/h) and follow directions for dose escalation as per the first infusion.
- If the patient tolerated the first infusion well, begin infusion at a rate of 100 mg/h.
- If no infusion reactions occur after 30 minutes, increase rate to 200 mg/h.
- If no infusion reactions occur, continue to escalate the infusion rate in 100 mg/h increments every 30 minutes, to a maximum of 400 mg/h.

Managing acute infusion reactions

MabThera® is associated with infusion reactions, which may be related to the release of cytokines and/or other chemical mediators. As a protein, anaphylactic or hypersensitivity reactions may also occur after IV administration of MabThera®.

- Symptoms suggesting an acute infusion reaction are represented by pruritus, fever, urticaria/rash, chills, pyrexia, rigors, sneezing, angioneurotic edema, throat irritation, cough and bronchospasm, with or without associated hypo- or hypertension.

- Most infusion events reported are mild to moderate in severity. Serious infusion reactions are uncommon (experienced by <1% of RA patients in clinical trials).

- The proportion of affected patients decreases with subsequent infusions. During placebo controlled studies, an acute infusion reaction occurred during the first infusion in 15% of patients (placebo 5%). Following the second infusion, 2% of MabThera® and 2% of placebo patients respectively experienced an acute infusion reaction.

- The reactions reported are usually reversible with a reduction in rate, or interruption, of MabThera® infusion and administration of an anti-pyretic, an antihistamine, and, occasionally oxygen, IV saline or bronchodilators, and glucocorticoids if required.

- In case of severe infusion reaction, the infusion should be interrupted and medications and supportive care measures should be available and instituted as medically indicated. This may include, but is not limited to: epinephrine, antihistamines, glucocorticoids, intravenous fluids, vasopressors, oxygen, bronchodilators, acetaminophen/paracetamol.

- In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved.

- The presence of HACA (human anti-chimeric antibodies) may be associated with worsening infusion or allergic reactions during subsequent infusions. In clinical trials 9.2% of RA patients tested positive following treatment with MabThera® (the emergence of HACA, was generally not associated with clinical deterioration).

Post infusion monitoring

- Following MabThera® infusion, monitor the patient for the period of time specified by the physician.
- Instruct patients and family members or attendants about symptoms to watch for in the days following the infusion. Provide clear instructions on what actions to take in the event of post-infusion complications.

References

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2. Emery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment. Results of a phase IIb randomised, double-blind, placebo-controlled, dose-ranging trial (DANCER study). *Arthritis Rheum* 2006; 54(5): 1390–1400

3. Cohen SB, Greenwald M, Dougados MR, Emery P, Furie R, Shaw TM, et al. Efficacy and safety of rituximab in active RA patients who experienced an inadequate response to one or more anti-TNF therapies (REFLEX study). *Arthritis Rheum*. In press

4. MabThera® (rituximab) Summary of Product Characteristics

Notes

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