MABTHERA® (RITUXIMAB®)

A comparison card to differentiate between the two formulations of MabThera® (subcutaneous and intravenous).

This leaflet has been produced by Roche for physicians, nurses and pharmacists for the safe and efficient use of MabThera® solution for subcutaneous injection (referred to as MabThera® SC) in patients with NHL

Please refer to the approved package insert for further information or contact your local Roche representative

Roche Products (Pty) Ltd
Reg. No.1947/027044/07
P.O. Box 1469, Halfway House, 1685
South Africa

M-ZA-00001073
Version 2.1

MabThera SC, 1400 mg is indicated in adults for Non-Hodgkin's Lymphoma (NHL)

- Monotherapy in patients with CD20-positive follicular non-Hodgkin's lymphoma (stage III–IV) who have relapsed after, or failed to respond to, chemotherapy.
- Treatment of previously untreated patients with CD20-positive follicular non-Hodgkin's lymphoma (stage III–IV) with high tumour burden in combination with CVP or CHOP.
- Maintenance therapy of patients with relapsed or refractory CD20-positive follicular non-Hodgkin's lymphoma (stage III–IV) who have responded to induction therapy with CHOP with or without rituximab.
- Treatment of patients with CD20-positive diffuse large B-cell non-Hodgkin's lymphoma (DLBCL) in combination with standard CHOP (8 cycles of cyclophosphamide, doxorubicin, vincristine and prednisone).

- Mabthera 1400 mg is only for subcutaneous use in NHL.
- The recommended dosage is a fixed dose of 1400 mg irrespective of the patient's BSA.

Important Reminder

For more information about MabThera SC

- Send email: iIlovo.med_info@roche.com

To report an adverse event

- Roche Drug Safety: global.irt_sahubtcs@roche.com
- Tel: +27 11 504 4746

For other pharmacovigilance related matters, please email: south_africa.drugsafety@roche.com

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MabThera® (rituximab)

Solutions for subcutaneous injection

Guide to supply, storage, handling and administration of Mabhera subcutaneous formulations

Supply, storage and handling of MabThera® SC

How is MabThera SC supplied?

- Each carton contains one glass vial.
- Each vial contains a sterile, non-pyrogenic and preservative-free solution (extractable volume is equivalent to one dose for administration to the patient) of: — 11.7 ml (1400 mg) for NHL
- The solution is clear to opalescent, colourless to yellowish. Do not use if you notice unusual coloration or presence of visible particles.
- Composition:

  – The active ingredient of MabThera® SC is rituximab.

  – The excipients are:
  - Recombinant human hyaluronidase (rHuPH20): this is an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. It allows the injection of larger volumes via the subcutaneous route.
  - Other excipients: L-histidine, L-histidine hydrochloride monohydrate, α,α-trehalose dihydrate, L-methionine, polysorbate 80 and water for injections. – The pH of the solution is between 5 and 6.

How MabThera® SC should be stored

- Keep the vial in the outer carton to protect MabThera® SC from light
- Store MabThera® SC in a refrigerator (2-8°C). Do not freeze.
- Check the expiry date on the outer carton.

Please refer to the approved package insert for further information.

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How to handle MabThera® SC:

Before handling MabThera® SC, please check the packaging to ensure you have the correct formulation. This is in order to avoid any confusion with MabThera® concentrate for solution for infusion, which has a different packaging colour code.

Check for the specific MabThera® SC packaging characteristics:

1. Red labelling:' For subcutaneous use only', 'solution for subcutaneous injection' and 'SC'
2. Pink flip-off cap

- MabThera® SC does not contain any antimicrobial preservative and, as with all unpreserved sterile solutions, should be used immediately.
- No incompatibilities have been observed between MabThera® SC and the following: polypropylene or polycarbonate syringe material, stainless steel transfer and injection needles, polyethylene Luer cone stoppers

How to administer MabThera® SC: Step-by-step guide

Important reminder:

• All patients must receive their first dose of MabThera® by intravenous infusion, using MabThera® concentrate for solution for infusion. MabThera® SC should only be given at the second or subsequent cycle of treatment.*

• Premedication consisting of an anti-pyretic and an anti-histaminic, e.g. paracetamol and diphenhydramine, should always be given before each administration of MabThera®. Premedication with glucocorticoids should be considered if MabThera® is not given in combination with glucocorticoid containing chemotherapy.

• MabThera® SC should be administered in an environment where full resuscitation facilities are immediately available and under the close supervision of an experienced healthcare professional.

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1. Prepare the patient for injection

The patient should be asked to lean back in a reclining chair or bed and to make their abdominal region accessible for injection.

2. Prepare the injection site

- The selected abdominal site should be thoroughly disinfected as per local practice.
- Each injection should be given at a different site and never into areas where the skin is red, bruised, tender, hard, or into areas where there are moles or scars.

3. Prepare MabThera® SC for injection

- The syringe should be prepared at the time of its administration.
- Ensure use of a needle suitable for subcutaneous injection.
- Attach the hypodermic injection needle to the syringe immediately prior to administration to avoid potential needle clogging.
- The whole content of the vial should be injected:

— 11.7 ml (1400 mg) for NHL

4. Perform the injection

- Pinch the skin of the abdomen with one hand to create a skin fold: this will facilitate the injection.
- Insert the injection needle into the skin fold with the other hand, using a sterile technique.
- Release the skin fold and apply pressure on the syringe, slowly injecting MabThera® SC into the subcutaneous tissue.

- MabThera® SC should be administered over approximately 5–7 minutes

- Using the palm of the hand to depress the plunger can help to maintain a constant flow rate.
- Ensure the full content of the syringe is injected into the subcutaneous

5. Inform the patient that they may leave

- The patient should be observed for at least 15 minutes following MabThera® SC administration. A longer period of observation may be appropriate in patients with an increased risk of hypersensitivity reactions.
- If the patient is not receiving any further treatment after the MabThera® SC injection, and if the patient is not presenting with any adverse reaction to the injection, the patient may leave the clinic.
- Many patients experience some side effects at or around the MabThera® SC injection site. These local side effects include pain, swelling, induration, bleeding, skin redness, itching and rash.
- The patient should be instructed to contact their doctor immediately if the following symptoms occur: breathing difficulties, tongue or throat swelling, vomiting or palpitations, as they could be indicative of an allergic reaction.

MabThera® SC 1400 mg: Standard BSS

S4 **MabThera® SC 1400 mg**: South Africa: 49/30.1/0466; Namibia: NS2 18/26/0023; Zimbabwe: PP 2017/9.7/5511. Abbreviated product information. For full prescribing information refer to the professional information approved by the Health Regulatory Authority.

COMPOSITION: Single dose vials contain 1400 mg/11,7 mL for subcutaneous injection. Each mL contains 120 mg of rituximab.

INDICATIONS: MabThera SC 1400 mg is indicated for the treatment of Non-Hodgkin's lymphoma (NHL):
- patients with relapsed or chemo-resistant low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma
- previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy
- patients with follicular lymphoma as maintenance treatment, after response to induction therapy
- patients with high grade CD20-positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP (Cyclophosphamide - C, Doxorubicin - H, Vincristine - O, Prednisone - P) chemotherapy.

DOSAGE: MabThera SC 1400 mg is NOT intended for intravenous administration. MabThera SC 1400 mg is intended for subcutaneous administration in non-Hodgkin's lymphoma (NHL) only, and in patients who tolerated a first IV administration.

Dosage adjustments during treatment: No dose reductions of MabThera are recommended. When MabThera is given in combination with chemotherapy, standard dose reductions for the chemotherapeutics medicines should be applied.

Low-grade/CD20 positive or Follicular B-cell Non-Hodgkin's lymphoma

All patients must always receive their first dose of MabThera by intravenous administration.

First administration: MabThera IV:

The first administration of MabThera must always be given by intravenous infusion at a dose of 375 mg/m^2 body surface area (BSA).

Initial treatment: ***Follicular B-cell Non-Hodgkin's lymphoma:***
- *Subcutaneous monotherapy:* MabThera SC 1400 mg used as monotherapy for adult patients is subcutaneous injection at a fixed dose of 1400 mg irrespective of the patient's body surface area, once weekly for 3 weeks following MabThera IV at week 1 (1st week R-IV then 3 weeks R-SC; 4 weeks in total).
- *Subcutaneous combination therapy:* MabThera in combination with chemotherapy for induction treatment of previously untreated or relapsed/refractory patients with follicular lymphoma is: first cycle with MabThera IV formulation 375 mg/m^2 body surface area, followed by subsequent cycles with MabThera SC formulation injected at a fixed dose of 1400 mg per cycle for up to 8 cycles.

MabThera SC 1400 mg should be administered on day 0 or day 1 of each chemotherapy cycle after administration of the glucocorticoid component of the chemotherapy, if applicable. The recommended dosage in combination with any chemotherapy is MabThera IV (R-IV) 375 mg/m^2 BSA IV for the first cycle followed by SC injection of MabThera SC (R-SC) at a fixed dose of 1400 mg irrespective of the patient's body surface area.
- 1st cycle R-IV with CVP + 7 cycles R-SC with CVP (21 days/cycle)
- 1st cycle R-IV with MCP + 7 cycles R-SC with MCP (28 days/cycle)
- 1st cycle R-IV with CHOP + 7 cycles R-SC with CHOP (21 days/cycle); or a total of 6 cycles
- (1st cycle R-IV then 5 cycles R-SC) if complete remission is achieved after 4 cycles
- 1st cycle R-IV with CHVP-Interferon + 5 cycles R-SC with CHVP-Interferon (21 days/cycle).

Re-treatment following relapse:
Patients who have responded to MabThera IV or SC initially may be treated again with MabThera SC at a fixed dose of 1400 mg, administered as a subcutaneous injection once weekly, following a first administration of MabThera given by intravenous infusion at a dose of 375 mg/m^2 BSA (1st week R-IV then 3 weeks R-SC; 4 weeks in total).
Maintenance treatment:

- Previously untreated patients after response to induction treatment may receive maintenance therapy with MabThera SC 1400 mg given at a fixed dose of 1400 mg once every 2 months until disease progression or for a maximum period of two years (12 administrations in total).
- Relapsed/refractory patients after response to induction treatment may receive maintenance therapy with MabThera SC given at a fixed dose of 1400 mg once every 3 months until disease progression or for a maximum period of two years (8 administrations in total).

High grade/CD 20 positive or Diffuse Large B-cell/Non-Hodgkin's Lymphoma: Intravenous Formulation
In patients with diffuse large B cell non-Hodgkin's lymphoma, MabThera IV should be used in combination with CHOP chemotherapy (R-CHOP). The recommended dosage is 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after IV administration of the glucocorticoid component of CHOP. The other components of CHOP should be given after the administration of MabThera IV. Safety and efficacy of MabThera have not been established in combination with other chemotherapies in diffuse large B cell non-Hodgkin's lymphoma.
All patients must always receive their first dose of MabThera by IV administration. The SC formulation must only be given at the second or subsequent cycles. In patients with diffuse large B cell non-Hodgkin's lymphoma MabThera SC 1400 should be used in combination with CHOP (cyclophosphamide, doxorubicin, prednisone and vincristine) chemotherapy.
First administration: Intravenous formulation The first administration of MabThera must always be given by intravenous infusion at a dose of 375 mg/m^2 BSA.
Subsequent administrations: Subcutaneous formulation
Patients unable to receive the full MabThera IV infusion dose should continue to receive subsequent cycles with MabThera IV until a full IV dose is successfully administered. For patients who are able to receive the full MabThera IV infusion dose, the second or subsequent MabThera doses can be given subcutaneously using the MabThera SC 1400 mg SC formulation.
The recommended dosage of MabThera SC 1400 mg SC is a fixed dose of 1400 mg, irrespective of the patient's BSA, administered on day 1 of each chemotherapy cycle for 8 cycles (1st cycle R-IV with CHOP + 7 cycles R-SC with CHOP; 8 cycles in total) after IV administration of the glucocorticoid component of CHOP.

CONTRAINDICATIONS: Hypersensitivity to rituximab or to any of the excipients or to murine proteins. Active, severe infections. Patients in a severely immunocompromised state. Severe heart failure (New York Heart Association Class IV) or severe, uncontrolled cardiac disease. Pregnancy and lactation.

WARNINGS AND PRECAUTIONS:
***Infusion-related reactions*:** Infusion-related deaths (death within 24 hours of infusion) have been reported. Most fatal infusion-related events occurred in association with the first Infusion.
Tumour Lysis Syndrome (TLS): Acute renal failure requiring dialysis and with instances of fatal outcome. Prophylaxis for TLS should be considered for patients at risk of developing rapid tumour lysis. These patients should be followed closely and appropriate laboratory monitoring performed.
General: The use of MabThera SC 1400 mg as monotherapy in patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy cannot be recommended as the safety of the once weekly subcutaneous administration has not been established.
Progressive Multifocal Leukoencephalopathy (PML): MabThera SC 1400 mg may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML). Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. If a patient develops PML, MabThera must be permanently discontinued. ***Infusion/Administration-related reactions****:* MabThera is associated with infusion-related reactions (IRRs). Severe infusion-related reactions with fatal outcome have been reported with the IV formulation, characterised by pulmonary events and in some cases included rapid tumour lysis and features of tumour lysis syndrome, in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms. Patients with a high number (> 25 x 10^9/L) of circulating malignant cells or high tumour burden who may be at higher risk of especially severe IRRs should only be treated with extreme caution.
Severe cytokine release syndrome: Characterised by severe dyspnoea, fatal outcomes have been reported. Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately and should receive aggressive symptomatic treatment.

Hypersensitivity reactions/Anaphylaxis: Anaphylactic and other hypersensitivity reactions have been reported following the IV administration of proteins to patients. Hypersensitivity reactions occur within minutes after starting infusion. Additional reactions were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia.
Administration-related reactions: Local cutaneous reactions, including injection site reactions, have been reported. Symptoms included pain, swelling, induration, haemorrhage, erythema, pruritus and rash. **All patients must always receive their first dose of MabThera by intravenous administration in order to avoid an irreversible administration of the full MabThera SC dose during Cycle 1.** During this cycle the patient would have the highest risk of experiencing an IRR that can be treated effectively by slowing or stopping the infusion. The subcutaneous formulation must only be given at the second or subsequent cycles.
Pulmonary events*:* included hypoxia, lung infiltration, and acute respiratory failure. Some have been preceded by severe bronchospasm and dyspnoea.
Rapid tumour lysis: MabThera IV/SC mediates the rapid lysis of benign and malignant CD20-positive cells. If signs and symptoms (e.g., hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, acute renal failure, elevated LDH) develop, treatment should be stopped immediately.
Cardiovascular: Since hypotension may occur during MabThera IV/SC administration, consideration should be given to withholding antihypertensive medicines 12 hours prior to and throughout MabThera IV/SC administration. Angina pectoris or cardiac dysrhythmia, such as atrial flutter and fibrillation, heart failure or myocardial infarction have occurred in patients treated with MabThera IV/SC. Less frequently, patients experienced an exacerbation of pre-existing cardiac conditions such as angina pectoris or congestive heart failure.
Monitoring of blood counts (haematological toxicities): Caution should be exercised in patients with neutrophil counts of $< 1,5 \times 10^9$/L and/or platelet counts of $< 75 \times 10^9$/L.
Infections: Treatment should not be initiated in patients with severe infections. Serious infections, including fatalities, can occur. Treatment should not be administered to patients with active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections), or severely immunocompromised patients (e.g. where levels of CD4 or CD8 are very low). Patients treated with MabThera should avoid exposure to patients with tuberculosis and should avoid contact with children and adults recently vaccinated with attenuated live vaccines.
Tuberculosis: All patients should be screened for active or latent tuberculosis (TB) infection prior to starting therapy. Patients with active or latent TB should be treated with standard anti-mycobacterial therapy before initiating MabThera.
Hepatitis B Infections: Cases of hepatitis B reactivation have been reported, including reports of fulminant hepatitis, some of which were fatal. Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment. Patients with active hepatitis B disease should not be treated with MabThera. Very rare cases of PML have been reported with intravenous formulation.
Skin reactions: Severe skin reactions such as Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome, some with fatal outcome, have been reported. In case of such an event, with a suspected relationship to MabThera, treatment should be permanently discontinued.
Immunisation: Vaccination with live virus vaccines is not recommended but patients may receive non-live vaccinations.

SIDE EFFECTS: Local cutaneous reactions, including injection site reactions, were very common. The most frequent serious adverse drug reactions (ADRs) were infusion-related reactions (including cytokine-release syndrome, tumour-lysis syndrome), infections and cardiovascular events. Other serious ADRs reported include hepatitis B reactivation and PML. ADRs reported fall under the following System Organ Classes: Infections and infestations; Blood and lymphatic system disorders; Immune system disorders; Metabolism and nutrition disorders; Psychiatric disorders; Nervous system disorders; Eye disorders, Ear and labyrinth disorders; Cardiac disorders; Vascular disorders; Respiratory, thoracic and mediastinal disorders; Gastrointestinal disorders; Skin and subcutaneous tissue disorders; Musculoskeletal, connective tissue and bone disorders; Renal and urinary disorders; General disorders and administration site conditions; Investigations.

PACK SIZES: Pack of 1 vial.

Full details are available from Roche Products (Pty) Ltd, PO Box 55922, Northlands, 2116. Tel: 011 502 5000 or Toll-free on REAL (Roche Ethical Assistance Line): 0800 21 21 25. www.roche.co.za
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