1. NAME OF THE MEDICINAL PRODUCT

MABTHERA 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 single-use vial contains 100 mg (in 10 ml) of rituximab.

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable regions sequences. The antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MABTHERA is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

4.2 Posology and method of administration

The recommended dosage of MABTHERA used as a single agent for adult patients is 375 mg/m^2 body surface, administered as an intravenous infusion once weekly for four weeks.

Mabthera infusions should be administered in a hospital environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced oncologist/haematologist.

Premedication consisting of a pain-reliever and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be administered before each infusion of MABTHERA. Premedication with corticosteroids should also be considered.

Patients should be closely monitored for the onset of cytokine release syndrome (see section 4.4*)*. Patients who develop evidence of severe reactions, especially severe dyspnoea, bronchospasm or hypoxia should have the infusion interrupted immediately. The patient should then be evaluated for evidence of tumour lysis syndrome including appropriate laboratory tests and, for pulmonary infiltration, with a chest x-ray. The infusion should not be restarted until complete resolution of all symptoms, and

normalisation of laboratory values and chest x-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for a second time the decision to stop the treatment should be seriously considered on a case by case basis.

Mild or moderate infusion-related reactions (section 4.8) usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.

***First infusion*:** The prepared MABTHERA solution should be administered by intravenous infusion through a dedicated line. The recommended initial rate for infusion is 50 mg/hr; after the first 30 minutes, it can be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr

***Subsequent infusions*:** Subsequent doses of MABTHERA can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minutes intervals, to a maximum of 400 mg/hr.

Retreatment following relapse: Patients who have responded to MABTHERA initially have been treated again with MABTHERA. Response rate seems to be comparable in these retreated patients.

4.3 Contraindications

MABTHERA is contraindicated in patients with known hypersensitivity to any component of this product or to murine proteins.

4.4 Special warnings and special precautions for use

Patients with a high number (>50,000 mm^3) of circulating malignant cells or high tumour burden, who may be at higher risk of especially severe cytokine release syndrome, should only be treated with extreme caution and when other therapeutic alternatives have been exhausted. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients.

Severe cytokine release syndrome is characterised by severe dyspnea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of ***tumour lysis syndrome*** such as hyperuricemia, hyperkalemia, hypocalcemia, acute renal failure, elevated LDH and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray. The syndrome frequently manifests itself within one or two hours of initiating the first infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution. Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately (see Section 4.2) and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until tumour lysis syndrome and pulmonary infiltration have

resolved or been ruled out. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe cytokine release syndrome.

Infusion related adverse reactions including cytokine release syndrome (see Section 4.8) accompanied by hypotension and bronchospasm have been observed in 10% of patients treated with MABTHERA. These symptoms are usually reversible with interruption of MABTHERA infusion and administration of a pain-reliever, an antihistaminic, and, occasionally, oxygen, intravenous saline or bronchodilators, and corticosteroids if required. Please see cytokine release syndrome above for severe reactions.

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines and corticosteroids, should be available for immediate use in the event of an allergic reaction during administration of MABTHERA. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome (described above). Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release.

Since hypotension may occur during MABTHERA infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the MABTHERA infusion.

Angina pectoris, or cardiac arrythmias have occured in patients treated with MABTHERA. Therefore patients with a history of cardiac disease should be monitored closely.

Although MABTHERA is not myelosuppressive, caution should be exercised when considering treatment of patients with neutrophils $<1.5 \times 10^9$/l and/or platelet counts $<75 \times 10^9$/l , as clinical experience in this population is limited. MABTHERA has been used in 21 patients who underwent autologous bone transplantation and other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity.

Periodic monitoring of a complete blood count with platelet count should be considered during therapy with MABTHERA.

Do not administer the prepared infusion solutions as an intravenous push or bolus.

Paediatric Use

The safety and efficacy of MABTHERA in children have not been established.

4.5 Interaction with other medicinal products and other forms of interaction

Currently, no data are available on possible drug interactions with MABTHERA. Patients with human anti-mouse antibody or human anti-chimeric antibody (HAMA/HACA) titres may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.

The tolerability of simultaneously or sequential combination of MABTHERA with agents liable to cause depletion of normal B-cells is not well defined. However, no

synergistic toxicity was observed in *40* patients treated with MABTHERA in combination with CHOP *(cyclophosphamide, doxorubicin, vincristine, prednisolone).*

4.6 Use during pregnancy and lactation

Pregnancy

Animal reproduction studies have not been conducted with rituximab. It is also not known whether MABTHERA can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. However, since IgG is known to pass the placental barrier, rituximab may cause B-cell depletion in the fetus. For these reasons MABTHERA should not be given to a pregnant woman unless the potential benefit outweighs the potential risk.

Due to the long retention time of rituximab in B-cell depleted patients, women of childbearing potential should use effective contraceptive methods during treatment and up to 12 months following MABTHERA therapy.

Nursing Mothers

Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, MABTHERA should not be given to a nursing woman.

4.7 Effects on ability to drive and use machines

It is not known whether rituximab has an effect on the ability to drive and to use machines, although the pharmacological activity and adverse events reported to date do not indicate that such an effect is likely.

4.8 Undesirable effects

Patients with high tumour burden defined as single lesions with a diameter > 10 cm have an increased incidence of severe (grade 3-4) adverse reactions.

Infusion Related Adverse Reactions

Infusion-related adverse reactions including cytokine release syndrome occurred in more than 50% of patients, and were predominantly seen during the first infusion, usually during the first one to two hours. These events mainly comprised fever, chills, and rigours. Other symptoms include flushing, angioedema, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, vomiting, and tumour pain. These symptoms were accompanied by hypotension and bronchospasm in about 10% of the cases. Less frequently, patients experienced an exacerbation of pre-existing cardiac conditions such as angina pectoris or congestive heart failure. The incidence of infusion-related events decreases substantially with subsequent infusions.

Fatal outcomes have been reported for patients who developed severe cytokine release syndrome, occasionally associated with signs and symptoms of tumour lysis syndrome leading to multi-organ failure, respiratory failure, and renal failure (see Section 4.4).

Haematologic Adverse Reactions

Haematologic abnormalities occur in a minority of patients and are usually mild and reversible. Severe thrombocytopenia and neutropenia occurred in 1.3% and 1.9% of patients respectively, and severe anaemia occurred in 1.0% of patients. A single occurence of transient aplastic anaemia (pure red cell aplasia) and infrequent occurences of hemolytic anaemia following MABTHERA treatment were reported.

Other Adverse Reactions

Pulmonary adverse reaction, including severe bronchoconstriction and rarely fatalities from respiratory failure, have been reported with MABTHERA therapy.

Anaphylaxis has been reported in patients treated with MABTHERA (see Section 4.4).

Although MABTHERA induces B-cell depletion and can be associated with decreased serum immunoglobulins, the incidence of infection does not appear to be greater than expected in this patient population, and serious or opportunistic infections were considerably less than reported with conventional chemotherapy. During treatment and up to one year following therapy, approximately 17% and 16%, respectively, of patients developed infections which were usually common, non opportunistic and mild.

Additional adverse events which occurred in ≥ 1% of patients observed in clinical trials are listed below.

Body as a Whole—asthenia, abdominal pain, back pain, chest pain, malaise, abdominal enlargement, pain at infusion site;
Cardiovascular System—hypertension, bradycardia, tachycardia, arrythmia, postural hypotension;
Digestive System—diarrhea, dyspepsia, anorexia;
Haemic and Lymphatic System— lymphadenopathy;
Metabolic and Nutritional disorders—hyperglycemia, peripheral oedema, LDH increase, hypocalcemia;
Musculo-Skeletal System—arthralgia, myalgia, pain, hypertonia;
Nervous System—dizziness, anxiety, paresthesia, hypesthesia, agitation, insomnia, nervousness;
Respiratory System—cough increase, sinusitis, bronchitis, respiratory disease;
Skin and Appendages—night sweats, sweating, herpes simplex, herpes zoster;
Special Senses—lacrimation disorder, conjunctivitis, taste perversion.

Additional severe adverse events occurring in < 1% of patients are listed below.

Haemic and Lymphatic System—coagulation disorder;
Respiratory System--asthma, lung disorder.

4.9 Overdose

There has been no experience of overdosage in human clinical trials. However, single doses higher than 500 mg/m^2 body surface have not been tested.

5. **5. PHARMACOLOGICAL PROPERTIES**

6. **5.1 Pharmacodynamic properties**

7.

8. Pharmaco-therapeutic group : Antineoplastic Agents**,** ATC code: L01X X21

Rituximab binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. The antigen is expressed on > 95% of all B-cell non-Hodgkin's lymphomas (NHLs).

CD20 is found on both normal and malignant B-cells, but not on haematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissue. This antigen does not internalise upon antibody binding and is not shed from the cell surface. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding.

The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and recruits immune effector functions to mediate B-cell lysis via the Fc domain. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more of the Fcγ receptors on the surface of granulocytes, macrophages and NK cells.

Median peripheral B-cell counts declined below normal following completion of the first dose, with recovery beginning after 6 months. B-cell levels returned to normal between 9 and 12 months following completion of therapy.

Clinical Laboratory Findings

Of 67 patients evaluated for human anti-mouse antibody (HAMA), no responses were noted. Of 355 patients evaluated for HACA, less then 1.0% (3 patients) were positive.

5.2 Pharmacokinetic properties

In patients treated with either 125, 250 or 375 mg/m^2 body surface of MABTHERA, given as an intravenous infusion once weekly for four weeks, serum antibody concentrations increased with increasing dose. In patients receiving the 375 mg/m^2 dose, the mean serum half-life of rituximab was 68.1 hr, the C_{max} was 238.7 μg/ml and the mean plasma clearance was 0.0459 L/hr after the first infusion; after the fourth infusion, the mean values for serum half-life, C_{max} and plasma clearance were 189.9 hr, 480.7 μ g/ml and 0.0145 L/hr, respectively. However, variability in serum levels was large.

Rituximab serum concentrations were statistically significantly higher in responding patients compared to non-responding patients just prior to and after the fourth infusion and post treatment. Serum concentrations were negatively correlated with tumour burden. Typically, rituximab was detectable for 3 to 6 months.

5.3 Preclinical safety data

Rituximab has shown to be highly specific to the CD20 antigen on B-cells. Toxicity studies in cynomolgus monkeys have shown no other effect than the expected pharmacological depletion of B-cells in peripheral blood and in lymphoid tissue. The recovery of the peripheral B cells was marked by large intraindividual variability. However, peripheral B-cell recovery usually started two weeks after treatment, and median B-cells counts reached 40% of baseline levels after a 3 month period. No adverse reactions unrelated to the targeted effect were seen, whether in single or in multiple dose studies in the cynomolgus monkey.

No long-term animal studies have been performed to establish the carcinogenic potential of rituximab, or to determine its effects on fertility in males or females. Standard tests to investigate mutagenicity have not been carried out, since such tests are not relevant for this molecule. However, due to its character its is unlikely that rituximab has any mutagenic potential.

9.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Polysorbate 80
Sodium chloride
Sodium hydroxide
Hydrochloric acid
Water for injection

6.2 Incompatibilities

No incompatibilities between MABTHERA and polyvinyl chloride or polyethylene bags or infusion sets have been observed.

6.3 Shelf-life

24 months

6.4 Special precautions for storage

Store vials between 2-8 °C. Protect undiluted vials from direct sunlight.

Prepared infusion solutions of MABTHERA should be used immediately after dilution and are stable for 12 hours at room temperature. If necessary, the prepared solutions may be stored in the refrigerator (at 2-8 °C) and are chemically stable for up to 24 hours. MABTHERA does not contain any antimicrobial preservative; therefore, care must be taken to ensure the sterility of the prepared solution.

6.5 Nature and content of container

Single-use, preservative-free, clear glass vials with butyl rubber stopper containing 100 mg of rituximab in 10 ml (10 mg/ml).

Packs of 2 vials.

6.6 Instructions for use, handling and disposal (if appropriate)

MABTHERA is a clear, colourless liquid provided in sterile, preservative-free, non-pyrogenic, single use vials.

Aseptically withdraw the necessary amount of MABTHERA, and dilute to a calculated concentration of 1 to 4 mg/ml rituximab into an infusion bag containing sterile, pyrogen-free 0.9% Sodium Chloride or 5% Dextrose in water. For mixing the solution, gently invert the bag in order to avoid foaming. Care must be taken to ensure the sterility of prepared solutions. Since the drug product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited, 40 Broadwater Road, Welwyn Garden City, Hertfordshire, AL7 3AY, U.K.

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/98/067/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2 June 1998

10. DATE OF REVISION OF TEXT

1. NAME OF THE MEDICINAL PRODUCT

MABTHERA 500 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 single-use vial contains 500 mg (in 50 ml) of rituximab.

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable regions sequences. The antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MABTHERA is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

4.2 Posology and method of administration

The recommended dosage of MABTHERA used as a single agent for adult patients is 375 mg/m^2 body surface, administered as an intravenous infusion once weekly for four weeks.

Mabthera infusions should be administered in a hospital environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced oncologist/haematologist.

Premedication consisting of a pain-reliever and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be administered before each infusion of MABTHERA. Premedication with corticosteroids should also be considered.

Patients should be closely monitored for the onset of cytokine release syndrome (see section 4.4*)*. Patients who develop evidence of severe reactions, especially severe dyspnoea, bronchospasm or hypoxia should have the infusion interrupted immediately. The patient should then be evaluated for evidence of tumour lysis syndrome including appropriate laboratory tests and, for pulmonary infiltration, with a chest x-ray. The infusion should not be restarted until complete resolution of all symptoms, and normalisation of laboratory values and chest x-ray findings. At this time, the infusion can

be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for a second time the decision to stop the treatment should be seriously considered on a case by case basis.

Mild or moderate infusion-related reactions (section 4.8) usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.

***First infusion*:** The prepared MABTHERA solution should be administered by intravenous infusion through a dedicated line. The recommended initial rate for infusion is 50 mg/hr; after the first 30 minutes, it can be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr

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Retreatment following relapse: Patients who have responded to MABTHERA initially have been treated again with MABTHERA. Response rate seems to be comparable in these retreated patients.

4.3 Contraindications

MABTHERA is contraindicated in patients with known hypersensitivity to any component of this product or to murine proteins.

4.4 Special warnings and special precautions for use

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Severe cytokine release syndrome is characterised by severe dyspnea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of ***tumour lysis syndrome*** such as hyperuricemia, hyperkalemia, hypocalcemia, acute renal failure, elevated LDH and may be associated with acute respiratory failure and death. The acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray. The syndrome frequently manifests itself within one or two hours of initiating the first infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution. Patients who develop severe cytokine release syndrome should have their infusion interrupted immediately (see Section 4.2) and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until tumour lysis syndrome and pulmonary infiltration have

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Angina pectoris, or cardiac arrythmias have occured in patients treated with MABTHERA. Therefore patients with a history of cardiac disease should be monitored closely.

Although MABTHERA is not myelosuppressive, caution should be exercised when considering treatment of patients with neutrophils $<1.5 \times 10^9$/l and/or platelet counts $<75 \times 10^9$/l , as clinical experience in this population is limited. MABTHERA has been used in 21 patients who underwent autologous bone transplantation and other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity.

Periodic monitoring of a complete blood count with platelet count should be considered during therapy with MABTHERA.

Do not administer the prepared infusion solutions as an intravenous push or bolus.

Paediatric Use

The safety and efficacy of MABTHERA in children have not been established.

4.5 Interaction with other medicinal products and other forms of interaction

Currently, no data are available on possible drug interactions with MABTHERA. Patients with human anti-mouse antibody or human anti-chimeric antibody (HAMA/HACA) titres may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.

The tolerability of simultaneously or sequential combination of MABTHERA with agents liable to cause depletion of normal B-cells is not well defined. However, no synergistic toxicity was observed in *40* patients treated with MABTHERA in combination with CHOP *(cyclophosphamide, doxorubicin, vincristine, prednisolone).*

4.6 Use during pregnancy and lactation

Pregnancy

Animal reproduction studies have not been conducted with rituximab. It is also not known whether MABTHERA can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. However, since IgG is known to pass the placental barrier, rituximab may cause B-cell depletion in the fetus. For these reasons MABTHERA should not be given to a pregnant woman unless the potential benefit outweighs the potential risk.

Due to the long retention time of rituximab in B-cell depleted patients, women of childbearing potential should use effective contraceptive methods during treatment and up to 12 months following MABTHERA therapy.

Nursing Mothers

Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, MABTHERA should not be given to a nursing woman.

4.7 Effects on ability to drive and use machines

It is not known whether rituximab has an effect on the ability to drive and to use machines, although the pharmacological activity and adverse events reported to date do not indicate that such an effect is likely.

4.8 Undesirable effects

Patients with high tumour burden defined as single lesions with a diameter > 10 cm have an increased incidence of severe (grade 3-4) adverse reactions.

Infusion Related Adverse Reactions

Infusion-related adverse reactions including cytokine release syndrome occurred in more than 50% of patients, and were predominantly seen during the first infusion, usually during the first one to two hours. These events mainly comprised fever, chills, and rigours. Other symptoms include flushing, angioedema, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, vomiting, and tumour pain. These symptoms were accompanied by hypotension and bronchospasm in about 10% of the cases. Less frequently, patients experienced an exacerbation of pre-existing cardiac conditions such as angina pectoris or congestive heart failure. The incidence of infusion-related events decreases substantially with subsequent infusions.

Fatal outcomes have been reported for patients who developed severe cytokine release syndrome, occasionally associated with signs and symptoms of tumour lysis syndrome leading to multi-organ failure, respiratory failure, and renal failure (see Section 4.4).

Haematologic Adverse Reactions

Haematologic abnormalities occur in a minority of patients and are usually mild and reversible. Severe thrombocytopenia and neutropenia occurred in 1.3% and 1.9% of patients respectively, and severe anaemia occurred in 1.0% of patients. A single occurence of transient aplastic anaemia (pure red cell aplasia) and infrequent occurences of hemolytic anaemia following MABTHERA treatment were reported.

Other Adverse Reactions

Pulmonary adverse reaction, including severe bronchoconstriction and rarely fatalities from respiratory failure, have been reported with MABTHERA therapy.

Anaphylaxis has been reported in patients treated with MABTHERA (see Section 4.4).

Although MABTHERA induces B-cell depletion and can be associated with decreased serum immunoglobulins, the incidence of infection does not appear to be greater than expected in this patient population, and serious or opportunistic infections were considerably less than reported with conventional chemotherapy. During treatment and up to one year following therapy, approximately 17% and 16%, respectively, of patients developed infections which were usually common, non opportunistic and mild.

Additional adverse events which occurred in ≥ 1% of patients observed in clinical trials are listed below.

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Digestive System—diarrhea, dyspepsia, anorexia;
Haemic and Lymphatic System— lymphadenopathy;
Metabolic and Nutritional disorders—hyperglycemia, peripheral oedema, LDH increase, hypocalcemia;
Musculo-Skeletal System—arthralgia, myalgia, pain, hypertonia;
Nervous System—dizziness, anxiety, paresthesia, hypesthesia, agitation, insomnia, nervousness;
Respiratory System—cough increase, sinusitis, bronchitis, respiratory disease;
Skin and Appendages—night sweats, sweating, herpes simplex, herpes zoster;
Special Senses—lacrimation disorder, conjunctivitis, taste perversion.

Additional severe adverse events occurring in < 1% of patients are listed below.

Haemic and Lymphatic System—coagulation disorder;
Respiratory System--asthma, lung disorder.

4.9 Overdose

There has been no experience of overdosage in human clinical trials. However, single doses higher than 500 mg/m^2 body surface have not been tested.

10. 5. PHARMACOLOGICAL PROPERTIES

11. 5.1 Pharmacodynamic properties

12.

13. Pharmaco-therapeutic group : Antineoplastic Agents**,** ATC code: L01X X21

Rituximab binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. The antigen is expressed on > 95% of all B-cell non-Hodgkin's lymphomas (NHLs).

CD20 is found on both normal and malignant B-cells, but not on haematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissue. This antigen does not internalise upon antibody binding and is not shed from the cell surface. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding.

The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and recruits immune effector functions to mediate B-cell lysis via the Fc domain. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more of the Fcγ receptors on the surface of granulocytes, macrophages and NK cells.

Median peripheral B-cell counts declined below normal following completion of the first dose, with recovery beginning after 6 months. B-cell levels returned to normal between 9 and 12 months following completion of therapy.

Clinical Laboratory Findings

Of 67 patients evaluated for human anti-mouse antibody (HAMA), no responses were noted. Of 355 patients evaluated for HACA, less then 1.0% (3 patients) were positive.

5.2 Pharmacokinetic properties

In patients treated with either 125, 250 or 375 mg/m^2 body surface of MABTHERA, given as an intravenous infusion once weekly for four weeks, serum antibody concentrations increased with increasing dose. In patients receiving the 375 mg/m^2 dose, the mean serum half-life of rituximab was 68.1 hr, the C_{max} was 238.7 μg/ml and the mean plasma clearance was 0.0459 L/hr after the first infusion; after the fourth infusion, the mean values for serum half-life, C_{max} and plasma clearance were 189.9 hr, 480.7 μg/ml and 0.0145 L/hr, respectively. However, variability in serum levels was large.

Rituximab serum concentrations were statistically significantly higher in responding patients compared to non-responding patients just prior to and after the fourth infusion and post treatment. Serum concentrations were negatively correlated with tumour burden. Typically, rituximab was detectable for 3 to 6 months.

5.3 Preclinical safety data

Rituximab has shown to be highly specific to the CD20 antigen on B-cells. Toxicity studies in cynomolgus monkeys have shown no other effect than the expected pharmacological depletion of B-cells in peripheral blood and in lymphoid tissue. The recovery of the peripheral B cells was marked by large intraindividual variability. However, peripheral B-cell recovery usually started two weeks after treatment, and median B-cells counts reached 40% of baseline levels after a 3 month period. No adverse reactions unrelated to the targeted effect were seen, whether in single or in multiple dose studies in the cynomolgus monkey.

No long-term animal studies have been performed to establish the carcinogenic potential of rituximab, or to determine its effects on fertility in males or females. Standard tests to investigate mutagenicity have not been carried out, since such tests are not relevant for this molecule. However, due to its character its is unlikely that rituximab has any mutagenic potential.

14.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Polysorbate 80
Sodium chloride
Sodium hydroxide
Hydrochloric acid
Water for injection

6.2 Incompatibilities

No incompatibilities between MABTHERA and polyvinyl chloride or polyethylene bags or infusion sets have been observed.

6.3 Shelf-life

24 months

6.4 Special precautions for storage

Store vials between 2-8 °C. Protect undiluted vials from direct sunlight.

Prepared infusion solutions of MABTHERA should be used immediately after dilution and are stable for 12 hours at room temperature. If necessary, the prepared solutions may be stored in the refrigerator (at 2-8 °C) and are chemically stable for up to 24 hours. MABTHERA does not contain any

antimicrobial preservative; therefore, care must be taken to ensure the sterility of the prepared solution.

6.5 Nature and content of container

Single-use, preservative-free, clear glass vials with butyl rubber stopper containing 500 mg of rituximab in 50 ml (10 mg/ml).
Packs of 1 vial.

6.6 Instructions for use, handling and disposal (if appropriate)

MABTHERA is a clear, colourless liquid provided in sterile, preservative-free, non-pyrogenic, single use vials.

Aseptically withdraw the necessary amount of MABTHERA, and dilute to a calculated concentration of 1 to 4 mg/ml rituximab into an infusion bag containing sterile, pyrogen-free 0.9% Sodium Chloride or 5% Dextrose in water. For mixing the solution, gently invert the bag in order to avoid foaming. Care must be taken to ensure the sterility of prepared solutions. Since the drug product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited, 40 Broadwater Road, Welwyn Garden City, Hertfordshire, AL7 3AY, U.K.

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/98/067/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2 June 1998

10. DATE OF REVISION OF TEXT

PACKAGE LEAFLET

(MABTHERA vials 100 mg)

Name of the medicinal product

MABTHERA 100 mg

Rituximab

If you want to know more about this product, or if you are not sure about a particular item in this leaflet, ask your doctor or pharmacist.

Composition

The active substance of MABTHERA is rituximab. The 10 ml vial contains 100 mg of rituximab.

The vial also contains the excipients (additional ingredients) sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid and water for injection.

Pharmaceutical form and contents

MABTHERA is supplied as a concentrate for solution for infusion. Vials of 10 ml are available as a pack of 2 vials. Before infusion the concentrate needs to be diluted.

Type of medicine

Rituximab is a monoclonal antibody. Monoclonal antibodies are proteins which specifically recognise and bind to a unique other protein called antigen. Rituximab binds to an antigen on the surface of specific white blood cells, the B lymphocytes, thereby stopping the pathological growth of these cells.

Marketing authorisation holder

The Marketing Authorisation Holder is Roche Registration Limited, 40 Broadwater Road, Welwyn Garden City, Hertfordshire, AL7 3AY, United Kingdom.

Manufacturer, responsible for batch release, and importer

Hoffmann-La Roche AG, Postfach 1270, 79630 Grenzach-Wyhlen, Germany

When should MABTHERA be used?

MABTHERA is used for the treatment of patients with a certain type of disease affecting the lymphatic system. It is especially used in conditions where other treatments proved unsuccessful.

Important information before using MABTHERA

When should MABTHERA not be used?
You should not receive MABTHERA if it is known that you are allergic to rituximab or to any of the ingredients the vial contains, or to proteins of similar origin. Your doctor will inform you accordingly.

Appropriate precautions for use
If you are treated with MABTHERA, reactions like breathing difficulties, fever, chills, rash, and reduction in blood pressure may occur. These effects mainly occur with the first infusion. You will be observed by a health professional during infusions. If you develop a reaction, your doctor will slow down or interrupt infusion and treat you appropriately. After improvement of the symptoms, the infusion may be continued. If you develop a severe reaction, especially a severe breathing difficulty, your doctor will interrupt the infusion, perform tests on your blood, and will take an x-ray of your chest. The infusion will not be started again unless your doctor is sure that you have recovered completely from the reaction.

Because of the possible reduction in blood pressure at the beginning of the treatment, patients taking medicines for high blood pressure may be advised by their doctor to stop taking them 12 hours prior to MABTHERA infusion. If you have a history of heart disease (i.e. angina pectoris, cardiac arrhythmias, or congestive heart failure) or a history of breathing problems your doctor will take special care of you during therapy with MABTHERA.

Therapy with MABTHERA may cause abnormalities of your blood. Therefore, your doctor will perform blood tests periodically during therapy.

Interaction with other medicinal products and other forms of interaction
Before starting treatment, make sure your doctor knows if you are taking other medicines (including those not prescribed by your doctor). This is extremely important, as using more than one medicine at the same time can strengthen or weaken their effect. Therefore, MABTHERA should not be used with other drugs without your doctor's consent. It is possible that after treatment with MABTHERA you may experience allergic reactions if you are treated with other medications containing monoclonal antibodies.

Use in children
At present, there is insufficient information to recommend the use of MABTHERA in children.

Use during pregnancy and breast-feeding
You must tell your doctor if you are pregnant, if you think you are pregnant or if you intend to become pregnant. Your doctor will discuss with you the risks and benefits of taking MABTHERA during pregnancy.

If you are a woman of childbearing potential, you must take an effective method of birth control during therapy with MABTHERA and up to 12 months following therapy.

You should not breast-feed your baby during treatment with MABTHERA as it is not known whether MABTHERA is secreted into human milk.

Effect on ability to drive and use machinery
It is not known whether MABTHERA has an effect on your ability to drive a car or operate machinery.

Use of prepared infusion solutions
Prepared infusion solutions of MABTHERA should be used immediately after dilution and are stable for 12 hours at room temperature. If necessary, the prepared solutions may be stored in the refrigerator (at 2-8 °C) and are chemically stable for up to 24 hours. MABTHERA does not contain any antimicrobial preservative; therefore, care must be taken to ensure the sterility of the prepared solution.

How to use MABTHERA

Dosage and frequency of administration
Your doctor will give you a medicine to prevent or reduce pain and/or fever and allergy before each infusion of MABTHERA.

The doctor will administer a suitable dose of MABTHERA in the form of an infusion once weekly for four weeks. The dose depends on your body weight and body height. The standard treatment you will receive is a total of 4 infusions. However, depending on the circumstances of your disease or response to the drug your doctor may change the dose and/or the number of infusions. Repeated treatment courses with MABTHERA are possible.

Method and route of administration
MABTHERA is administered by a health care professional after dilution as an intravenous infusion. For dilution pyrogen-free 0.9% sodium chloride or 5% Dextrose in water can be used. Dilution should result in a concentration of 1 to 4 mg rituximab per ml infusion solution.

Duration of treatment
A course of treatment usually lasts for 22 days.

Undesirable effects

Along with its desired effects, a medicine may cause some unwanted effects. Especially within the first 2 hours of the first infusion you may develop fever, chills and shivering. Other infusion-related effects are: blisters and itching of your skin, sickness, tiredness, headache, breathing difficulties, sensation of the tongue or throat swelling, itchy, runny nose, vomiting, flushing, irregular heart rate and tumour pain. Pre-existing heart conditions such as angina pectoris or congestive heart failure may get worse. The frequency of these reactions decreases during the subsequent infusions. MABTHERA may also cause abnormalities of your blood and affect liver function. Infections have been observed during or after treatment.

Additionally you may experience infrequently some of the following undesirable effects: pain, in particular pain of the abdomen, back, chest, muscles and joints, and pain at the infusion site, feeling unwell, abdominal enlargement, changes in blood pressure, changes in heart rate, diarrhoea, dyspepsia (stomach indigestion), anorexia, anemia and disorders of the lymphatic system, blood-clotting disorders, increased muscle tension, dizziness, anxiety, paresthesia (an abnormal sensation at the extremities, such as of burning, pricking, tickling, or tingling), hypesthesia (diminished sensitivity of the skin), agitation, insomnia (inability to sleep), nervousness, cough increase, sinusitis (inflammation of the sinuses), bronchitis (inflammation in the lungs), herpes simplex (viral infection), herpes zoster (viral infection), sweating, lacrimation disorder (abnormal tears), conjunctivitis (inflammation of the surface of the eye), changes to taste.

Some severe reactions, in particular severe breathing difficulties, have been fatal. This is why your doctor will watch you closely, and why it is important for you to tell your doctor immediately if you experience any difficulty in breathing.

If you experience these effects, or in particular if you experience any undesirable effect which is not mentioned in this leaflet, please talk to your doctor or pharmacist (chemist).

How to store MABTHERA

Always store the vials in the closed original pack between 2-8°C (in the refrigerator).

This medicine should always be kept out of sight and reach of children.

Do not use this medicine after the expiry date shown on the outer pack and on the vial label.

Date of last revision

Other information

If you like to have further information about this product please contact the local representative of the Marketing Authorisation Holder:

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PACKAGE LEAFLET

(MABTHERA vials 500 mg)

Name of the medicinal product

MABTHERA 500 mg

Rituximab

If you want to know more about this product, or if you are not sure about a particular item in this leaflet, ask your doctor or pharmacist.

Composition

The active substance of MABTHERA is rituximab. The 50 ml vial contains 500 mg of rituximab.

The vial also contains the excipients (additional ingredients) sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid and water for injection.

Pharmaceutical form and contents

MABTHERA is supplied as a concentrate for solution for infusion. Vials of 50 ml are available as a pack of 1 vial. Before infusion the concentrate needs to be diluted.

Type of medicine

Rituximab is a monoclonal antibody. Monoclonal antibodies are proteins which specifically recognise and bind to a unique other protein called antigen. Rituximab binds to an antigen on the surface of specific white blood cells, the B lymphocytes, thereby stopping the pathological growth of these cells.

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Appropriate precautions for use
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