ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MabThera 100 mg
Concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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 region 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.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

MabThera is a clear, colourless liquid.

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.

MabThera is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with CVP chemotherapy.

MabThera is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP chemotherapy.

See section 5.1 (Pharmacodynamic properties) for further information.

4.2 Posology and method of administration

Standard dosage
The prepared MabThera solution should be administered as an IV infusion through a dedicated line.

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 if MabThera is not given in combination with CHOP chemotherapy.

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.

Follicular non-Hodgkin's lymphoma
The recommended dosage of MabThera used as a single agent for adult patients is 375 mg/m^2 body surface, administered as an IV infusion once weekly for four weeks.

The recommended dosage of MabThera in combination with CVP chemotherapy is 375 mg/m^2 body surface area for 8 cycles (21 days/cycle), administered on day 1 of each chemotherapy cycle after IV administration of the corticosteroid component of CVP.

Retreatment following relapse in non-Hodgkin's lymphoma: Patients who have responded to MabThera initially have been treated again with MabThera at a dose of 375 mg/m^2 body surface area, administered as an IV infusion once weekly for four weeks (see section 5.1).

Diffuse large B cell non-Hodgkin's lymphoma
MabThera should be used in combination with CHOP chemotherapy. 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 corticosteroid component of CHOP. Safety and efficacy of MabThera have not been established in combination with other chemotherapies.

First infusion: 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.

Dosage adjustments during treatment
No dose reductions of MabThera are recommended. When MabThera is given in combination with CHOP or CVP chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied.

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 tumour burden or with a high number ($\geq$25 x 10^9/l) of circulating malignant cells, 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 hyperuricaemia, hyperkalaemia, hypocalcaemia, 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 been resolved or 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, IV 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 IV administration of proteins to patients. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Medicinal products 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 arrhythmias such as atrial flutter and fibrillation heart failure or myocardial infarction have occurred in patients treated with MabThera. Therefore patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.

Although MabThera is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophils < 1.5 x 10^9/l and/or platelet counts < 75 x 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.

Consideration should be given to the need for regular full blood counts, including platelet counts, during monotherapy with MabThera. When MabThera is given in combination with CHOP or CVP chemotherapy, regular full blood counts should be performed according to usual medical practice.

Very rare cases of hepatitis B reactivation, including reports of fulminant hepatitis, have been reported in subjects receiving rituximab, although these subjects were also exposed to cytotoxic chemotherapy. The reports are confounded by both the underlying disease state and the cytotoxic chemotherapy. Patients with a history of hepatitis B infection should be carefully monitored for signs of active hepatitis B infection when rituximab is used in association with cytotoxic chemotherapy.

Do not administer the prepared infusion solutions as an IV 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 chemotherapy other than CHOP or CVP, or agents which are liable to cause depletion of normal B cells is not well defined.

4.6 Pregnancy and lactation

Pregnancy

Animal reproduction studies have not been conducted with rituximab. It is also not known whether MabThera can cause foetal 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.

Lactation

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 women who are breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed, although the pharmacological activity and adverse events reported to date do not indicate that such an effect is likely.

4.8 Undesirable effects

Monotherapy

The following data are based on 356 patients treated in single-arm studies of MabThera administered as single agent (see section 5.1). Most patients received MabThera 375 mg/m^2 weekly for 4 doses. These include 39 patients with bulky disease (lesions ≥ 10 cm) and 58 patients who received more than one course of MabThera (60 re-treatments). Thirty-seven patients received 375 mg/m^2 for eight doses and 25 patients received doses other than 375 mg/m^2 for four doses and up to 500 mg/m^2 single dose in the Phase I setting.

The following table shows adverse events that were considered to be at least possibly related to MabThera during or up to 12 months after treatment. Adverse events were graded according to the four-scale National Cancer Institute (NCI) Common Toxicity Criteria.

Table 1. Summary of adverse events reported in ≥ 1 % of 356 patients receiving MabThera monotherapy in clinical trials

	All grades	**Grade 3 and 4**
Body system Adverse event	**%**	**%**
Any adverse event	91.0	17.7
Body as a whole		
Fever	48.3	0.6
Chills	31.7	2.2

	All grades	Grade 3 and 4
Body system Adverse event	**%**	**%**
Asthenia	18.0	0.3
Headache	12.6	0.6
Throat irritation	7.6	-
Abdominal pain	7.0	0.6
Back pain	4.5	0.3
Pain	4.2	-
Flushing	4.2	-
Chest pain	2.2	-
Malaise	2.0	-
Tumour pain	1.7	-
Cold syndrome	1.4	-
Neck pain	1.1	-
Cardiovascular system		
Hypotension	9.8	0.8
Hypertension	4.5	0.3
Tachycardia	1.4	-
Arrhythmia	1.4	0.6
Orthostatic hypotension	1.1	-
Digestive system		
Nausea	17.1	0.3
Vomiting	6.7	0.3
Diarrhoea	4.2	-
Dyspepsia	2.8	-
Anorexia	2.8	-
Dysphagia	1.4	0.3
Stomatitis	1.4	-
Constipation	1.1	-
Blood and lymphatic system		
Leukopenia	12.4	2.8
Neutropenia	11.2	4.2
Thrombocytopenia	9.6	1.7
Anaemia	3.7	1.1
Metabolic and nutritional disorders		
Angioedema	10.7	0.3
Hyperglycaemia	5.3	0.3
Peripheral oedema	4.8	-
LDH increase	2.2	-
Hypocalcaemia	2.2	-
Facial oedema	1.1	-
Weight decrease	1.1	-
Musculoskeletal system		
Myalgia	8.1	0.3
Arthralgia	5.9	0.6
Hypertonia	1.4	-
Pain	1.1	0.3
Nervous system		
Dizziness	7.3	-
Paresthesia	2.5	-
Anxiety	2.2	-
Insomnia	2.2	-
Vasodilatation	1.7	-
Hypoaesthesia	1.4	-

	All grades	Grade 3 and 4
Body system Adverse event	**%**	**%**
Agitation	1.4	-
Respiratory system		
Bronchospasm	7.9	1.4
Rhinitis	7.3	0.3
Increased cough	5.1	0.3
Dyspnoea	2.2	0.8
Chest pain	1.1	-
Respiratory disease	1.1	-
Skin and appendages		
Pruritus	12.4	0.3
Rash	11.2	0.3
Urticaria	7.3	0.8
Night sweats	2.8	-
Sweating	2.8	-
Special senses		
Lacrimation disorder	3.1	-
Conjunctivitis	1.4	-
Ear pain	1.1	-
Tinnitus	1.1	-

The following adverse events were also reported (< 1 %): coagulation disorders, asthma, lung disorder, bronchiolitis obliterans, hypoxia, abdominal enlargement, pain at the infusion site, bradycardia, lymphadenopathy, nervousness, depression, dysgeusia.

Infusion-related reactions: Infusion-related reactions 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 rigors. Other symptoms included 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 symptoms decreases substantially with subsequent infusions (see section 4.4).

Infections: MabThera induced B cell depletion in 70 % to 80 % of patients but was associated with decreased serum immunoglobulins only in a minority of patients. Infectious events, irrespective of causal assessment, occurred in 30.3 % of 356 patients: 18.8 % of patients had bacterial infections, 10.4 % had viral infections, 1.4 % had fungal infections, and 5.9 % had infections of unknown aetiology. Severe infectious events (grade 3 or 4), including sepsis occurred in 3.9 % of patients; in 1.4 % during the treatment period and in 2.5 % during the follow up period. As these were single-arm trials, the contributory role of MabThera or of the underlying NHL and its previous treatment to the development of these infectious events cannot be determined.

Haematologic Adverse Reactions: Haematological abnormalities occurred in a minority of patients and are usually mild and reversible. Severe (grade 3 and 4) thrombocytopenia and neutropenia were reported in 1.7 % and 4.2 % of patients respectively, and severe anaemia was reported in 1.1 % of patients. A single occurrence of transient aplastic anaemia (pure red cell aplasia) and infrequent occurrences of haemolytic anaemia following MabThera treatment were reported.

Cardiovascular events: Cardiovascular events were reported in 18.8 % of patients during the treatment period. The most frequently reported events were hypotension and hypertension. Two patients (0.6 %) experienced grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) during a MabThera infusion and one patient with a history of myocardial infarction experienced angina pectoris, evolving into myocardial infarction 4 days later.

Subpopulations:

Elderly patients: (≥ 65 years): The incidence of any adverse event and of grade 3 and 4 adverse events was similar in elderly (N=94) and younger (N=237) patients (88.3 % versus 92.0 % for any adverse event and 16.0 % versus 18.1 % for grade 3 and 4 adverse events).

Bulky disease: Patients with bulky disease (N=39) had a higher incidence of grade 3 and 4 adverse events than patients without bulky disease (N=195) (25.6 % versus 15.4 %). The incidence of any adverse event was similar in these two groups (92.3 % in bulky disease versus 89.2 % in non-bulky disease).

Re-treatment: The percentage of patients reporting any adverse event and grade 3 and 4 adverse events upon re-treatment (N=60) with further courses of MabThera was similar to the percentage of patients reporting any adverse event and grade 3 and 4 adverse events upon initial exposure (N=203) (95.0 % versus 89.7 % for any adverse event and 13.3 % versus 14.8 % for grade 3 and 4 adverse events).

Adverse reactions reported in other monotherapy clinical trials: One case of serum sickness has been reported in a clinical trial using MabThera monotherapy for treatment of diffuse large B cell lymphoma.

In combination with CVP chemotherapy

The following data are based on 321 patients from a randomised phase III clinical trial comparing MabThera plus CVP (R-CVP) to CVP alone (162 R-CVP, 159 CVP).

Differences between the treatment groups with respect to the type and incidence of adverse event were mainly accounted for by typical adverse events associated with MabThera monotherapy.

The following grade 3 to 4 clinical adverse events were reported in ≥ 2 % higher incidence in patients receiving R-CVP compared to CVP treatment group and therefore may be attributable to R-CVP. Adverse events were graded according to the four-scale National Cancer Institute (NCI) Common Toxicity Criteria:

- Fatigue: 3.7 % (R-CVP), 1.3 % (CVP)

- Neutropenia: 3.1 % (R-CVP), 0.6 % (CVP)

Infusion-related reactions: The signs and symptoms of severe or life-threatening (NCI CTC grades 3 and 4) infusion-related reactions (defined as starting during or within one day of an infusion with MabThera) occurred in 9 % of all patients who received R-CVP. These results are consistent with those observed during monotherapy (see section 4.4 and 4.8, Undesirable effects, monotherapy), and included rigors, fatigue, dyspnoea, dyspepsia, nausea, rash NOS, flushing.

Infections: The overall proportion of patients with infections or infestations during treatment and for 28 days after trial treatment end was comparable between the treatment groups (33 % R-CVP, 32 % CVP). The most common infections were upper respiratory tract infections which were reported for 12.3 % patients on R-CVP and 16.4 % patients receiving CVP; most of these infections were nasopharyngitis.

Serious infections were reported in 4.3 % of the patients receiving R-CVP and 4.4 % of the patients receiving CVP. No life threatening infections were reported during this study.

Haematologic laboratory abnormalities: 24 % of patients on R-CVP and 14 % of patients on CVP experienced grade 3 or 4 neutropenia during treatment. The proportion of patients with grade 4 neutropenia was comparable between the treatment groups. These laboratory findings were reported as adverse events and resulted in medical intervention in 3.1 % of patients on R-CVP and 0.6 % of patients on CVP. All other laboratory abnormalities were not treated and resolved without any

intervention. In addition, the higher incidence of neutropenia in the R-CVP group was not associated with a higher incidence of infections and infestations.

No relevant difference between the two treatment arms was observed with respect to grade 3 and 4 anaemia (0.6 % R-CVP and 1.9 % CVP) and thrombocytopenia (1.2 % in the R-CVP group and no events reported in the CVP group).

Cardiac events: The overall incidence of cardiac disorders in the safety population was low (4 % R-CVP, 5 % CVP), with no relevant differences between the treatment groups.

In combination with CHOP chemotherapy

The following table shows grade 3 to 4 clinical adverse events, including grade 2 infections, from a randomised phase III clinical trial comparing MabThera plus CHOP (R-CHOP) to CHOP alone in a safety population of 398 patients. Events shown were reported at a greater than 2 % higher incidence with R-CHOP when compared to CHOP alone and therefore may be attributable to R-CHOP (absolute incidence cut off at 2 %). Adverse events were graded according to the four-scale National Cancer Institute of Canada (NCIC) Common Toxicity Criteria.

Table 2: Excess incidence (>= 2 %) of grade 3 and 4 adverse events (including grade 2 infections) with R-CHOP compared with CHOP (overall cut off of 2 %)

	R-CHOP	**CHOP**
	N=202	**N=196**
	%	%
Infections and infestations		
Bronchitis	11.9	8.2
Herpes zoster	4.0	1.5
Acute bronchitis	2.5	0.5
Sinusitis	2.5	-
Respiratory disorders		
Dyspnoea	8.9	3.6
General disorders and administration site disorders		
Shivering	3.5	1.0
Vascular disorders		
Hypertension	2.5	0.5
Cardiac disorder		
Atrial fibrillation	2.5	0.5

Infusion-related reactions: Grade 3 and 4 infusion-related reactions (defined as starting during or within one day of an infusion with MabThera) occurred in approximately 9 % of patients at the time of the first cycle of R-CHOP. The incidence of grade 3 and 4 infusion-related reactions decreased to less than 1 % by the eighth cycle of R-CHOP. The signs and symptoms were consistent with those observed during monotherapy (see section 4.4 and 4.8, Undesirable effects, monotherapy), and included fever, chills, hypotension, hypertension, tachycardia, dyspnoea, bronchospasm, nausea, vomiting, pain and features of tumour lysis syndrome. Additional reactions reported in isolated cases at the time of R-CHOP therapy were myocardial infarction, atrial fibrillation and pulmonary oedema.

Infections: The proportion of patients with grade 2 to 4 infections and/or febrile neutropenia was 55.4 % in the R-CHOP group and 51.5 % in the CHOP group. Febrile neutropenia (i.e. no report of concomitant documented infection) was reported only during the treatment period, in 20.8 % in the R-CHOP group and 15.3 % in the CHOP group. The overall incidence of grade 2 to 4 infections was 45.5 % in the R-CHOP group and 42.3 % in the CHOP group with no difference in the incidence of systemic bacterial and fungal infections. Grade 2 to 4 fungal infections were more frequent in the R-CHOP group (4.5 % vs 2.6 % in the CHOP group); this difference was due to a higher incidence of localised Candida infections during the treatment period. The incidence of grade 2 to 4 herpes zoster,

including ophthalmic herpes zoster, was higher in the R-CHOP group (4.5 %) than in the CHOP group (1.5 %), with 7 of a total of 9 cases in the R-CHOP group occurring during the treatment phase.

Haematologic events: After each treatment cycle, grade 3 and 4 leucopenia (88 % vs 79 %) and neutropenia (97 % vs 88 %) occurred more frequently in the R-CHOP group than in the CHOP group. There was no evidence that neutropenia was more prolonged in the R-CHOP group. No difference between the two treatment arms was observed with respect to grade 3 and 4 anaemia (19 % in the CHOP group vs 14 % in the R-CHOP group) and thrombocytopenia (16 % in the CHOP group vs 15 % in the R-CHOP group). The time to recovery from all haematological abnormalities was comparable in the two treatment groups.

Cardiac events: The incidence of grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (14 patients, 6.9 %) as compared to the CHOP group (3 patients, 1.5 %). All of these arrhythmias either occurred in the context of a MabThera infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease. No difference between the R-CHOP and CHOP group was observed in the incidence of other grade 3 and 4 cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease.

Neurologic events: During the treatment period, four patients (2 %) in the R-CHOP group, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment groups in the incidence of other thromboembolic events. In contrast, three patients (1.5 %) had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period.

Post-marketing experience

As part of the continuing post-marketing surveillance of MabThera safety, the following serious adverse reactions have been observed:

Blood and lymphatic system disorders	
Rare (≥ 1/10,000, < 1/1000):	Late neutropenia[1]
Very rare (< 1/10,000):	Pancytopenia Aplastic anaemia Transient increase in serum IgM levels[2]
Cardiovascular system	
Rare (≥ 1/10,000, < 1/1000):	*Severe cardiac events[3]
Very rare (< 1/10,000):	*Heart failure[3] *Myocardial infarction[3]
Ear and labyrinth disorders	
Very rare (< 1/10,000):	†Hearing loss
Eye disorders	
Very rare (< 1/10,000):	†Severe vision loss
General disorders and administration site conditions	
Very rare (< 1/10,000):	*Multi-organ failure
Immune system disorders	
Uncommon (≥ 1/1000, < 1/100):	Infusion related reactions
Rare (≥ 1/10,000, < 1/1000):	Anaphylaxis
Very rare (< 1/10,000):	*Tumour lysis syndrome *Cytokine release syndrome Serum sickness Hepatitis B reactivation[4]
Nervous system disorders	
Very rare (< 1/10,000):	Cranial neuropathy Peripheral neuropathy

	†Facial nerve palsy †Loss of other senses
Renal and urinary disorders	
Very rare (< 1/10,000):	*Renal failure
Respiratory, thoracic and mediastinal disorders	
Rare (≥ 1/10,000, < 1/1000):	*Bronchospasm
Very rare (< 1/10,000):	*Respiratory failure Pulmonary infiltrates Interstitial pneumonitis
Skin and subcutaneous tissue disorders	
Very rare (< 1/10,000):	Severe bullous skin reactions Toxic epidermal necrolysis[5]
Vascular disorders	
Very rare (< 1/10,000):	Vasculitis (predominately cutaneous) Leukocytoclastic vasculitis

*Associated with infusion-related reactions. Rarely fatal cases reported
† Signs and symptoms of cranial neuropathy. Occurred at various times up to several months after completion of MabThera therapy
[1] Neutropenia that has occurred more than four weeks after the last infusion of MabThera.
[2] In post-marketing studies of rituximab in patients with Waldenstrom's macroglobulinaemia, transient increases in serum IgM levels have been observed following treatment initiation, which may be associated with hyperviscosity and related symptoms. The transient IgM increase usually returned to at least baseline level within 4 months.
[3] Observed mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and were mostly associated with infusion-related reactions
[4] Very rare cases of hepatitis B reactivation, have been reported in subjects receiving rituximab in combination with cytotoxic chemotherapy.
[5] Including fatal cases

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic Agents, ATC code: L01X C02

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 the Fc domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms of effector-mediated 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. Rituximab binding to CD 20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis.

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.

Follicular non-Hodgkin's lymphoma:
Monotherapy: *Initial treatment, weekly for 4 doses:* In the pivotal study, 166 patients with relapsed or chemoresistant low-grade or follicular B cell NHL received 375 mg/m^2 of MabThera as an IV infusion once weekly for four weeks. The overall response rate (ORR) in the intent-to-treat (ITT) population was 48 % ($CI_{95\,\%}$ 41 % - 56 %) with a 6 % complete response (CR) and a 42 % partial response (PR) rate. The projected median time to progression (TTP) for responding patients was 13.0 months. In a subgroup analysis, the ORR was higher in patients with IWF B, C, and D histological subtypes as compared to IWF A subtype (58 % vs. 12 %), higher in patients whose largest lesion was < 5 cm vs. > 7 cm in greatest diameter (53 % vs. 38 %), and higher in patients with chemosensitive relapse as compared to chemoresistant (defined as duration of response < 3 months) relapse (50 % vs. 22 %). ORR in patients previously treated with autologous bone marrow transplant (ABMT) was 78 % versus 43 % in patients with no ABMT. Neither age, sex, lymphoma grade, initial diagnosis, presence or absence of bulky disease, normal or high LDH nor presence of extranodal disease had a statistically significant effect (Fisher's exact test) on response to MabThera. A statistically significant correlation was noted between response rates and bone marrow involvement. 40 % of patients with bone marrow involvement responded compared to 59 % of patients with no bone marrow involvement (p=0.0186). This finding was not supported by a stepwise logistic regression analysis in which the following factors were identified as prognostic factors: histological type, bcl-2 positivity at baseline, resistance to last chemotherapy and bulky disease.

Initial treatment, weekly for 8 doses: In a multi-centre, single-arm study, 37 patients with relapsed or chemoresistant, low grade or follicular B cell NHL received 375 mg/m^2 of MabThera as IV infusion weekly for eight doses. The ORR was 57 % ($CI_{95\,\%}$ 41 % – 73 %; CR 14 %, PR 43 %) with a projected median TTP for responding patients of 19.4 months (range 5.3 to 38.9 months).

Initial treatment, bulky disease, weekly for 4 doses: In pooled data from three studies, 39 patients with relapsed or chemoresistant, bulky disease (single lesion ≥ 10 cm in diameter), low grade or follicular B cell NHL received 375 mg/m^2 of MabThera as IV infusion weekly for four doses. The ORR was 36 % ($CI_{95\,\%}$ 21 % – 51 %; CR 3 %, PR 33 %) with a median TTP for responding patients of 9.6 months (range 4.5 to 26.8 months).

Re-treatment, weekly for 4 doses: In a multi-centre, single-arm study, 58 patients with relapsed or chemoresistant low grade or follicular B cell NHL, who had achieved an objective clinical response to a prior course of MabThera, were re-treated with 375 mg/m^2 of MabThera as IV infusion weekly for four doses. Three of the patients had received two courses of MabThera before enrollment and thus were given a third course in the study. Two patients were re-treated twice in the study. For the 60 re-treatments on study, the ORR was 38 % ($CI_{95\,\%}$ 26 % – 51 %; 10 % CR, 28 % PR) with a projected median TTP for responding patients of 17.8 months (range 5.4 – 26.6). This compares favourably with the TTP achieved after the prior course of MabThera (12.4 months).

Initial treatment, in combination with CVP: In an open-label randomised trial, a total of 322 previously untreated low-grade or follicular B cell NHL patients were randomised to receive either CVP chemotherapy (cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1 –5) every 3 weeks for 8 cycles or MabThera 375 mg/m^2 in combination with CVP (R-CVP). MabThera was administered on the first day of each treatment cycle. A total of 321 patients (162 R-CVP, 159 CVP) received therapy and were analysed for efficacy. At the time of the analysis, the median observation time was 18 months. R-CVP led to a significant benefit over CVP for the primary endpoint, time to treatment failure (25.9 months vs. 6.7 months, p < 0.0001, log-rank test). The risk of experiencing a treatment failure event was reduced by 67 % (95 % CI: 56 % - 76 %) with R-CVP compared with CVP alone, using a Cox regression

analysis. The Kaplan-Meier estimated event free rate at 12 months was 69 % in the R-CVP group compared with 32 % in the CVP group. The proportion of patients with a tumour response (CR, CRu, PR) was significantly higher ($p< 0.0001$ Chi-Square test) in the R-CVP group (80.9 %) than the CVP group (57.2 %). At 18 months, the median duration of response had not been reached in the R-CVP group and was 9.8 months in the CVP group ($p < 0.0001$, log-rank test). Amongst responding patients, Cox regression analysis showed that the risk of relapse was reduced by 70 % (95 % CI: 55 % - 81 %) in the R-CVP group compared to the CVP group.

The time to institution of new lymphoma treatment or death was significantly longer in the R-CVP group (not estimable), compared to the CVP group (12.3 months) ($p < 0.0001$, log-rank test). Treatment with R-CVP significantly prolonged the time to disease progression compared to CVP, 27 months and 14.5 months, respectively. At 12 months, 81 % in the R-CVP group had not relapsed compared to 58 % of patients receiving CVP.

The benefit of adding rituximab to CVP was seen consistently throughout the population recruited in study M39021 (randomised according to BNLI criteria (no versus yes), age (≤ 60 years, > 60 years), number of extra-nodal sites (0-1 versus > 1), bone marrow involvement (no versus yes), LDH (elevated, not elevated), β_2-microglobulin (elevated, not elevated), B symptoms (absent, present), bulky disease (absent, present), number of nodal sites (< 5 versus ≥ 5), haemoglobin (≤ 12 g/dL versus > 12 g/dL), IPI (≤ 1 versus > 1), and FLIPI index (0-2 versus 3-5)).

Due to the number of events at the time of analysis and the relatively short observation time of 18 months, conclusion regarding differences for overall survival cannot be drawn.

Diffuse large B cell non-Hodgkin's lymphoma: In a randomised, open-label trial, a total of 399 previously untreated elderly patients (age 60 to 80 years) with diffuse large B cell lymphoma received standard CHOP chemotherapy (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisone 40 mg/m^2/day on days 1-5) every 3 weeks for eight cycles, or MabThera 375 mg/m^2 plus CHOP (R-CHOP). MabThera was administered on the first day of the treatment cycle.

The final efficacy analysis included all randomised patients (197 CHOP, 202 R-CHOP), and had a median follow-up duration of approximately 31 months. The two treatment groups were well balanced in baseline disease characteristics and disease status. The final analysis confirmed that R-CHOP treatment was associated with a clinically relevant and statistically significant improvement in the duration of event-free survival (the primary efficacy parameter; where events were death, relapse or progression of lymphoma, or institution of a new anti-lymphoma treatment) ($p = 0.0001$). Kaplan Meier estimates of the median duration of event-free survival were 35 months in the R-CHOP arm compared to 13 months in the CHOP arm, representing a risk reduction of 41 %. At 24 months, estimates for overall survival were 68.2 % in the R-CHOP arm compared to 57.4 % in the CHOP arm. A subsequent analysis of the duration of overall survival, carried out with a median follow-up duration of 38 months, confirmed the benefit of R-CHOP over CHOP treatment ($p=0.0094$), representing a risk reduction of 33 %.

The analysis of all secondary parameters (response rates, progression-free survival, disease-free survival, duration of response) verified the treatment effect of R-CHOP compared to CHOP. The complete response rate after cycle 8 was 76.2 % in the R-CHOP group and 62.4 % in the CHOP group ($p=0.0028$). The risk of disease progression was reduced by 46 % and the risk of relapse by 51 %. In all patients subgroups (gender, age, age adjusted IPI, Ann Arbor stage, ECOG, β2 microglobulin, LDH, albumin, B symptoms, bulky disease, extranodal sites, bone marrow involvement), the risk ratios for event-free survival and overall survival (R-CHOP compared with CHOP) were less than 0.83 and 0.95 respectively. R-CHOP was associated with improvements in outcome for both high- and low-risk patients according to age adjusted IPI.

Clinical Laboratory Findings

Of 67 patients evaluated for human anti-mouse antibody (HAMA), no responses were noted. Of 356 patients evaluated for HACA, 1.1 % (4 patients) were positive.

5.2 Pharmacokinetic properties

Pharmacokinetic studies performed in a phase I study in which patients (n=15) with relapsed B cell lymphoma were given single doses of rituximab at 10, 50, 100 or 500 mg/m^2 indicated that serum levels and half-life of rituximab were proportional to dose. In a cohort of 14 patients among the 166 patients with relapsed or chemoresistant low-grade or follicular non-Hodgkin's lymphoma enrolled in the phase III pivotal trial and given rituximab 375 mg/m^2 as an IV infusion for 4 weekly doses, the mean serum half-life was 76.3 hours (range, 31.5 to 152.6 hours) after the first infusion and 205.8 hours (range, 83.9 to 407.0 hours) after the fourth infusion. The mean C_{max} after the first and fourth infusion were 205.6 ± 59.9 µg/ml and 464.7 ± 119.0 µg/ml, respectively. The mean plasma clearance after the first and fourth infusion was 0.0382 ± 0.0182 L/h and 0.0092 ± 0.0033 L/h, 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 and the number of circulating B cells at baseline. Typically, rituximab was detectable for 3 to 6 months.

Elimination and distribution have not been extensively studied in patients with diffuse large B cell non-Hodgkin's lymphoma, but available data indicate that serum levels of rituximab in these patients are comparable to those in patients with follicular non-Hodgkin's lymphoma following treatment with similar doses.

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 it is unlikely that rituximab has any mutagenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

30 months

The prepared infusion solution of MabThera is physically and chemically stable for 24 hours at 2 °C – 8 °C and subsequently 12 hours at room temperature.

6.4 Special precautions for storage

Store vials at 2 °C - 8 °C (in a refrigerator). Keep the container in the outer carton in order to protect from light.

The prepared infusion solution of MabThera is physically and chemically stable for 24 hours at 2 °C – 8 °C and subsequently 12 hours at room temperature.

From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C – 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Single-use, preservative-free, clear Type I 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 and handling and disposal

MabThera is 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.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/067/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2 June 1998 / 28 July 2003

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

MabThera 500 mg
Concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 single-use vial contains 500 mg of rituximab in 50 ml (10 mg/ml).

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 region 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.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

MabThera is a clear, colourless liquid.

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.

MabThera is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with CVP chemotherapy.

MabThera is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP chemotherapy.

See section 5.1 (Pharmacodynamic properties) for further information.

4.2 Posology and method of administration

Standard dosage
The prepared MabThera solution should be administered as an IV infusion through a dedicated line.

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 if MabThera is not given in combination with CHOP chemotherapy.

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.

Follicular non-Hodgkin's lymphoma

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

The recommended dosage of MabThera in combination with CVP chemotherapy is 375 mg/m^2 body surface area for 8 cycles (21 days/cycle), administered on day 1 of each chemotherapy cycle after IV administration of the corticosteroid component of CVP.

Retreatment following relapse in non-Hodgkin's lymphoma: Patients who have responded to MabThera initially have been treated again with MabThera at a dose of 375 mg/m^2 body surface area, administered as an IV infusion once weekly for four weeks (see section 5.1).

Diffuse large B cell non-Hodgkin's lymphoma
MabThera should be used in combination with CHOP chemotherapy. 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 corticosteroid component of CHOP. Safety and efficacy of MabThera have not been established in combination with other chemotherapies.

First infusion: 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.

Dosage adjustments during treatment
No dose reductions of MabThera are recommended. When MabThera is given in combination with CHOP or CVP chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied.

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 tumour burden or with a high number ($\geq$25 x 10^9/l)) of circulating malignant cells, 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 hyperuricaemia,

hyperkalaemia, hypocalcaemia, 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 been resolved or 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, IV 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 IV administration of proteins to patients. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Medicinal products 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 arrhythmias such as atrial flutter and fibrillation, heart failure or myocardial infarction have occurred in patients treated with MabThera. Therefore patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.

Although MabThera is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophils < 1.5 x 10^9/l and/or platelet counts < 75 x 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.

Consideration should be given to the need for regular full blood counts, including platelet counts, during monotherapy with MabThera. When MabThera is given in combination with CHOP or CVP chemotherapy, regular full blood counts should be performed according to usual medical practice

Very rare cases of hepatitis B reactivation, including reports of fulminant hepatitis, have been reported in subjects receiving rituximab, although these subjects were also exposed to cytotoxic chemotherapy. The reports are confounded by both the underlying disease state and the cytotoxic chemotherapy. Patients with a history of hepatitis B infection should be carefully monitored for signs of active hepatitis B infection when rituximab is used in association with cytotoxic chemotherapy.

Do not administer the prepared infusion solutions as an IV 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 withchemotherapy other than CHOP or CVP, or agents which are liable to cause depletion of normal B cells is not well defined.

4.6 Pregnancy and lactation

Pregnancy

Animal reproduction studies have not been conducted with rituximab. It is also not known whether MabThera can cause foetal 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.

Lactation

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 women who are breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed, although the pharmacological activity and adverse events reported to date do not indicate that such an effect is likely.

4.8 Undesirable effects

Monotherapy

The following data are based on 356 patients treated in single-arm studies of MabThera administered as single agent (see section 5.1). Most patients received MabThera 375 mg/m^2 weekly for 4 doses. These include 39 patients with bulky disease (lesions ≥ 10 cm) and 58 patients who received more than one course of MabThera (60 re-treatments). Thiry-seven patients received 375 mg/m^2 for eight doses and 25 patients received doses other than 375 mg/m^2 for four doses and up to 500 mg/m^2 single dose in the Phase I setting.

The following table shows adverse events that were considered to be at least possibly related to MabThera during or up to 12 months after treatment. Adverse events were graded according to the four-scale National Cancer Institute (NCI) Common Toxicity Criteria.

Table 1. Summary of adverse events reported in ≥ 1 % of 356 patients receiving MabThera monotherapy in clinical trials

	All grades	Grade 3 and 4
Body system Adverse event	**%**	**%**
Any adverse event	91.0	17.7
Body as a whole		
Fever	48.3	0.6
Chills	31.7	2.2

	All grades	Grade 3 and 4
Body system Adverse event	**%**	**%**
Asthenia	18.0	0.3
Headache	12.6	0.6
Throat irritation	7.6	-
Abdominal pain	7.0	0.6
Back pain	4.5	0.3
Pain	4.2	-
Flushing	4.2	-
Chest pain	2.2	-
Malaise	2.0	-
Tumour pain	1.7	-
Cold syndrome	1.4	-
Neck pain	1.1	-
Cardiovascular system		
Hypotension	9.8	0.8
Hypertension	4.5	0.3
Tachycardia	1.4	-
Arrhythmia	1.4	0.6
Orthostatic hypotension	1.1	-
Digestive system		
Nausea	17.1	0.3
Vomiting	6.7	0.3
Diarrhoea	4.2	-
Dyspepsia	2.8	-
Anorexia	2.8	-
Dysphagia	1.4	0.3
Stomatitis	1.4	-
Constipation	1.1	-
Blood and lymphatic system		
Leukopenia	12.4	2.8
Neutropenia	11.2	4.2
Thrombocytopenia	9.6	1.7
Anaemia	3.7	1.1
Metabolic and nutritional disorders		
Angioedema	10.7	0.3
Hyperglycaemia	5.3	0.3
Peripheral oedema	4.8	-
LDH increase	2.2	-
Hypocalcaemia	2.2	-
Facial oedema	1.1	-
Weight decrease	1.1	-
Musculoskeletal system		
Myalgia	8.1	0.3
Arthralgia	5.9	0.6
Hypertonia	1.4	-
Pain	1.1	0.3
Nervous system		
Dizziness	7.3	-
Paresthesia	2.5	-
Anxiety	2.2	-
Insomnia	2.2	-
Vasodilatation	1.7	-
Hypoaesthesia	1.4	-

	All grades	Grade 3 and 4
Body system Adverse event	**%**	**%**
Agitation	1.4	-
Respiratory system		
Bronchospasm	7.9	1.4
Rhinitis	7.3	0.3
Increased cough	5.1	0.3
Dyspnoea	2.2	0.8
Chest pain	1.1	-
Respiratory disease	1.1	-
Skin and appendages		
Pruritus	12.4	0.3
Rash	11.2	0.3
Urticaria	7.3	0.8
Night sweats	2.8	-
Sweating	2.8	-
Special senses		
Lacrimation disorder	3.1	-
Conjunctivitis	1.4	-
Ear pain	1.1	-
Tinnitus	1.1	-

The following adverse events were also reported (< 1 %): coagulation disorders, asthma, lung disorder, bronchiolitis obliterans, hypoxia, abdominal enlargement, pain at the infusion site, bradycardia, lymphadenopathy, nervousness, depression, dysgeusia.

Infusion-related reactions: Infusion-related reactions 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 rigors. Other symptoms included 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 symptoms decreases substantially with subsequent infusions (see section 4.4).

Infections: MabThera induced B cell depletion in 70 % to 80 % of patients but was associated with decreased serum immunoglobulins only in a minority of patients. Infectious events, irrespective of causal assessment, occurred in 30.3 % of 356 patients: 18.8 % of patients had bacterial infections, 10.4 % had viral infections, 1.4 % had fungal infections, and 5.9 % had infections of unknown aetiology. Severe infectious events (grade 3 or 4), including sepsis occurred in 3.9 % of patients; in 1.4 % during the treatment period and in 2.5 % during the follow up period. As these were single-arm trials, the contributory role of MabThera or of the underlying NHL and its previous treatment to the development of these infectious events cannot be determined.

*Haematologic Adverse Reactions:*Haematological abnormalities occurred in a minority of patients and are usually mild and reversible. Severe (grade 3 and 4) thrombocytopenia and neutropenia were reported in 1.7 % and 4.2 % of patients respectively, and severe anaemia was reported in 1.1 % of patients. A single occurrence of transient aplastic anaemia (pure red cell aplasia) and infrequent occurrences of haemolytic anaemia following MabThera treatment were reported.

Cardiovascular events: Cardiovascular events were reported in 18.8 % of patients during the treatment period. The most frequently reported events were hypotension and hypertension. Two patients (0.6 %) experienced grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) during a MabThera infusion and one patient with a history of myocardial infarction experienced angina pectoris, evolving into myocardial infarction 4 days later.

Subpopulations:

Elderly patients: (≥ 65 years): The incidence of any adverse event and of grade 3 and 4 adverse events was similar in elderly (N=94) and younger (N=237) patients (88.3 % versus 92.0 % for any adverse event and 16.0 % versus 18.1 % for grade 3 and 4 adverse events).

Bulky disease: Patients with bulky disease (N=39) had a higher incidence of grade 3 and 4 adverse events than patients without bulky disease (N=195) (25.6 % versus 15.4 %). The incidence of any adverse event was similar in these two groups (92.3 % in bulky disease versus 89.2 % in non-bulky disease).

Re-treatment: The percentage of patients reporting any adverse event and grade 3 and 4 adverse events upon re-treatment (N=60) with further courses of MabThera was similar to the percentage of patients reporting any adverse event and grade 3 and 4 adverse events upon initial exposure (N=203) (95.0 % versus 89.7 % for any adverse event and 13.3 % versus 14.8 % for grade 3 and 4 adverse events).

Adverse reactions reported in other monotherapy clinical trials: One case of serum sickness has been reported in a clinical trial using MabThera monotherapy for treatment of diffuse large B cell lymphoma.

In combination with CVP chemotherapy

The following data are based on 321 patients from a randomised phase III clinical trial comparing MabThera plus CVP (R-CVP) to CVP alone (162 R-CVP, 159 CVP).

Differences between the treatment groups with respect to the type and incidence of adverse event were mainly accounted for by typical adverse events associated with MabThera monotherapy.

The following grade 3 to 4 clinical adverse events were reported in ≥ 2 % higher incidence in patients receiving R-CVP compared to CVP treatment group and therefore may be attributable to R-CVP. Adverse events were graded according to the four-scale National Cancer Institute (NCI) Common Toxicity Criteria:

- Fatigue: 3.7 % (R-CVP), 1.3 % (CVP)

- Neutropenia: 3.1 % (R-CVP), 0.6 % (CVP)

Infusion-related reactions: The signs and symptoms of severe or life-threatening (NCI CTC grades 3 and 4) infusion-related reactions (defined as starting during or within one day of an infusion with MabThera) occurred in 9 % of all patients who received R-CVP. These results are consistent with those observed during monotherapy (see section 4.4 and 4.8, Undesirable effects, monotherapy), and included rigors, fatigue, dyspnoea, dyspepsia, nausea, rash NOS, flushing.

Infections: The overall proportion of patients with infections or infestations during treatment and for 28 days after trial treatment end was comparable between the treatment groups (33 % R-CVP, 32 % CVP). The most common infections were upper respiratory tract infections which were reported for 12.3 % patients on R-CVP and 16.4 % patients receiving CVP; most of these infections were nasopharyngitis.

Serious infections were reported in 4.3 % of the patients receiving R-CVP and 4.4 % of the patients receiving CVP. No life threatening infections were reported during this study.

Haematologic laboratory abnormalities: 24 % of patients on R-CVP and 14 % of patients on CVP experienced grade 3 or 4 neutropenia during treatment. The proportion of patients with grade 4 neutropenia was comparable between the treatment groups. These laboratory findings were reported as adverse events and resulted in medical intervention in 3.1 % of patients on R-CVP and 0.6 % of patients on CVP. All other laboratory abnormalities were not treated and resolved without any

intervention. In addition, the higher incidence of neutropenia in the R-CVP group was not associated with a higher incidence of infections and infestations.

No relevant difference between the two treatment arms was observed with respect to grade 3 and 4 anaemia (0.6 % R-CVP and 1.9 % CVP) and thrombocytopenia (1.2 % in the R-CVP group and no events reported in the CVP group).

Cardiac events: The overall incidence of cardiac disorders in the safety population was low (4 % R-CVP, 5 % CVP), with no relevant differences between the treatment groups.

In combination with CHOP chemotherapy

The following table shows grade 3 to 4 clinical adverse events, including grade 2 infections, from a randomised phase III clinical trial comparing MabThera plus CHOP (R-CHOP) to CHOP alone in a safety population of 398 patients. Events shown were reported at a greater than 2 % higher incidence with R-CHOP when compared to CHOP alone and therefore may be attributable to R-CHOP (absolute incidence cut off at 2 %).Adverse events were graded according to the four-scale National Cancer Institute of Canada (NCIC) Common Toxicity Criteria.

Table 2: Excess incidence (>= 2 %) of grade 3 and 4 adverse events (including grade 2 infections) with R-CHOP compared with CHOP (overall cut off of 2 %)

	R-CHOP	**CHOP**
	N=202	**N=196**
	%	%
Infections and infestations		
Bronchitis	11.9	8.2
Herpes zoster	4.0	1.5
Acute bronchitis	2.5	0.5
Sinusitis	2.5	-
Respiratory disorders		
Dyspnoea	8.9	3.6
General disorders and administration site disorders		
Shivering	3.5	1.0
Vascular disorders		
Hypertension	2.5	0.5
Cardiac disorder		
Atrial fibrillation	2.5	0.5

Infusion-related reactions: Grade 3 and 4 infusion-related reactions (defined as starting during or within one day of an infusion with MabThera) occurred in approximately 9 % of patients at the time of the first cycle of R-CHOP. The incidence of grade 3 and 4 infusion-related reactions decreased to less than 1 % by the eighth cycle of R-CHOP. The signs and symptoms were consistent with those observed during monotherapy (see section 4.4 and 4.8, Undesirable effects, monotherapy), and included fever, chills, hypotension, hypertension, tachycardia, dyspnoea, bronchospasm, nausea, vomiting, pain and features of tumour lysis syndrome. Additional reactions reported in isolated cases at the time of R-CHOP therapy were myocardial infarction, atrial fibrillation and pulmonary oedema.

Infections: The proportion of patients with grade 2 to 4 infections and/or febrile neutropenia was 55.4 % in the R-CHOP group and 51.5 % in the CHOP group. Febrile neutropenia (i.e. no report of concomitant documented infection) was reported only during the treatment period, in 20.8 % in the R-CHOP group and 15.3 % in the CHOP group. The overall incidence of grade 2 to 4 infections was 45.5 % in the R-CHOP group and 42.3 % in the CHOP group with no difference in the incidence of systemic bacterial and fungal infections. Grade 2 to 4 fungal infections were more frequent in the R-CHOP group (4.5 % vs 2.6 % in the CHOP group); this difference was due to a higher incidence of localised Candida infections during the treatment period. The incidence of grade 2 to 4 herpes zoster,

including ophthalmic herpes zoster, was higher in the R-CHOP group (4.5 %) than in the CHOP group (1.5 %), with 7 of a total of 9 cases in the R-CHOP group occurring during the treatment phase.

Haematologic events: After each treatment cycle, grade 3 and 4 leucopenia (88 % vs 79 %) and neutropenia (97 % vs 88 %) occurred more frequently in the R-CHOP group than in the CHOP group. There was no evidence that neutropenia was more prolonged in the R-CHOP group. No difference between the two treatment arms was observed with respect to grade 3 and 4 anaemia (19 % in the CHOP group vs 14 % in the R-CHOP group) and thrombocytopenia (16 % in the CHOP group vs 15 % in the R-CHOP group). The time to recovery from all haematological abnormalities was comparable in the two treatment groups.

Cardiac events: The incidence of grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (14 patients, 6.9 %) as compared to the CHOP group (3 patients, 1.5 %). All of these arrhythmias either occurred in the context of a MabThera infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease. No difference between the R-CHOP and CHOP group was observed in the incidence of other grade 3 and 4 cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease.

Neurologic events: During the treatment period, four patients (2 %) in the R-CHOP group, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment groups in the incidence of other thromboembolic events. In contrast, three patients (1.5 %) had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period.

Post-marketing experience

As part of the continuing post-marketing surveillance of MabThera safety, the following serious adverse reactions have been observed:

Blood and lymphatic system disorders	
Rare (≥ 1/10,000, < 1/1000):	Late neutropenia[1]
Very rare (< 1/10,000):	Pancytopenia Aplastic anaemia Transient increase in serum IgM levels[2]
Cardiovascular system	
Rare (≥ 1/10,000, < 1/1000):	*Severe cardiac events[3]
Very rare (< 1/10,000):	*Heart failure[3] *Myocardial infarction[3]
Ear and labyrinth disorders	
Very rare (< 1/10,000):	†Hearing loss
Eye disorders	
Very rare (< 1/10,000):	†Severe vision loss
General disorders and administration site conditions	
Very rare (< 1/10,000):	*Multi-organ failure
Immune system disorders	
Uncommon (≥ 1/1000, < 1/100):	Infusion related reactions
Rare (≥ 1/10,000, < 1/1000):	Anaphylaxis
Very rare (< 1/10,000):	*Tumour lysis syndrome *Cytokine release syndrome Serum sickness Hepatitis B reactivation[4]
Nervous system disorders	
Very rare (< 1/10,000):	Cranial neuropathy Peripheral neuropathy

	†Facial nerve palsy †Loss of other senses
Renal and urinary disorders	
Very rare (< 1/10,000):	*Renal failure
Respiratory, thoracic and mediastinal disorders	
Rare (≥ 1/10,000, < 1/1000):	*Bronchospasm
Very rare (< 1/10,000):	*Respiratory failure Pulmonary infiltrates Interstitial pneumonitis
Skin and subcutaneous tissue disorders	
Very rare (< 1/10,000):	Severe bullous skin reactions Toxic epidermal necrolysis[5]
Vascular disorders	
Very rare (< 1/10,000):	Vasculitis (predominately cutaneous) Leukocytoclastic vasculitis

*Associated with infusion-related reactions. Rarely fatal cases reported
† Signs and symptoms of cranial neuropathy. Occurred at various times up to several months after completion of MabThera therapy
[1] Neutropenia that has occurred more than four weeks after the last infusion of MabThera.
[2] In post-marketing studies of rituximab in patients with Waldenstrom's macroglobulinaemia, transient increases in serum IgM levels have been observed following treatment initiation, which may be associated with hyperviscosity and related symptoms. The transient IgM increase usually returned to at least baseline level within 4 months.
[3] Observed mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and were mostly associated with infusion-related reactions
[4] Very rare cases of hepatitis B reactivation, have been reported in subjects receiving rituximab in combination with cytotoxic chemotherapy.
[5] Including fatal cases

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic Agents, ATC code: L01X C02

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 the Fc domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms of effector-mediated 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. Rituximab binding to CD 20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis.

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.

Follicular non-Hodgkin's lymphoma:
Monotherapy: *Initial treatment, weekly for 4 doses:* In the pivotal study, 166 patients with relapsed or chemoresistant low-grade or follicular B cell NHL received 375 mg/m^2 of MabThera as an IV infusion once weekly for four weeks. The overall response rate (ORR) in the intent-to-treat (ITT) population was 48 % ($CI_{95\,\%}$ 41 % - 56 %) with a 6 % complete response (CR) and a 42 % partial response (PR) rate. The projected median time to progression (TTP) for responding patients was 13.0 months. In a subgroup analysis, the ORR was higher in patients with IWF B, C, and D histological subtypes as compared to IWF A subtype (58 % vs. 12 %), higher in patients whose largest lesion was < 5 cm vs. > 7 cm in greatest diameter (53 % vs. 38 %), and higher in patients with chemosensitive relapse as compared to chemoresistant (defined as duration of response < 3 months) relapse (50 % vs. 22 %). ORR in patients previously treated with autologous bone marrow transplant (ABMT) was 78 % versus 43 % in patients with no ABMT. Neither age, sex, lymphoma grade, initial diagnosis, presence or absence of bulky disease, normal or high LDH nor presence of extranodal disease had a statistically significant effect (Fisher's exact test) on response to MabThera. A statistically significant correlation was noted between response rates and bone marrow involvement. 40 % of patients with bone marrow involvement responded compared to 59 % of patients with no bone marrow involvement (p=0.0186). This finding was not supported by a stepwise logistic regression analysis in which the following factors were identified as prognostic factors: histological type, bcl-2 positivity at baseline, resistance to last chemotherapy and bulky disease.

Initial treatment, weekly for 8 doses: In a multi-centre, single-arm study, 37 patients with relapsed or chemoresistant, low grade or follicular B cell NHL received 375 mg/m^2 of MabThera as IV infusion weekly for eight doses. The ORR was 57 % ($CI_{95\,\%}$ 41 % – 73 %; CR 14 %, PR 43 %) with a projected median TTP for responding patients of 19.4 months (range 5.3 to 38.9 months).

Initial treatment, bulky disease, weekly for 4 doses: In pooled data from three studies, 39 patients with relapsed or chemoresistant, bulky disease (single lesion ≥ 10 cm in diameter), low grade or follicular B cell NHL received 375 mg/m^2 of MabThera as IV infusion weekly for four doses. The ORR was 36 % ($CI_{95\,\%}$ 21 % – 51 %; CR 3 %, PR 33 %) with a median TTP for responding patients of 9.6 months (range 4.5 to 26.8 months).

Re-treatment, weekly for 4 doses: In a multi-centre, single-arm study, 58 patients with relapsed or chemoresistant low grade or follicular B cell NHL, who had achieved an objective clinical response to a prior course of MabThera, were re-treated with 375 mg/m^2 of MabThera as IV infusion weekly for four doses. Three of the patients had received two courses of MabThera before enrollment and thus were given a third course in the study. Two patients were re-treated twice in the study. For the 60 re-treatments on study, the ORR was 38 % ($CI_{95\,\%}$ 26 % – 51 %; 10 % CR, 28 % PR) with a projected median TTP for responding patients of 17.8 months (range 5.4 – 26.6). This compares favourably with the TTP achieved after the prior course of MabThera (12.4 months).

Initial treatment, in combination with CVP: In an open-label randomised trial, a total of 322 previously untreated low-grade or follicular B cell NHL patients were randomised to receive either CVP chemotherapy (cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1 –5) every 3 weeks for 8 cycles or MabThera 375 mg/m^2 in combination with CVP (R-CVP). MabThera was administered on the first day of each treatment cycle. A total of 321 patients (162 R-CVP, 159 CVP) received therapy and were analysed for efficacy. At the time of the analysis, the median observation time was 18 months. R-CVP led to a significant benefit over CVP for the primary endpoint, time to treatment failure (25.9 months vs. 6.7 months, p < 0.0001, log-rank test). The risk of experiencing a treatment failure event was reduced by 67 % (95 % CI: 56 % - 76 %) with R-CVP compared with CVP alone, using a Cox regression

analysis. The Kaplan-Meier estimated event free rate at 12 months was 69 % in the R-CVP group compared with 32 % in the CVP group. The proportion of patients with a tumour response (CR, CRu, PR) was significantly higher ($p< 0.0001$ Chi-Square test) in the R-CVP group (80.9 %) than the CVP group (57.2 %). At 18 months, the median duration of response had not been reached in the R-CVP group and was 9.8 months in the CVP group ($p < 0.0001$, log-rank test). Amongst responding patients, Cox regression analysis showed that the risk of relapse was reduced by 70 % (95 % CI: 55 % - 81 %) in the R-CVP group compared to the CVP group.

The time to institution of new lymphoma treatment or death was significantly longer in the R-CVP group (not estimable), compared to the CVP group (12.3 months) ($p < 0.0001$, log-rank test). Treatment with R-CVP significantly prolonged the time to disease progression compared to CVP, 27 months and 14.5 months, respectively. At 12 months, 81 % in the R-CVP group had not relapsed compared to 58 % of patients receiving CVP.

The benefit of adding rituximab to CVP was seen consistently throughout the population recruited in study M39021 (randomised according to BNLI criteria (no versus yes), age (≤ 60 years, > 60 years), number of extra-nodal sites (0-1 versus > 1), bone marrow involvement (no versus yes), LDH (elevated, not elevated), β_2-microglobulin (elevated, not elevated), B symptoms (absent, present), bulky disease (absent, present), number of nodal sites (< 5 versus ≥ 5), haemoglobin (≤ 12 g/dL versus > 12 g/dL), IPI (≤ 1 versus > 1), and FLIPI index (0-2 versus 3-5)).

Due to the number of events at the time of analysis and the relatively short observation time of 18 months, conclusion regarding differences for overall survival cannot be drawn.

Diffuse large B cell non-Hodgkin's lymphoma: In a randomised, open-label trial, a total of 399 previously untreated elderly patients (age 60 to 80 years) with diffuse large B cell lymphoma received standard CHOP chemotherapy (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisone 40 mg/m^2/day on days 1-5) every 3 weeks for eight cycles, or MabThera 375 mg/m^2 plus CHOP (R-CHOP). MabThera was administered on the first day of the treatment cycle.

The final efficacy analysis included all randomised patients (197 CHOP, 202 R-CHOP), and had a median follow-up duration of approximately 31 months The two treatment groups were well balanced in baseline disease characteristics and disease status. The final analysis confirmed that R-CHOP treatment was associated with a clinically relevant and statistically significant improvement in the duration of event-free survival (the primary efficacy parameter; where events were death, relapse or progression of lymphoma, or institution of a new anti-lymphoma treatment) ($p = 0.0001$). Kaplan Meier estimates of the median duration of event-free survival were 35 months in the R-CHOP arm compared to 13 months in the CHOP arm, representing a risk reduction of 41 %. At 24 months, estimates for overall survival were 68.2 % in the R-CHOP arm compared to 57.4 % in the CHOP arm. A subsequent analysis of the duration of overall survival, carried out with a median follow-up duration of 38 months, confirmed the benefit of R-CHOP over CHOP treatment ($p=0.0094$), representing a risk reduction of 33 %.

The analysis of all secondary parameters (response rates, progression-free survival, disease-free survival, duration of response) verified the treatment effect of R-CHOP compared to CHOP. The complete response rate after cycle 8 was 76.2 % in the R-CHOP group and 62.4 % in the CHOP group ($p=0.0028$). The risk of disease progression was reduced by 46 % and the risk of relapse by 51 %. In all patients subgroups (gender, age, age adjusted IPI, Ann Arbor stage, ECOG, β2 microglobulin, LDH, albumin, B symptoms, bulky disease, extranodal sites, bone marrow involvement), the risk ratios for event-free survival and overall survival (R-CHOP compared with CHOP) were less than 0.83 and 0.95 respectively. R-CHOP was associated with improvements in outcome for both high- and low-risk patients according to age adjusted IPI.

Clinical Laboratory Findings

Of 67 patients evaluated for human anti-mouse antibody (HAMA), no responses were noted. Of 356 patients evaluated for HACA, 1.1 % (4 patients) were positive.

5.2 Pharmacokinetic properties

Pharmacokinetic studies performed in a phase I study in which patients (n=15) with relapsed B cell lymphoma were given single doses of rituximab at 10, 50, 100 or 500 mg/m^2 indicated that serum levels and half-life of rituximab were proportional to dose. In a cohort of 14 patients among the 166 patients with relapsed or chemoresistant low-grade or follicular non-Hodgkin's lymphoma enrolled in the phase III pivotal trial and given rituximab 375 mg/m^2 as an IV infusion for 4 weekly doses, the mean serum half-life was 76.3 hours (range, 31.5 to 152.6 hours) after the first infusion and 205.8 hours (range, 83.9 to 407.0 hours) after the fourth infusion. The mean C_{max} after the first and fourth infusion were 205.6 ± 59.9 µg/ml and 464.7 ± 119.0 µg/ml, respectively. The mean plasma clearance after the first and fourth infusion was 0.0382 ± 0.0182 L/h and 0.0092 ± 0.0033 L/h, 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 and the number of circulating B cells at baseline. Typically, rituximab was detectable for 3 to 6 months.

Elimination and distribution have not been extensively studied in patients with diffuse large B cell non-Hodgkin's lymphoma, but available data indicate that serum levels of rituximab in these patients are comparable to those in patients with follicular non-Hodgkin's lymphoma following treatment with similar doses.

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 it is unlikely that rituximab has any mutagenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

30 months

The prepared infusion solution of MabThera is physically and chemically stable for 24 hours at 2 °C - 8 °C and subsequently 12 hours at room temperature.

6.4 Special precautions for storage

Store vials at 2 °C- 8 °C (in a refrigerator). Keep the container in the outer carton in order to protect from light.

The prepared infusion solution of MabThera is physically and chemically stable for 24 hours at 2 °C - 8 °C and subsequently 12 hours at room temperature.

From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C - 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Single-use, preservative-free, clear Type I 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 and handling and disposal

MabThera is 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.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/067/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2 June 1998 / 28 July 2003

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Names and addresses of the manufacturers of the biological active substance

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990
USA

Genentech Inc.
1000 New Horizons Way
Vacaville, CA 95688
USA

Name and address of the manufacturer responsible for batch release

Hoffman La Roche Ltd
Emil-Barell-Str. 1
D-79639, Grenzach-Wyhlen
Germany

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2).

- **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

MabThera 100mg
Concentrate for solution for infusion
Rituximab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 100 mg rituximab.

3. LIST OF EXCIPIENTS

Sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
Pack of 2 vials of 10 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store at 2°C – 8°C (in a refrigerator). Keep the container in the outer carton, in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/067/001

13. MANUFACTURER'S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

vial label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

MabThera 100mg
Concentrate for solution for infusion
Rituximab

i.v. inf.

2. METHOD OF ADMINISTRATION

For intravenous use after dilution

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Vial of 10 ml (10 mg/ml)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

MabThera 500mg
Concentrate for solution for infusion
Rituximab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial contains 500 mg rituximab.

3. LIST OF EXCIPIENTS

Sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
Pack of 1 vial of 50 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store at 2°C – 8°C (in a refrigerator). Keep the container in the outer carton, in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/067/002

13. MANUFACTURER'S BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

vial label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

MabThera 500mg
Concentrate for solution for infusion
Rituximab

i.v. inf.

2. METHOD OF ADMINISTRATION

For intravenous use after dilution

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Vial of 50 ml (10 mg/ml)

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

MabThera 100 mg
Concentrate for solution for infusion
Rituximab

- The active substance of MabThera is rituximab. The 10 ml vial contains 100 mg of rituximab.
- The other ingredients are sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid and water for injections.

Marketing Authorisation Holder

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

Manufacturer, responsible for batch release, and importer

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

1. WHAT MABTHERA IS AND WHAT IT IS USED FOR

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.

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.

MabThera is used for the treatment of patients with a certain type of disease affecting the lymphatic system called non-Hodgkin's lymphoma. It is used as monotherapy in conditions where other treatments proved unsuccessful. It is also used in combination with chemotherapy agents.

2. BEFORE YOU USE MABTHERA

Do not take 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.

Take special care with MabThera:
- 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.

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

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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.

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

Driving and using machines:
It is not known whether MabThera has an effect on your ability to drive a car or operate machinery.

Taking other medicines:
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.

3. HOW TO USE MABTHERA

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Use of prepared infusion solutions
The prepared infusion solution of MabThera is physically and chemically stable for 24 hours at 2 °C - 8 °C and subsequently 12 hours at room temperature.

From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C - 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

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Severe cardiac events, including heart failure and myocardial infarction have been observed, mainly in patients with prior cardiac conditions and/or cardiotoxic chemotherapy and are mostly associated with infusion-related reactions.

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, pancytopenia, 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. Patients having Waldenstrom's macroglobulinaemia (a rare type of lymphoma), may experience temporarily overproduction of a protein called IgM, which can cause blood thickening.

Some severe reactions, in particular severe breathing difficulties and severe bullous skin reactions, 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 and any skin reactions. You should also contact your doctor if you experience impairment in vision, hearing or other senses.

If you are receiving MabThera in combination with chemotherapy, some of the side effects you may experience may be due to the chemotherapy agents.

If you experience any of these effects, or, if you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist (chemist) immediately.

5. STORING MABTHERA

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Store at 2-8 °C (in a refrigerator). Keep the container in the outer carton in order to protect from light.

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6. FURTHER INFORMATION

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PACKAGE LEAFLET

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

MabThera 500 mg
Concentrate for solution for infusion
Rituximab

- The active substance of MabThera is rituximab. The 50 ml vial contains 500 mg of rituximab.
- The other ingredients are sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid and water for injections.

Marketing Authorisation Holder

Roche Registration Limited
6 Falcon Way
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Welwyn Garden City
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United Kingdom

Manufacturer, responsible for batch release, and importer

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

1. WHAT MABTHERA IS AND WHAT IT IS USED FOR

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

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.

MabThera is used for the treatment of patients with a certain type of disease affecting the lymphatic system called non-Hodgkin's lymphoma. It is used as monotherapy in conditions where other treatments proved unsuccessful. It is also used in combination with chemotherapy agents.

2. BEFORE YOU USE MABTHERA

Do not take 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.

Take special care with MabThera:
- 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.

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