1 NAME OF THE MEDICINAL PRODUCT

MabThera 1400 mg solution for subcutaneous injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 120 mg of rituximab.

Each vial contains 1400 mg/11.7 mL rituximab.

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable 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 the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear to opalescent, colourless to yellowish liquid with pH of 5.2 – 5.8 and osmolality of 300 - 400 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MabThera is indicated in adults for Non-Hodgkin's lymphoma (NHL):

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

MabThera maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.

MabThera is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

4.2 Posology and method of administration

MabThera should be administered under the close supervision of an experienced healthcare professional, and in an environment where full resuscitation facilities are immediately available (see section 4.4).

Premedication consisting of an anti-pyretic and an antihistaminic, e.g. paracetamol and diphenhydramine, should always be given before each administration of MabThera.

Premedication with glucocorticoids should be considered if MabThera is not given in combination with glucocorticoid-containing chemotherapy.

Posology

The recommended dose of MabThera subcutaneous formulation used for adult patients is a subcutaneous injection at a fixed dose of 1400 mg irrespective of the patient's body surface area.

Before starting MabThera subcutaneous injections, all patients must always receive beforehand, a full dose of MabThera by intravenous infusion, using MabThera intravenous formulation (see section 4.4).

If patients were not able to receive one full MabThera intravenous infusion dose prior to the switch, they should continue the subsequent cycles with MabThera intravenous formulation until a full intravenous dose is successfully administered.
Therefore, the switch to MabThera subcutaneous formulation can only occur at the second or subsequent cycles of treatment.

It is important to check the medicinal product labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) and strength is being given to the patient, as prescribed.

MabThera subcutaneous formulation is not intended for intravenous administration and should be given via subcutaneous injection only. The 1400 mg strength is intended for subcutaneous use in non Hodgkin lymphoma (NHL) only.

Follicular non-Hodgkin's lymphoma

Combination therapy
The recommended dose of MabThera in combination with chemotherapy for induction treatment of previously untreated or relapsed/ refractory patients with follicular lymphoma is: first cycle with MabThera intravenous formulation 375 mg/m^2 body surface area, followed by subsequent cycles with MabThera subcutaneous formulation injected at a fixed dose of 1400 mg per cycle for up to 8cycles.

MabThera should be administered on day 1 of each chemotherapy cycle, after administration of the glucocorticoid component of the chemotherapy if applicable.

Maintenance therapy

- Previously untreated follicular lymphoma

The recommended dose of MabThera subcutaneous formulation used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 1400 mg once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years (12 administrations in total).

- Relapsed/refractory follicular lymphoma

The recommended dose of MabThera subcutaneous formulation used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 1400 mg once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of two years (8 administrations in total).

Diffuse large B cell non-Hodgkin's lymphoma

MabThera should be used in combination with CHOP chemotherapy. The recommended dose is: first cycle, MabThera intravenous formulation: 375 mg/m^2 body surface area, followed by subsequent cycles with MabThera subcutaneous formulation injected at a fixed dose of 1400 mg per cycle. In total: 8 cycles.

MabThera is administered on day 1 of each chemotherapy cycle after intravenous infusion of the glucocorticoid component of CHOP.

Safety and efficacy of MabThera have not been established in combination with other chemotherapies in diffuse large B cell non-Hodgkin's lymphoma.

Dose adjustments during treatment

No dose reductions of MabThera are recommended. When MabThera is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied (see section 4.8).

Special populations

Paediatric population
The safety and efficacy of MabThera in children below 18 years has not been established. No data are available.

Elderly
No dose adjustment is required in elderly patients (aged >65 years).

Method of administration

Subcutaneous injections:
MabThera 1400 mg subcutaneous formulation should be administered as subcutaneous injection only, over approximately 5 minutes. The hypodermic injection needle must only be attached to the syringe immediately prior to administration to avoid potential needle clogging.

MabThera subcutaneous formulation should be injected subcutaneously into the abdominal wall and never into areas where the skin is red, bruised, tender, hard or areas where there are moles or scars.

No data are available on performing the injection in other sites of the body, therefore injections should be restricted to the abdominal wall.

During the treatment course with MabThera subcutaneous formulation, other medicinal products for subcutaneous administration should preferably be given at different sites.

If an injection is interrupted it can be resumed at the same site or another location may be used, if appropriate.

Intravenous infusion administration:
The Summary of Product Characteristics (SmPC) of MabThera100 mg and 500 mg concentrate for solution for infusion should be referred to for information on dosing instructions and method of administration.

4.3 Contraindications

Hypersensitivity to the active substance or to murine proteins, hyaluronidase or to any of the other excipients listed in section 6.1.

Active, severe infections (see section 4.4).

Patients in a severely immunocompromised state.

4.4 Special warnings and precautions for use

Traceability
In order to improve traceability of biological medicinal products, the tradename and batch number of the administered product should be clearly recorded.

The information provided in the section 4.4 pertains to the use of MabThera subcutaneous formulation in the approved indications *Treatment of non-Hodgkin's lymphoma (strength 1400 mg) and Treatment of Chronic Lymphocytic Leukaemia* (strength 1600 mg). For information related to the other indications, please refer to the SmPC of MabThera intravenous formulation.

The use of MabThera subcutaneous formulation as monotherapy in patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy cannot be recommended as the safety of the once weekly subcutaneous administration has not been established.

Progressive multifocal leukoencephalopathy

Use of MabThera may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML). Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML. Consultation with a neurologist should be considered as clinically indicated.

If any doubt exists, further evaluation, including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments, should be considered.

The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

If a patient develops PML, the dosing of MabThera must be permanently discontinued.

Following reconstitution of the immune system in immunocompromised patients with PML, stabilisation or improved outcome has been seen. It remains unknown if early detection of PML and suspension of MabThera therapy may lead to similar stabilisation or improved outcome.

Infusion/Administration-related reactions

MabThera is associated with infusion/administration-related reactions, which may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be clinically indistinguishable from acute hypersensitivity reactions.

This set of reactions which includes syndrome of cytokine release, tumor lysis syndrome and anaphylactic and hypersensitivity reactions are described below. They are not specifically related to the route of administration of MabThera and can be observed with both formulations.

Severe infusion-related reactions with fatal outcome have been reported during post-marketing use of the MabThera intravenous formulation, with an onset ranging within 30 minutes to 2 hours after starting the first MabThera intravenous infusion. They were characterized by pulmonary events and in some cases included rapid tumour lysis and features of tumour lysis syndrome in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms (see section 4.8).

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, hyperphosphaetemia, acute renal failure, elevated lactate dehydrogenase (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.

Patients with a high tumour burden or with a high number ($\geq 25 \times 10^9$/L) of circulating malignant cells, who may be at higher risk of especially severe cytokine release syndrome, should be treated with extreme caution. 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 or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still $>25 \times 10^9$/L.

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Medicinal products for the treatment of hypersensitivity reactions, e.g., epinephrine (adrenaline), antihistamines and glucocorticoids, 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.

Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia.

Since hypotension may occur during MabThera administration, consideration should be given to withholding anti-hypertensive medicines 12 hours prior to giving MabThera.

Infusion related adverse reactions of all kinds have been observed in 77% of patients treated with MabThera intravenous formulation (including cytokine release syndrome accompanied by hypotension and bronchospasm in 10 % of patients) see section 4.8. These symptoms are usually reversible with interruption of MabThera infusion and administration of an anti-pyretic, an antihistaminic, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required. Please see cytokine release syndrome above for severe reactions.

Administration related reactions have been observed in up to 50% of patients treated with MabThera subcutaneous formulation in clinical trials. The reactions occurring within 24 hours of the subcutaneous injection consisted primarily of erythema pruritus, rash and injections site reactions such as pain, swelling and redness and were generally of mild or moderate (grade 1 or 2) and transient nature (see section 4.8).

Local cutaneous reactions were very common in patients receiving MabThera subcutaneous in clinical trials. Symptoms included pain, swelling, induration, haemorrhage, erythema, pruritus and rash (see section 4.8). Some local cutaneous reactions occurred more than 24 hours after the MabThera subcutaneous administration. The majority of local cutaneous reactions seen following administration of MabThera subcutaneous formulation was mild or moderate and resolved without any specific treatment.

Before starting MabThera subcutaneous injections, all patients must always receive beforehand, a full dose of MabThera by intravenous infusion, using MabThera intravenous formulation. The highest risk of experiencing an administration related reaction is generally observed at cycle one. Beginning the therapy with MabThera intravenous infusion would allow a better handling of the administration reactions by slowing or stopping the intravenous infusion.

If patients were not able to receive one full MabThera intravenous infusion dose prior to the switch, they should continue the subsequent cycles with MabThera intravenous formulation until a full intravenous dose is successfully administered. Therefore, the switch to MabThera subcutaneous formulation can only occur at the second or subsequent cycles of treatment.

As with the intravenous formulation, MabThera subcutaneous formulation should be administered in an environment where full resuscitation facilities are immediately available and under the close supervision of an experienced healthcare professional. Premedication consisting of an analgesic/antipyretic and an antihistamine should always be administered before each dose of MabThera subcutaneous formulation. Premedication with glucocorticoids should also be considered.

Patients should be observed for at least 15 minutes following MabThera subcutaneous administration. A longer period may be appropriate in patients with an increased risk of hypersensitivity reactions.

Patients should be instructed to contact their treating physician immediately if symptoms that are suggestive of severe hypersensitivity or cytokine release syndrome occur at any time after medicinal product administration.

Cardiac disorders

Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/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.

Haematological toxicities

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. The MabThera intravenous formulation has been used in 21 patients who underwent autologous bone marrow transplantation and other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity.

Regular full blood counts, including neutrophil and platelet counts, should be performed during MabThera therapy.

Infections

Serious infections, including fatalities, can occur during therapy with MabThera (see section 4.8). MabThera should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections, see section 4.3).

Physicians should exercise caution when considering the use of MabThera in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection (see section 4.8).

Cases of hepatitis B reactivation have been reported in patients receiving the MabThera intravenous formulation including fulminant hepatitis with fatal outcome. The majority of these patients were also exposed to cytotoxic chemotherapy. Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with MabThera. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with MabThera. Patients with positive hepatitis B serology (either HBsAg or HBcAb) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Very rare cases of PML have been reported during post-marketing use of the MabThera intravenous formulation in NHL (see section 4.8). The majority of patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant.

Immunisation

The safety of immunisation with live viral vaccines, following MabThera therapy has not been studied for NHL patients and vaccination with live virus vaccines is not recommended. Patients treated with MabThera may receive non-live vaccinations; however, with non-live vaccines response rates may be reduced. In a non-randomized study, patients with relapsed low-grade NHL who received the MabThera intravenous formulation as monotherapy when compared to healthy untreated controls had a lower rate of response to vaccination with tetanus recall antigen (16% vs. 81%) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4% vs. 69% when assessed for >2-fold increase in antibody titer).

Mean pre-therapeutic antibody titers against a panel of antigens (Streptococcus pneumoniae, influenza A, mumps, rubella and varicella) were maintained for at least 6 months after treatment with MabThera.

Skin reactions

Severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's Syndrome) and Stevens - Johnson syndrome, some with fatal outcome, have been reported (see section 4.8). In case of such an event, with suspected relationship to MabThera, treatment should be permanently discontinued.

4.5 Interaction with other medicinal products and other forms of interaction

Currently, there are limited data on possible drug interactions with MabThera.

Co-administration with MabThera did not appear to have an effect on the pharmacokinetics of fludarabine or cyclophosphamide. In addition, there was no apparent effect of fludarabine and cyclophosphamide on the pharmacokinetics of MabThera.

Patients with human anti-mouse antibody (HAMA) or anti-drug antibody (ADA) titres may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential must employ effective contraceptive methods during and for 12 months after treatment with MabThera.

Pregnancy

IgG immunoglobulins are known to cross the placental barrier.

B-cell levels in human neonates following maternal exposure to MabThera have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to MabThera during pregnancy. Similar effects have been observed in animal studies (see section 5.3).For these reasons MabThera should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

Breast-feeding

Limited data on rituximab excretion into breast milk suggest very low rituximab concentrations in milk (relative infant dose less than 0.4%). Few cases of follow-up of breastfed infants describe normal growth and development up to 2 years. However, as these data are limited and the long-term outcomes of breastfed infants remain unknown, breast-feeding is not recommended while being treated with rituximab and optimally for 6 months following rituximab treatment.

Fertility

Animal studies did not reveal deleterious effects of rituximab or recombinant human hyaluronidase (rHuPH20) on reproductive organs.

4.7 Effects on ability to drive and use machines

No studies on the effects of MabThera on the ability to drive and use machines have been performed, although the pharmacological activity and adverse reactions reported to date suggest that MabThera would have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The information provided in this section pertains to the use of MabThera in oncology.
For information related to the autoimmune indications, please refer to the SmPC of MabThera intravenous formulation.

Summary of the safety profile

During the development programme, the safety profile of MabThera subcutaneous formulation was comparable to that of the intravenous formulation with the exception of local cutaneous reactions. Local cutaneous reactions, including injection site reactions were very common in patients receiving MabThera subcutaneous formulation. In the phase 3 SABRINA trial (BO22334), local cutaneous reaction were reported in up to 20% of patients receiving subcutaneous MabThera. The most common local cutaneous reactions in the Mabthera subcutaneous arm were injection erythema (13%), injection pain (7%) and injection site oedema (4%).Events seen following subcutaneous administration were mild or moderate, apart from one patient who reported a local cutaneous reaction of Grade 3 intensity (injection site rash) following the first MabThera subcutaneous administration (Cycle 2). Local cutaneous reactions of any grade in the MabThera subcutaneous arm were most common during the first subcutaneous cycle (Cycle 2), followed by the second, and the incidence decreased with subsequent injections.

Adverse reactions reported in MabThera subcutaneous formulation usage

The risk of acute administration-related reactions associated with the subcutaneous formulation of MabThera was assessed in two open-label trials involving patients with follicular lymphoma during induction and maintenance (SABRINA/BO22334) and during maintenance only (SparkThera/BP22333). InSABRINA, severe administration-related reactions (grade≥3) were reported in two patients (2%) following administration of MabThera subcutaneous formulation. These events were Grade 3 injection site rash and dry mouth. InSparkThera, no severe administration-related reactions were reported.

Adverse reactions reported in MabThera intravenous formulation usage

Experience from non-Hodgkin's lymphoma and chronic lymphocytic leukaemia

The overall safety profile of MabThera in non-Hodgkin's lymphoma and CLL is based on data from patients from clinical trials and from post-marketing surveillance. These patients were treated either with MabThera monotherapy (as induction treatment or maintenance treatment following induction treatment) or in combination with chemotherapy.

The most frequently observed adverse reactions (ADRs) in patients receiving MabThera were infusion-related reactions which occurred in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1 % after eight doses of MabThera.

Infectious events (predominantly bacterial and viral) occurred in approximately 30-55 % of patients during clinical trials in patients with NHL and in 30-50 % of patients during clinical trial in patients with CLL.

The most frequent reported or observed serious adverse reactions were:

- Infusion-related reactions (including cytokine-release syndrome, tumour-lysis syndrome), seesection 4.4.
- Infections, see section 4.4.
- Cardiovascular disorders, see section 4.4.

Other serious ADRs reported include hepatitis B reactivation and PML (see section 4.4.).

The frequencies of ADRs reported with MabThera alone or in combination with chemotherapy are summarised in Table 1. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The ADRs identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under "not known".

Tabulated list of adverse reactions

Table 1 ADRs reported in clinical trials or during postmarketing surveillance in patients with NHL and CLL disease treated with MabThera monotherapy/maintenance or in combination with chemotherapy

MedDRA System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations	bacterial infections, viral infections, +bronchitis	sepsis, +pneumonia, +febrile infection, +herpes zoster, +respiratory tract infection, fungal infections, infections of unknown aetiology, +acute bronchitis, +sinusitis, hepatitis B[1]		serious viral infection[2]		
Blood and lymphatic system disorders	neutropenia, leucopenia, +febrile neutropenia, +thrombocytopenia	anaemia, +pancytopenia, +granulocytopenia	coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy		transient increase in serum IgM levels[3]	late neutropenia[3]
Immune system disorders	infusion related reactions[4], angioedema	hypersensitivity		anaphylaxis	tumour lysis syndrome, cytokine release syndrome[4], serum sickness	infusion-related acute reversible thrombocytopenia [4]
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia				
Psychiatric disorders			depression, nervousness,			
Nervous system disorders		paraesthesia, hypoaesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	dysgeusia		peripheral neuropathy, facial nerve palsy[5]	cranial neuropathy, loss of other senses[5]
Eye disorders		lacrimation disorder, conjunctivitis			severe vision loss[5]	
Ear and labyrinth disorders		tinnitus, ear pain				hearing loss[5]

MedDRA System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Cardiac disorders		[+]myocardial infarction[4 and 6], arrhythmia, [+]atrial fibrillation, tachycardia, [+]cardiac disorder	[+]left ventricular failure, [+]supraventricular tachycardia, [+]ventricular tachycardia, [+]angina, [+]myocardial ischaemia, bradycardia	severe cardiac disorders [4 and 6]	heart failure[4 and 6]	
Vascular disorders		hypertension, orthostatic hypotension, hypotension			vasculitis (predominately cutaneous), leukocytoclastic vasculitis	
Respiratory, thoracic and mediastinal disorders		Bronchospasm[4], respiratory disease, chest pain, dyspnoea, increased cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia	interstitial lung disease[7]	respiratory failure[4],	lung infiltration,
Gastrointestinal disorders	nausea	vomiting , diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation	abdominal enlargement		gastro-intestinal perforation[7]	
Skin and subcutaneous tissue disorders	pruritis, rash, [+]alopecia	urticaria, sweating, night sweats, [+]skin disorder			severe bullous skin reactions, Stevens-Johnson Syndrome, toxic epidermal necrolysis (Lyell's Syndrome) [7]	
Musculoskeletal, connective tissue disorders		hypertonia, myalgia, arthralgia, back pain, neck pain, pain				
Renal and urinary disorders					renal failure[4]	
General disorders and administration site conditions	fever , chills, asthenia, headache	tumour pain, flushing, malaise, cold syndrome, [+]fatigue, [+]shivering, [+]multi-organ failure[4]	infusion site pain			

MedDRA System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Investigations	decreased IgG levels					

For each term, the frequency count was based on reactions of all grades (from mild to severe), except for terms marked with "+" where the frequency count was based only on severe (≥ grade 3 NCI common toxicity criteria) reactions. Only the highest frequency observed in the trials is reported

[1] includes reactivation and primary infections; frequency based on R-FC regimen in relapsed/refractory CLL

[2] see also section infection below

[3] see also section haematologic adverse reactions below

[4] see also section infusion-related reactions below. Rarely fatal cases reported

[5] signs and symptoms of cranial neuropathy. Occurred at various times up to several months after completion of MabThera therapy

[6] observed mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and were mostly associated with infusion-related reactions

[7] includes fatal cases

The following terms have been reported as adverse events during clinical trials, however, were reported at a similar or lower incidence in the MabThera-arms compared to control arms: haematotoxicity, neutropenic infection, urinary tract infection, sensory disturbance, pyrexia.

Signs and symptoms suggestive of an infusion-related reaction were reported in more than 50 % of patients in clinical trials involving MabThera intravenous formulation, and were predominantly seen during the first infusion, usually in the first one to two hours. These symptoms mainly comprised fever, chills and rigors. Other symptoms included flushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia, asthenia and features of tumour lysis syndrome. Severe infusion-related reactions (such as bronchospasm, hypotension) occurred in up to 12 % of the cases. Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia. Exacerbations of pre-existing cardiac conditions such as angina pectoris or congestive heart failure or severe cardiac disorders (heart failure, myocardial infarction, atrial fibrillation), pulmonary oedema, multi-organ failure, tumour lysis syndrome, cytokine release syndrome, renal failure, and respiratory failure were reported at lower or unknown frequencies. The incidence of infusion-related symptoms decreased substantially with subsequent intravenous infusions and is <1% of patients by the eighth cycle of MabThera (containing) treatment.

Description of selected adverse reactions

Infections

MabThera induces B-cell depletion in about 70-80% of patients, but was associated with decreased serum immunoglobulins only in a minority of patients.

Localized candida infections as well as Herpes zoster were reported at a higher incidence in the MabThera-containing arm of randomized studies. Severe infections were reported in about 4% of patients treated with MabThera monotherapy. Higher frequencies of infections overall, including grade 3 or 4 infections, were observed during MabThera maintenance treatment up to 2 years when compared to observation. There was no cumulative toxicity in terms of infections reported over a 2-year treatment period. In addition, other serious viral infections either new, reactivated or exacerbated, some of which were fatal, have been reported with MabThera treatment. The majority of patients had received MabThera in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (Cytomegalovirus, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (PML) and hepatitis C virus. Cases of fatal PML that occurred after disease progression and retreatment have also been reported in clinical trials. Cases of hepatitis B reactivation, have been reported, the majority of which were in patients receiving MabThera in combination with cytotoxic chemotherapy. Progression of Kaposi's sarcoma has been observed in MabThera-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive.

Haematologic adverse reactions
In clinical trials with MabThera monotherapy given for 4 weeks, haematological abnormalities occurred in a minority of patients and were usually mild and reversible. Severe (grade 3/4) neutropenia was reported in 4.2%, anaemia in 1.1% and thrombocytopenia in 1.7% of the patients. During MabThera maintenance treatment for up to 2 years, leucopoenia (5% vs. 2%, grade 3/4) and neutropenia (10% vs. 4%, grade 3/4) were reported at a higher incidence when compared to observation. The incidence of thrombocytopenia was low (<1 %, grade 3/4) and was not different between treatment arms. During the treatment course in studies with MabThera in combination with chemotherapy, grade 3/4 leucopoenia (R-CHOP 88% vs. CHOP 79%), neutropenia (R-CVP 24% vs. CVP 14%; R-CHOP 97% vs. CHOP 88%), were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with MabThera and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone. There were no differences reported for the incidence of anaemia. Some cases of late neutropenia occurring more than four weeks after the last infusion of MabThera were reported.

In studies of MabThera 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.

Cardiovascular adverse reactions
Cardiovascular reactions during clinical trials with MabThera monotherapy were reported in 18.8% of patients with the most frequently reported events being hypotension and hypertension. Cases of grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris during infusion were reported. During maintenance treatment, the incidence of grade 3/4 cardiac disorders was comparable between patients treated with MabThera and observation. Cardiac events were reported as serious adverse events (including atrial fibrillation, myocardial infarction, left ventricular failure, myocardial ischemia) in 3% of patients treated with MabThera compared to <1% on observation. In studies evaluating MabThera in combination with chemotherapy, 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.

Respiratory system
Cases of interstitial lung disease, some with fatal outcome have been reported.

Neurologic disorders
During the treatment period (induction treatment phase comprising of R-CHOP for at most eight cycles), four patients (2 %) treated with R-CHOP, 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.

Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognized risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.

Gastrointestinal disorders
Gastrointestinal perforation in some cases leading to death has been observed in patients receiving MabThera for treatment of Non-Hodgkin's lymphoma (NHL). In the majority of these cases, MabThera was administered with chemotherapy.

IgG levels
In the clinical trial evaluating MabThera maintenance treatment in relapsed/refractory follicular lymphoma, median IgG levels were below the lower limit of normal (LLN) (< 7 g/L) after induction treatment in both the observation and the MabThera groups. In the observation group, the median IgG level subsequently increased to above the LLN, but remained constant in the MabThera group. The proportion of patients with IgG levels below the LLN was about 60% in the MabThera group throughout the 2 year treatment period, while it decreased in the observation group (36% after 2 years).

Skin and subcutaneous tissue disorders
Toxic Epidermal Necrolysis (Lyell Syndrome) and Stevens-Johnson syndrome, some with fatal outcome, have been reported very rarely.

Patient subpopulations - MabThera monotherapy
Elderly (≥ 65 years):
The incidence of ADRs of all grades and grade 3 /4 ADR was similar in elderly patients compared to younger patients (<65 years).

Bulky disease:
There was a higher incidence of grade 3/4 ADRs in patients with bulky disease than in patients without bulky disease (25.6 % vs. 15.4 %). The incidence of ADRs of any grade was similar in these two groups.

Re-treatment:
The percentage of patients reporting ADRs upon re-treatment with further courses of MabThera was similar to the percentage of patients reporting ADRs upon initial exposure (any grade and grade 3/4 ADRs).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Limited experience with doses higher than the approved dose of intravenous MabThera formulation is available from clinical trials in humans. The highest intravenous dose of MabThera tested in humans to date is 5000 mg (2250 mg/m^2), tested in a dose escalation study in patients with CLL. No additional safety signals were identified.
Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.

Three patients in the MabThera subcutaneous formulation trial SABRINA (BO22334) were inadvertently administered subcutaneous formulation through the intravenous route up to a maximum rituximab dose of 2780 mg with no untoward effect.
Patients who experience overdose or medication error should be closely monitored.

In the post-marketing setting five cases of MabThera overdose have been reported. Three cases had no reported adverse event. The two adverse events that were reported were flu-like symptoms, with a dose of 1.8 g of rituximab and fatal respiratory failure, with a dose of 2 g of rituximab.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies, ATC code: L01X C02

MabThera subcutaneous formulation contains recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-administered substances when administered subcutaneously.

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.

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.

Peripheral B cell counts declined below normal following completion of the first dose of MabThera. In patients treated for hematological malignancies, B cell recovery began within 6 months of treatment and generally returned to normal levels within 12 months after completion of therapy, although in some patients this may take longer (up to a median recovery time of 23 months post-induction therapy). In rheumatoid arthritis patients, immediate depletion of B cells in the peripheral blood was observed following two infusions of 1000 mg MabThera separated by a 14 day interval. Peripheral blood B cell counts begin to increase from week 24 and evidence for repopulation is observed in the majority of patients by week 40, whether MabThera was administered as monotherapy or in combination with methotrexate.

<u>Clinical experience of MabThera subcutaneous formulation in Non-Hodgkin's lymphoma</u>

The clinical experience of MabThera subcutaneous formulation in Non-Hodgkin's lymphoma is based on data from a phase III clinical trial (SABRINA BO22334) in patients with follicular lymphoma (FL) and a phase Ib dose-finding/dose-confirmation trial (SparkThera BP22333) in patients with FL. Results from trial BP22333 are presented in section 5.2.

Trial BO22334 (SABRINA)
A two-stage phase III, international, multi-centre, randomised, controlled, open-label trial was conducted in patients with previously untreated follicular lymphoma, to investigate the non-inferiority of the pharmacokinetic profile, together with efficacy and safety of MabThera subcutaneous formulation in combination with CHOP or CVP versus MabThera intravenous formulation in combination with CHOP or CVP.

The objective of the first stage was to establish the rituximab subcutaneous dose that resulted in comparable MabThera subcutaneous formulation serum C_{trough} levels compared with MabThera intravenous formulation, when given as part of induction treatment every 3 weeks (see section 5.2). Stage 1 enrolled previously untreated patients (n=127) CD20-positive, Follicular Lymphoma (FL) Grade 1, 2 or 3a.

The objective of stage 2 was to provide additional efficacy and safety data for subcutaneous rituximab compared with rituximab intravenous using the 1400 mg subcutaneous dose established in stage 1. Previously untreated patients with CD20-positive, Follicular Lymphoma Grade 1, 2 or 3a (n=283) were enrolled in the stage 2.

The overall trial design was identical among both stages and patients were randomized into the following two treatment groups:

- MabThera subcutaneous formulation (n= 205): first cycle MabThera intravenous formulationplus 7 cycles of MabThera subcutaneous formulation in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks.

MabThera intravenous formulation was used at the standard dose of 375 mg/m^2 body surfacearea.
MabThera subcutaneous formulation was given at a fixed dose of 1400 mg.
Patients achieving at least partial response (PR) were entered on the MabThera subcutaneousformulation maintenance therapy once every 8 weeks for 24 months.

- MabThera intravenous formulation (n= 205): 8 cycles of MabThera intravenous formulation in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. MabThera intravenous formulation was used at the standard dose of 375 mg/m^2.
  Patients achieving at least PR were entered on MabThera intravenous formulation maintenance therapy once every 8 weeks for 24 months.

Key efficacy results for the pooled analysis of 410 patients in SABRINA stages 1 and 2 are shown in table 2.

Table 2 Efficacy results for SABRINA (BO22334) (Intent to Treat Population)

		Pooled Stages 1 & 2 N = 410	
		Rituximab intravenous formulation (n = 205)	**Rituximab subcutaneous formulation (n = 205)**
ORR [a]	**Point estimate**	**84.9% (n = 174)**	**84.4% (n = 173)**
	95% CI	**[79.2%, 89.5%]**	**[78.7%, 89.1%]**
CRR	**Point estimate**	**31.7% (n = 65)**	**32.2% (n = 66)**
	95% CI	**[25.4%, 38.6%]**	**[25.9%, 39.1%]**
PFS[b]	**Proportion with PFS event**	**34.6% (n = 71)**	**31.7% (n = 65)**
	Hazard ratio (95% CI)	**0.90 [0.64%, 1.26%]**	

ORR – Overall Response Rate
CRR – Complete Response Rate
PFS – Progression-Free Survival (proportion with event, disease progression/relapse or death from any cause)
[a] – at end of Induction
[b] – at time of final analysis (median follow-up 58 months)

Exploratory analyses showed response rates among BSA, chemotherapy and gender subgroups were not notably different from the ITT population.

Immunogenicity
Data from the development programme of MabThera subcutaneous formulation indicate that the formation of anti-rituximab antibodies after subcutaneous administration is comparable with that observed after intravenous administration. In the SABRINA trial (BO22334) the incidence of treatment-induced/enhanced anti-rituximab antibodies was low and similar in the intravenous and subcutaneous groups (1.9% vs. 2%, respectively). The incidence of treatment-induced/enhanced anti-rHuPH20 antibodies was 8% in the intravenous group compared with 15% in the subcutaneous group, and none of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies.

The overall proportion of patients found to have anti-rHuPH20 antibodies remained generally constant over the follow-up period in both cohorts. The clinical relevance of the development of anti-rituximab antibodies or anti-rHuPH20 antibodies after treatment with MabThera subcutaneous formulation is not known.
There was no apparent impact of the presence of anti-rituximab or anti-rHuPH20 antibodies on safety or efficacy.

Clinical experience of MabThera concentrate for solution for infusion in Non-Hodgkin's lymphoma

Follicular lymphoma

Initial treatment in combination with chemotherapy

In an open-label randomised trial, a total of 322 previously untreated patients with follicular lymphoma 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. The median follow up of patients was 53 months. R-CVP led to a significant benefit over CVP for the primary endpoint, time to treatment failure (27 months vs. 6.6 months, $p < 0.0001$, log-rank test). 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 %). Treatment with R-CVP significantly prolonged the time to disease progression or death compared to CVP, 33.6 months and 14.7 months, respectively ($p < 0.0001$, log-rank test). The median duration of response was 37.7 months in the R-CVP group and was 13.5 months in the CVP group ($p < 0.0001$, log-rank test).

The difference between the treatment groups with respect to overall survival showed a significant clinical difference ($p=0.029$, log-rank test stratified by center): survival rates at 53 months were 80.9 % for patients in the R-CVP group compared to 71.1 % for patients in the CVP group.

Results from three other randomized trials using MabThera in combination with chemotherapy regimen other than CVP (CHOP, MCP, CHVP/Interferon-α) have also demonstrated significant improvements in response rates, time-dependent parameters as well as in overall survival. Key results from all four trials are summarized in table 3.

Table 3 Summary of key results from four phase III randomized trials evaluating the benefit of MabThera with different chemotherapy regimens in follicular lymphoma

Trial	Treatment, N	Median FU, months	ORR, %	CR, %	Median TTF/PFS/ EFS mo	OS rates, %
M39021	CVP, 159 R-CVP, 162	53	57 81	10 41	Median TTP: 14.7 33.6 P<0.0001	53-months 71.1 80.9 p=0.029
GLSG'00	CHOP, 205 R-CHOP, 223	18	90 96	17 20	Median TTF: 2.6 years Not reached p < 0.001	18-months 90 95 p = 0.016
OSHO-39	MCP, 96 R-MCP, 105	47	75 92	25 50	Median PFS: 28.8 Not reached p < 0.0001	48-months 74 87 p = 0.0096
FL2000	CHVP-IFN, 183 R-CHVP-IFN, 175	42	85 94	49 76	Median EFS: 36 Not reached p < 0.0001	42-months 84 91 p = 0.029

EFS – Event Free Survival
TTP – Time to progression or death
PFS – Progression-Free Survival
TTF – Time to Treatment Failure
OS rates – survival rates at the time of the analyses

Maintenance therapy

Previously untreated follicular lymphoma
In a prospective, open label, international, multi-center, phase III trial 1193 patients with previously untreated advanced follicular lymphoma received induction therapy with R-CHOP (n=881), R-CVP (n=268) or R-FCM (n=44), according to the investigators' choice. A total of 1078 patients responded to induction therapy, of which 1018 were randomized to MabThera maintenance therapy (n=505) or observation (n=513). The two treatment groups were well balanced with regards to baseline characteristics and disease status. MabThera maintenance treatment consisted of a single infusion of MabThera at 375 mg/m2 body surface area given every 2 months until disease progression or for a maximum period of two years.

The pre-specified primary analysis was conducted at a median observation time of 25 months from randomization, maintenance therapy with MabThera resulted in a clinically relevant and statistically significant improvement in the primary endpoint of investigator assessed progression-free survival (PFS) as compared to observation in patients with previously untreated follicular lymphoma (Table 4).

Significant benefit from maintenance treatment with MabThera was also seen for the secondary endpoints event-free survival (EFS), time to next anti-lymphoma treatment (TNLT) time to next chemotherapy (TNCT) and overall response rate (ORR) in the primary analysis (Table 4).

Data from extended follow-up of patients in the study (median follow-up 9 years) confirmed the long-term benefit of MabThera maintenance therapy in terms of PFS, EFS, TNLT and TNCT (Table 4).

Table 4 Overview of efficacy results for MabThera maintenance vs. observation at the protocol-defined primary analysis and after 9 years median follow-up (final analysis)

	Primary analysis (median FU: 25 months)		Final analysis (median FU: 9.0 years)	
	Observation N=513	MabThera N=505	Observation N=513	MabThera N=505
Primary efficacy				
Progression-free survival (median)	NR	NR	4.06 years	10.49 years
log-rank p value	<0.0001		<0.0001	
hazard ratio (95% CI)	0.50 (0.39, 0.64)		0.61 (0.52, 0.73)	
risk reduction	50%		39%	
Secondary efficacy				
Overall survival (median)	NR	NR	NR	NR
log-rank p value	0.7246		0.7948	
hazard ratio (95% CI)	0.89 (0.45, 1.74)		1.04 (0.77, 1.40)	
risk reduction	11%		-6%	
Event-free survival (median)	38 months	NR	4.04 years	9.25 years
log-rank p value	<0.0001		<0.0001	
hazard ratio (95% CI)	0.54 (0.43, 0.69)		0.64 (0.54, 0.76)	
risk reduction	46%		36%	
TNLT (median)	NR	NR	6.11 years	NR
log-rank p value	0.0003		<0.0001	
hazard ratio (95% CI)	0.61 (0.46, 0.80)		0.66 (0.55, 0.78)	
risk reduction	39%		34%	
TNCT (median)	NR	NR	9.32 years	NR
log-rank p value	0.0011		0.0004	
hazard ratio (95% CI)	0.60 (0.44, 0.82)		0.71 (0.59, 0.86)	
risk reduction	40%		39%	
Overall response rate*	55%	74%	61%	79%
chi-squared test p value	<0.0001		<0.0001	
odds ratio (95% CI)	2.33 (1.73, 3.15)		2.43 (1.84, 3.22)	
Complete response (CR/CRu) rate*	48%	67%	53%	67%
chi-squared test p value	<0.0001		<0.0001	
odds ratio (95% CI)	2.21 (1.65, 2.94)		2.34 (1.80, 3.03)	

* at end of maintenance/observation; final analysis results based on median follow-up of 73 months.
FU: follow-up; NR: not reached at time of clinical cut off, TNCT: time to next chemotherapy treatment; TNLT: time to next anti lymphoma treatment.

MabThera maintenance treatment provided consistent benefit in all predefined subgroups tested: gender (male, female), age (< 60 years, >= 60 years), FLIPI score (<=1, 2 or >= 3), induction therapy (R-CHOP, R-CVP or R-FCM) and regardless of the quality of response to induction treatment (CR/CRu or PR). Exploratory analyses of the benefit of maintenance treatment showed a less pronounced effect in elderly patients (> 70 years of age), however sample sizes were small.

Relapsed/Refractory follicular lymphoma
In a prospective, open label, international, multi-centre, phase III trial, 465 patients with relapsed/refractory follicular lymphoma were randomised in a first step to induction therapy with either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone; n=231) or MabThera plus CHOP (R-CHOP, n=234). The two treatment groups were well balanced with regard to baseline characteristics and disease status. A total of 334 patients achieving a complete or partial remission following induction therapy were randomised in a second step to MabThera maintenance therapy (n=167) or observation (n=167). MabThera maintenance treatment consisted of a single infusion of MabThera at 375 mg/m^2 body surface area given every 3 months until disease progression or for a maximum period of two years.

The final efficacy analysis included all patients randomized to both parts of the trial. After a median observation time of 31 months for patients randomised to the induction phase, R-CHOP significantly improved the outcome of patients with relapsed/refractory follicular lymphoma when compared to CHOP (see Table 5).

Table 5 Induction phase: overview of efficacy results for CHOP vs. R-CHOP (31 months median observation time)

	CHOP	R-CHOP	p-value	Risk Reduction[1)]
Primary efficacy				
ORR[2)]	74 %	87 %	0.0003	Na
CR[2)]	16 %	29 %	0.0005	Na
PR[2)]	58 %	58 %	0.9449	Na

[1)] Estimates were calculated by hazard ratios
[2)] Last tumour response as assessed by the investigator. The "primary" statistical test for "response" was the trend test of CR versus PR versus non-response ($p < 0.0001$)
Abbreviations: NA, not available; ORR: overall response rate; CR: complete response; PR: partial response

For patients randomized to the maintenance phase of the trial, the median observation time was 28 months from maintenance randomisation. Maintenance treatment with MabThera led to a clinically relevant and statistically significant improvement in the primary endpoint, PFS, (time from maintenance randomisation to relapse, disease progression or death) when compared to observation alone ($p< 0.0001$ log-rank test).The median PFS was 42.2 months in the MabThera maintenance arm compared to 14.3 months in the observation arm. Using a cox regression analysis, the risk of experiencing progressive disease or death was reduced by 61 % with MabThera maintenance treatment when compared to observation (95 % CI; 45 %-72 %). Kaplan-Meier estimated progression-free rates at 12 months were 78 % in the MabThera maintenance group vs. 57 % in the observation group. An analysis of overall survival confirmed the significant benefit of MabThera maintenance over observation ($p=0.0039$ log-rank test). MabThera maintenance treatment reduced the risk of death by 56 % (95 % CI; 22 %-75 %).

Table 6 Maintenance phase: overview of efficacy results MabThera vs. observation (28 months median observation time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Risk Reduction
	Observation (N = 167)	MabThera (N=167)	Log-Rank p value	
Progression-free survival (PFS)	*14.3*	*42.2*	*< 0.0001*	*61 %*
Overall survival	*NR*	*NR*	*0.0039*	*56 %*
Time to new lymphoma treatment	*20.1*	*38.8*	*< 0.0001*	*50 %*
Disease-free survival[a]	*16.5*	*53.7*	*0.0003*	*67 %*
Subgroup analysis PFS				
CHOP	*11.6*	*37.5*	*< 0.0001*	*71 %*
R-CHOP	*22.1*	*51.9*	*0.0071*	*46 %*
CR	*14.3*	*52.8*	*0.0008*	*64 %*
PR	*14.3*	*37.8*	*< 0.0001*	*54 %*
OS				
CHOP	*NR*	*NR*	*0.0348*	*55 %*
R-CHOP	*NR*	*NR*	*0.0482*	*56 %*

NR: not reached; [a]: only applicable to patients achieving a CR

The benefit of MabThera maintenance treatment was confirmed in all subgroups analysed, regardless of induction regimen (CHOP or R-CHOP) or quality of response to induction treatment (CR or PR) (table 6). MabThera maintenance treatment significantly prolonged median PFS in patients responding to CHOP induction therapy (median PFS 37.5 months vs. 11.6 months, p< 0.0001) as well as in those responding to R-CHOP induction (median PFS 51.9 months vs. 22.1 months, p=0.0071). Although subgroups were small, MabThera maintenance treatment provided a significant benefit in terms of overall survival for both patients responding to CHOP and patients responding to R-CHOP, although longer follow-up is required to confirm this observation.

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 prednisolone 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 60 months, confirmed the benefit of R-CHOP over CHOP treatment (p=0.0071), representing a risk reduction of 32 %.

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 HAMA, no responses were noted. Of 356 patients evaluated for ADA, 1.1 % (4 patients) were positive.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with rituximab in all subsets of the paediatric population with follicular lymphoma. See Section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

Rituximab pharmacokinetics following single dose administration of MabThera subcutaneous 375 mg/m^2, 625 mg/ m^2 and 800 mg/ m^2 were compared with MabThera intravenous 375 mg/ m^2 in FL patients. Following subcutaneous administration, the absorption of rituximab is slow, reaching maximal concentrations about 3 days after administration. Based on popPK analysis an absolute bioavailability of 71% was estimated. Rituximab exposure increased dose proportional over the 375 mg/m^2 to 800 mg/m^2 subcutaneous dose range. Pharmacokinetic parameters such as clearance, distribution volume, and elimination half-life were comparable for both formulations.

Trial BP22333 (SparkThera)
A two-stage phase Ib trial to investigate the pharmacokinetics, safety and tolerability of MabThera subcutaneous formulation in patients with follicular lymphoma (FL) as part of maintenance treatment. In stage 2, MabThera subcutaneous formulation at a fixed dose of 1400 mg was administered as subcutaneous injection during maintenance treatment, after at least one cycle of MabThera intravenous formulation to FL patients who had previously responded to MabThera intravenous formulation in induction.

The comparison of predicted median C_{max} data for MabThera subcutaneous formulation and intravenous formulation are summarized in Table 7.

Table 7: Trial BP22333 (SparkThera): Absorption - Pharmacokinetic parameters of MabTheraSC compared to MabThera IV

	MabThera subcutaneous	MabThera intravenous
Predicted median C_{max} (q2m) µg/mL	201	209
Predicted median C_{max} (q3m) µg/mL	189	184

The median T_{max} in the MabThera subcutaneous formulation was approximately 3 days as compared to the T_{max} occuring at or close to the end of the infusion for the intravenous formulation.

Trial BO22334 (SABRINA)
MabThera subcutaneous formulation at a fixed dose of 1400 mg was administered for 6 cycles subcutaneously during induction at 3-weekly intervals, following the first cycle of MabThera intravenous formulation, in previously untreated FL patients in combination with chemotherapy. The serum rituximab C_{max} at cycle 7 was similar between the two treatment arms, with geometric mean (CV%) values of 250.63 (19.01) µg/mL and 236.82 (29.41) µg/mL for the intravenous and the subcutaneous formulations respectively, with the resulting geometric mean ratio ($C_{max, SC}/C_{max, IV}$) of 0.941 (90% CI: 0.872, 1.015).

Distribution/Elimination

Geometric mean C_{trough} and geometric mean AUCτ from the BP22333 and BO22334 trials are summarized in Table 8.

Table 8: Distribution/Elimination - Pharmacokinetic parameters of MabThera subcutaneous compared to MabThera intravenous

Trial BP22333 (SparkThera)				
	Geometric mean C_{trough} (q2m) µg/mL	Geometric mean C_{trough} (q3m) µg/mL	Geometric mean AUCτ cycle 2 (q2m) µg.day/mL	Geometric mean AUCτ cycle 2 (q3m) µg.day/mL
MabThera subcutaneous formulation	32.2	12.1	5430	5320
MabThera intravenous formulation	25.9	10.9	4012	3947
Trial BO22334 (SABRINA)				
	Geometric mean C_{trough} values at pre-dose cycle 8 µg/mL		Geometric mean AUC values at cycle 7 µg.day/mL	
MabThera subcutaneous formulation	134.6		3778	
MabThera intravenous formulation	83.1		2734	

In a population pharmacokinetic analysis in 403 follicular lymphoma patients who received subcutaneous and/or intravenous MabThera, single or multiple infusions of MabThera as a single agent or in combination with chemotherapy, the population estimates of nonspecific clearance (CL_1), initial specific clearance (CL_2) likely contributed by B cells or tumour burden, and central compartment volume of distribution (V_1) were 0.194 L/day, 0.535 L/day, and 4.37 L/day, respectively. The estimated median terminal elimination half-life of MabThera subcutaneous formulation was 29.7 days (range, 9.9 to 91.2 days).The analysis data set contained 6003 quantifiable samples from 403 patients administered SC and/or IV rituximab in trials BP22333 (3736 samples from 277 patients) and BO22334 (2267 samples from126 patients). Twenty nine (0.48%) post-dose observations (all from trial BP22333) were below the quantification limit. There were no missing covariate values except baseline B-cell count. Baseline tumour load was available only in trial BO22334.

Special populations

In clinical trial BO22334, an effect was observed between body size and exposure ratios reported in cycle 7, between rituximab subcutaneous formulation 1400 mg q3w and rituximab intravenous formulation 375 mg/m2 q3w with C_{trough} ratios of 2.29, 1.31, and 1.41 in patients with low, medium and high BSA, respectively (low BSA ≤ 1.70 m^2; 1.70 m^2 < medium BSA < 1.90 m^2; high BSA ≥ 1.90 m^2). The corresponding AUCτ ratios were 1.66, 1.17 and 1.32.

There was no evidence of clinically relevant dependencies of rituximab pharmacokinetics on age and sex.

Anti-rituximab antibodies were detected in only 13 patients and did not result in any clinically relevant increase in steady-state clearance.

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.

Developmental toxicity studies have been performed in cynomolgus monkeys at doses up to 100 mg/kg (treatment on gestation days 20-50) and have revealed no evidence of toxicity to the foetus due to rituximab. However, dose-dependent pharmacologic depletion of B cells in the lymphoid organs of the foetuses was observed, which persisted post natally and was accompanied by a decrease in IgG level in the newborn animals affected. B cell counts returned to normal in these animals within 6 months of birth and did not compromise the reaction to immunization.

Standard tests to investigate mutagenicity have not been carried out, since such tests are not relevant for this molecule. No long-term animal studies have been performed to establish the carcinogenic potential of rituximab.
Specific studies to determine the effects of rituximab or rHuPH20 on fertility have not been performed. In general toxicity studies in cynomolgus monkeys no deleterious effects on reproductive organs in males or females were observed. Additionally, no effects on semen quality were shown for rHuPH20.

In embryofetal developmental studies in mice, rHuPH20 caused reduced fetal weight and loss of implantations at systemic exposures sufficiently in excess of human therapeutic exposure.
There is no evidence of dysmorphogenesis (i.e. teratogenesis) resulting from systemic exposure to rHuPH20.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Recombinant human hyaluronidase (rHuPH20)
L-histidine
L-histidine hydrochloride monohydrate
α,α-trehalose dihydrate
L-methionine
Polysorbate 80 (E433)
Water for injections

6.2 Incompatibilities

No incompatibilities between MabThera subcutaneous formulation and polypropylene or polycarbonate syringe material or stainless steel transfer and injection needles and polyethylene Luer cone stoppers have been observed.

6.3 Shelf life

Unopened vial
3 years

After first opening
Once transferred from the vial into the syringe, the solution of MabThera subcutaneous formulation is physically and chemically stable for 48 hours at 2 °C - 8 °C and subsequently for 8 hours at 30°C in diffuse daylight.

From a microbiological point of view, the product should be used immediately. If not used immediately, preparation should take place in controlled and validated aseptic conditions. In-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Keep the container in the outer carton in order to protect from light.
For storage conditions after first opening see section 6.3.

6.5 Nature and contents of container

Colourless type I glass vial with butyl rubber stopper with aluminium over seal and a pink plastic flip-off disk, containing 1400 mg/11.7 mL of rituximab.

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

MabThera is provided in sterile, preservative-free, non-pyrogenic, single use vials. Use sterile needle and syringe to prepare MabThera. A peel-off sticker is included on the vials which specifies the strength, route of administration and indication. This sticker should be removed from the vial and stuck onto the syringe prior to use. The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused
- Place all used needles and syringes into a sharps container (puncture-proof disposablecontainer).

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

7 MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8 MARKETING AUTHORISATION NUMBER(S)

EU/1/98/067/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2 June 1998
Date of latest renewal: 20 May 2008