AUSTRALIAN PRODUCT INFORMATION
MabThera® SC (rituximab)

WARNING

Use of MabThera may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Patients must be monitored for any new or worsening neurological symptoms or signs suggestive of PML. If such symptoms occur, further administration of MabThera should be immediately suspended until a diagnosis of PML has been excluded. To establish or exclude a diagnosis of PML evaluation including MRI scan, CSF testing for JC viral DNA and repeat neurological assessments, should be considered. If a diagnosis of PML is confirmed MabThera must be permanently discontinued (see section 4.4 Special warnings and precautions for use).

1. NAME OF THE MEDICINE
rituximab

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
MabThera SC 1400mg
Each mL contains 120 mg of rituximab. Each vial contains 1400 mg/11.7 mL rituximab.

MabThera SC 1600mg
Each mL contains 120 mg of rituximab. Each vial contains 1600 mg/ 13.4 mL rituximab.

Excipients with known effect
MabThera SC contains less than 1mmol sodium per dose, i.e. essentially sodium free.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM
Solution for injection.

Clear to opalescent, colourless to yellowish liquid.

Target pH 5.5.

4. CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Non-Hodgkin's Lymphoma
MabThera SC 1400mg is indicated for treatment of patients with:
- CD20 positive, previously untreated, Stage III/IV follicular, B-cell non-Hodgkin's lymphoma,
- CD20 positive, relapsed or refractory low grade or follicular, B-cell non-Hodgkin's lymphoma,
- CD20 positive, diffuse large B-cell non-Hodgkin's lymphoma, in combination with chemotherapy.

Chronic Lymphocytic Leukaemia
MabThera SC 1600 mg is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

MabThera SC is not intended for IV administration and should be given via SC injection only. It is important to check the product labels to ensure that the appropriate formulation (IV or SC) and strength is being given to the patient, as prescribed.

MabThera SC 1400 mg is intended for use in NHL only.

MabThera SC 1600 mg is intended for use in CLL only.

MabThera SC may be administered in an outpatient setting. MabThera SC should be administered as an SC injection in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced healthcare professional.

First intravenous administration:
All patients must always receive their first dose of MabThera by intravenous infusion using the MabThera intravenous formulation. During their first cycle the patient is at the highest risk of experiencing an infusion / administration related reaction. Beginning therapy with MabThera by intravenous infusion allows management of infusion / administration related reactions by slowing or stopping the intravenous infusion (see section 4.8 Adverse effects (Undesirable effects)).

Subsequent subcutaneous administrations:
The subcutaneous formulation must only be given at the second or subsequent cycles.

Dosage
Non-Hodgkin's Lymphoma
Subcutaneous Formulation (1400 mg): The recommended dosage of MabThera SC is a fixed dose of 1400 mg, given as an SC injection, irrespective of the patient's body surface area. It should be administered over approximately 5 minutes (see Method of Administration below).

Premedication, consisting of an analgesic/antipyretic (such as paracetamol) and an antihistamine should always be administered 30 to 60 minutes before each injection of MabThera SC. Premedication with glucocorticoids should also be considered, particularly if MabThera is not given in combination with steroid-containing chemotherapy (see section 4.4 Special warnings and precautions for use).

First intravenous administration:
Before starting MabThera SC injections, all patients must always receive beforehand, a full dose of MabThera by intravenous infusion, using the intravenous MabThera formulation (see section 4.4 Special warnings and precautions for use).

Subsequent subcutaneous administrations:
Patients should not receive MabThera SC until they have been able to tolerate a full intravenous infusion dose of MabThera. If a patient is unable to do so, they should continue being given the IV formulation of MabThera for subsequent cycles until a full intravenous dose can be successfully administered. Once a patient has been able to receive one full

intravenous dose of MabThera, subsequent cycles can be given subcutaneously using the MabThera SC formulation (given on day 1 of each cycle).

Please refer to the separate Product Information for intravenous MabThera formulation for full instructions on dosing, method of administration, preparation and storage.

Relapsed or refractory Low Grade or Follicular non-Hodgkin's lymphoma
The recommended dosage of MabThera when used in monotherapy is: first cycle with intravenous MabThera 375 mg/m^2 administered as an intravenous infusion, followed by subsequent cycles with MabThera SC at a fixed dose of 1400 mg per cycle, once weekly. In total: four weeks.

The recommended dosage of MabThera when used in combination with CHOP chemotherapy is: first cycle with intravenous MabThera 375 mg/m^2 administered as an intravenous infusion, followed by subsequent cycles with MabThera SC injected at a fixed dose of 1400 mg per cycle. In total: 6 cycles. MabThera should be administered on day 1 of each chemotherapy cycle.

Previously untreated stage III/IV Follicular non-Hodgkin’s lymphoma
The recommended dosage of MabThera in combination with chemotherapy as induction therapy is: first cycle with intravenous MabThera 375 mg/m^2 administered as an intravenous infusion, followed by subsequent cycles with MabThera SC injected at a fixed dose of 1400 mg per cycle. In total: for up to 8 cycles. MabThera should be administered on day 1 of each chemotherapy cycle.

MabThera should be administered prior to the administration of chemotherapy. Any administration-related reactions should have settled before chemotherapy is instituted.

Maintenance treatment in follicular lymphoma
Previously untreated patients who have responded to induction treatment may receive maintenance therapy with MabThera SC. The recommended dose of MabThera SC is 1400 mg injected at a fixed dose once every 2 months until disease progression or for a maximum period of two years.

Relapsed/refractory patients who have responded to induction treatment may receive maintenance therapy with MabThera SC given at 1400 mg once every 3 months until disease progression or for a maximum period of two years.

Diffuse large B-cell non-Hodgkin's lymphoma
The recommended dosage for MabThera in combination with CHOP chemotherapy is: first dose with intravenous MabThera 375 mg/m^2 administered as an intravenous infusion followed by subsequent cycles with MabThera SC injected at a fixed dose of 1400 mg per cycle. In total: for up to 8 cycles. MabThera should be administered on day 1 of each chemotherapy cycle after IV administration of the glucocorticoid component of CHOP.

Chronic Lymphocytic Leukaemia
Subcutaneous Formulation (1600 mg)
The recommended dosage of MabThera SC in combination with chemotherapy is a fixed dose of 1600 mg, given as an SC injection, irrespective of the patient’s body surface area. It should be administered over approximately 7 minutes (see Method of Administration of MabThera SC formulation below).

Premedication, consisting of an analgesic/antipyretic such as paracetamol and an antihistamine should always be administered 30 to 60 minutes before each injection of MabThera SC. Premedication with glucocorticoids should also be considered, particularly if MabThera is not given in combination with steroid-containing chemotherapy (see section 4.4 Special warnings and precautions for use).

Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to the start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome. For CLL patients whose lymphocyte counts are >25 $x10^9$/L it is recommended to administer methylprednisolone 100 mg IV shortly before MabThera administration to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

First intravenous administration:
Before starting MabThera SC, all patients must always receive beforehand a full dose of intravenous MabThera by intravenous infusion (see section 4.4 Special warnings and precautions for use). The first administration of intravenous MabThera should be given by infusion at a dose of 375 mg/m^2.

Subsequent subcutaneous administrations:
Patients should not receive MabThera SC until they have been able to tolerate a full intravenous infusion dose of MabThera. If a patient is unable to do so, they should continue being given the IV formulation of MabThera for subsequent cycles until a full intravenous dose can be successfully administered. Once a patient has been able to receive one full intravenous dose of MabThera, subsequent cycles can be given subcutaneously using the MabThera SC formulation (given on day 1 of each cycle). The total number of treatments / cycles for a patient is 6 cycles.

Please refer to the separate Product Information for intravenous MabThera formulation for full instructions on dosing, method of administration, preparation and storage.

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

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

Method of Administration
MabThera SC should be injected subcutaneously into the abdominal wall and never into areas where the skin is red, bruised, tender or hard or into 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.

MabThera SC 1400 mg should be injected over approximately 5 minutes. MabThera SC 1600 mg should be injected over approximately 7 minutes. The hypodermic injection needle must only be attached to the syringe immediately prior to administration to avoid potential needle clogging.

Appropriate subcutaneous injection technique should be used. Inadvertent intramuscular injection may result in systemic exposure and overdose. To prevent inadvertent intravenous injection, draw back on the syringe once the needle has been inserted to ensure that the needle has not entered a blood vessel.

During the treatment course with MabThera SC, other medications for subcutaneous administration should preferably be administered at different sites.

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

As with all parenteral products, appropriate aseptic technique should be used during the administration of MabThera.

MabThera SC should not be self-administered by the patient.

4.3 CONTRAINDICATIONS

MabThera is contraindicated in patients with known hypersensitivity to rituximab, to any of its excipients or to murine proteins.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Progressive multifocal leukoencephalopathy (PML)

Use of MabThera may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML). Patients must be monitored for any new or worsening neurological symptoms or signs suggestive of PML. Physicians treating patients should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

Physicians should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). If such symptoms occur, further administration of MabThera should be immediately suspended until a diagnosis of PML has been excluded. To establish or exclude a diagnosis of PML evaluation including MRI scan, CSF testing for JC viral DNA and repeat neurological assessments, should be considered. Once PML has been excluded, the administration of MabThera may resume. If a diagnosis of PML is confirmed MabThera must be permanently discontinued. 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.

Cases of PML have been reported during use of MabThera in NHL and CLL. The majority of patients had received MabThera in combination with chemotherapy or as part of a haematopoietic stem cell transplant. (see Boxed Warning and section 4.8 Adverse effects (Undesirable effects)).

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 indistinguishable from acute hypersensitivity reactions.

Administration-related reactions for MabThera SC

Local cutaneous reactions, including injection site reactions, have been reported in patients receiving MabThera SC. Symptoms included pain, swelling, induration, haemorrhage,

erythema, pruritus and rash (see section 4.8 Adverse effects (Undesirable effects)). Some local cutaneous reactions occurred more than 24 hours after the MabThera SC administration. The majority of local cutaneous reactions seen following administration of MabThera SC were mild or moderate and resolved without any specific treatment.

All patients must always receive their first dose of MabThera by intravenous administration, using the intravenous formulation, in order to avoid an irreversible administration of the full MabThera SC dose during cycle 1. During this cycle the patient would have the highest risk of experiencing an infusion-related reaction that can be treated effectively by slowing or stopping the infusion. MabThera SC must only be given at the second or subsequent cycles.

If patients were not able to receive one full MabThera intravenous infusion dose, they should continue the subsequent cycles with intravenous MabThera until a full IV dose is successfully administered. Therefore, the switch to MabThera SC can only occur at the second or subsequent cycles of treatment (see section 4.2 Dose and method of administration). As with the intravenous formulation, MabThera SC should be administered in an environment where full resuscitation facilities are immediately available and under the close supervision of a healthcare professional. Premedication consisting of an analgesic/antipyretic and an antihistamine should always be administered before each dose of MabThera SC. Premedication with glucocorticoids should also be considered, particularly if MabThera SC is not given in combination with steroid-containing chemotherapy (see section 4.2 Dose and method of administration).

Patients should be observed for at least 15 minutes following MabThera SC administration. A longer period may be appropriate for 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 reactions or cytokine release syndrome occur at any time after drug administration.

Infusion-related reactions for intravenous MabThera

Severe infusion-related reactions with fatal outcome have been reported during post-marketing use. Severe reactions usually manifested within 30 minutes to 2 hours after starting the first MabThera infusion, were characterised by pulmonary events and included, in some cases, rapid tumour lysis and features of tumour lysis syndrome in addition to fever, chills, rigors, hypotension, urticaria, angio-oedema and other symptoms. Patients with a high tumour burden or with a high number ($>25 \times 10^9$/L) of circulating malignant cells such as patients with mantle cell lymphoma may be at higher risk of developing severe infusion-related reactions. Infusion reaction symptoms are usually reversible with interruption of the infusion. Treatment of infusion-related symptoms with an antihistamine and an analgesic/antipyretic (such as paracetamol) is recommended. Additional treatment with bronchodilators or IV saline may be indicated. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved. Most patients who have experienced non-life threatening infusion-related reactions have been able to complete the full course of MabThera therapy. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe infusion-related reactions.

Patients with a high number ($>25 \times 10^9$/L) of circulating malignant cells or high tumour burden such as patients with mantle cell lymphoma, who may be at higher risk of especially severe infusion-related reactions, 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, or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still >25 x 10^9/L.

Hypersensitivity Reactions/Anaphylaxis

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. Adrenaline, antihistamines and corticosteroids should be available for immediate use in the event of a hypersensitivity reaction to intravenous MabThera.

Pulmonary events

Pulmonary events have included hypoxia, lung infiltration, and acute respiratory failure. Some of these events have been preceded by severe bronchospasm and dyspnoea. In some cases, symptoms worsened over time, while in others initial improvement was followed by clinical deterioration. Therefore, patients experiencing pulmonary events or other severe infusion-related symptoms should be closely monitored until complete resolution of their symptoms occurs. 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. Acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray. The syndrome usually manifests itself within one or two hours of initiating the first IV infusion. Patients who experience severe pulmonary events should have their intravenous MabThera or MabThera SC administration interrupted immediately and should receive aggressive symptomatic treatment. Since initial improvement of clinical symptoms may be followed by deterioration, these patients should be closely monitored until the pulmonary event has resolved.

Rapid tumour lysis

MabThera mediates the rapid lysis of benign and malignant CD20-positive cells. Signs and symptoms (e.g. hyperuricaemia, hyperkalaemia, hypocalcaemia, acute renal failure, elevated LDH) consistent with tumour lysis syndrome (TLS) have been reported to occur after the first MabThera intravenous infusion in patients with high numbers of circulating malignant lymphocytes. Prophylaxis for TLS should be considered for patients at risk of developing rapid tumour lysis (e.g. patients with a high tumour burden or with a high number (>25 x 10^9/L) of circulating malignant cells such as patients with mantle cell lymphoma). These patients should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should be provided for patients who develop signs and symptoms consistent with rapid tumour lysis. Following treatment for and complete resolution of signs and symptoms, subsequent intravenous MabThera therapy has been administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

Cardiovascular

Since hypotension may occur during MabThera administration, consideration should be given to withholding antihypertensive medications 12 hours prior to and throughout MabThera administration. Angina pectoris or cardiac arrhythmia, 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 should be monitored closely. Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias.

Monitoring of Blood Counts

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

counts of <75 x 10^9/L, as clinical experience with such patients is limited. Intravenous Mabthera has been used in patients who underwent autologous bone marrow transplantation and in 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.

Infections

MabThera treatment should not be initiated in patients with severe active infections.

Cases of Hepatitis B virus (HBV) reactivation, occasionally with fulminant hepatitis, hepatic failure, and death have been reported in some patients with haematologic malignancies treated with intravenous MabThera. The majority of patients received MabThera in combination with chemotherapy. Isolated cases have been reported in patients who either had evidence of antibodies against Hepatitis B surface antigen before treatment or did not have any such antibodies. The median time to diagnosis of hepatitis was approximately 4 months after the initiation of MabThera and approximately one month after the last dose. Analysis of events revealed MabThera use has been associated with hepatitis B (HB) reactivation in patients with positive HB surface antigen (HBsAg+ve) as well as negative HB surface antigen and positive anti-HB core antibody (HBsAg-ve/HBcAb+ve), particularly when administered in combination with steroids or chemotherapy.

HBV screening should be performed in all patients before initiation of treatment with MabThera. At a minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active HB disease should not be treated with MabThera. Reactivation of HBV infection is a well-known complication in patients with chronic hepatitis B, especially in those receiving cytotoxic or immunosuppressive therapy. In addition, non-Hodgkin's lymphoma of itself may be an independent risk factor for HBV reactivation. Patients with positive HB serology should consult a liver disease specialist before the start of treatment and should be monitored and managed according to guidelines to prevent HB reactivation.

In patients who develop reactivation of viral hepatitis B, MabThera and any concomitant chemotherapy should be discontinued and appropriate treatment including antiviral therapy initiated. There are insufficient data regarding the safety of resuming therapy with MabThera in patients who develop hepatitis subsequent to HBV reactivation.

The following additional serious viral infections, either new, reactivated or exacerbated, have been identified in clinical studies or post-marketing reports. The majority of patients were profoundly immune-suppressed. These viral infections included JC virus [progressive multifocal leukoencephalopathy (PML)], cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus and hepatitis C. In some cases, the viral infections occurred up to one year following discontinuation of MabThera and have resulted in death.

Skin Reactions

Severe skin reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome, some with fatal outcome, have been reported (see section 4.8 Adverse effects (Undesirable

effects)). In case of such an event, with a suspected relationship to MabThera, treatment should be permanently discontinued.

Pharmacokinetic differences between MabThera 1400mg SC and IV formulations
Fixed 1400 mg dose MabThera SC results in a higher systemic exposure to rituximab than is seen with intravenous MabThera at recommended doses in NHL (see section 5.2 Pharmacokinetic properties). This increase in systemic exposure is more pronounced in subjects with low body surface area (BSA), but is also apparent in those with average and high BSA. Currently available data from the MabThera SC clinical development program indicate that greater exposure occurring after MabThera SC administration, particularly in patients with low BSA, is not associated with a major increased risk of adverse effects.

Immunisation
The safety of immunisation with live viral vaccines, following MabThera therapy has not been studied 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-randomised study, patients with relapsed low-grade NHL who received intravenous MabThera 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. 76% 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, varicella) were maintained for at least 6 months after treatment with intravenous MabThera.

Use in the Elderly
No data available

Paediatric use
The safety and effectiveness of MabThera in paediatric patients have not been established. Hypogammaglobulinaemia has been observed in paediatric patients treated with MabThera, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in paediatric patients are unknown.

Effects on laboratory tests'
No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

In CLL patients, co-administration with intravenous 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 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 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No animal studies have been performed to determine the effect of rituximab on fertility in males or females.

MabThera SC contains vorhyaluronidase alfa (see section 6.1 List of excipients). There is the potential for anti-vorhyaluronidase alfa antibodies to impair fertility. In the SABRINA clinical study, anti-vorhyaluronidase alfa antibodies were observed in 2/57 (4%) and 2/53 (4%) of patients in the IV and SC cohorts, respectively, among patients who were antibody-negative at baseline (see section 4.8 Adverse effects (Undesirable effects)).

Specific studies to determine the effects of the vorhyaluronidase alfa or anti-vorhyaluronidase alfa antibodies on fertility have not been performed. However, in general toxicity studies of vorhyaluronidase alfa in cynomolgus monkeys, no deleterious effects on reproductive organs in males or females were observed and no effects on semen quality were shown.

Use in Pregnancy (Category C)

It is not known whether MabThera can cause foetal harm when administered to a pregnant woman. 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 rituximab.

In clinical studies in patients with rheumatoid arthritis, three pregnancies occurred following exposure to intravenous MabThera + MTX with two resulting in spontaneous abortions and the third ongoing at the time. In the SparkThera study, a pregnancy occurred following treatment with both MabThera SC and intravenous MabThera resulting in a spontaneous abortion. This event was not considered related to the study medication.

Rituximab has been shown to cause B-cell depletion in the monkey foetus. MabThera should not be given to a pregnant woman, unless the potential benefit outweighs the potential risk.

Women of child-bearing potential must use effective contraceptive methods during treatment and for 12 months following MabThera therapy.

Developmental toxicity studies with rituximab performed in cynomolgus monkeys revealed no evidence of embryotoxicity in utero at relative exposure levels (AUC) similar to that anticipated clinically. New born offspring of maternal animals exposed to MabThera during lactation and/or gestation showed no untoward toxicity except for depleted B cell populations during the post-natal phase at the same relative exposure. B cell levels in human neonates following maternal exposure to MabThera have not been studied.

MabThera SC contains vorhyaluronidase alfa (see section 6.1 List of excipients). Developmental toxicity studies in mice demonstrate reductions in foetal weight and increases in the number of resorptions following injection of vorhyaluronidase alfa. The no effect level (360,000 U/kg/day) is estimated to be at least 69 times the dose used clinically (based on body surface area).

Use in Lactation

It is not known whether rituximab is excreted in human milk. In monkey studies, rituximab was excreted in the milk and was detected in the serum of breast-fed infants. Reversible B-cell depletion was observed in all monkey infants exposed to rituximab via maternal transfer during lactation and/or gestation. It is recommended that a nursing woman discontinue breastfeeding whilst undergoing treatment with MabThera.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

It is not known whether MabThera has an effect on the ability to drive and operate machines, though the pharmacologic activity and adverse events reported to date do not indicate that such an effect is to be expected.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Subcutaneous Formulation

Local cutaneous reactions, including injection site reactions were very common in patients receiving MabThera SC in the SparkThera and SABRINA studies; reported in up to 50% of patients at some time during treatment. Symptoms included pain, swelling, induration, haemorrhage, erythema, pruritus and rash. Similar events were observed in the SAWYER study (BO25341) and were reported in up to 42% of patients in the MabThera SC arm. The most common local cutaneous reactions were injection site erythema (26%), injection site pain (16%), and injection site swelling (5%). Events seen following subcutaneous administration were mild or moderate, apart from one patient in the SABRINA study who reported a local cutaneous reaction of Grade 3 intensity (injection site rash) and two patients in the SAWYER study who experienced Grade 3 local cutaneous reactions (injection site erythema, injection site pain, and injection site swelling). Local cutaneous reactions of any grade in the MabThera SC arm were most common during the first SC cycle (Cycle 2), followed by the second, and the incidence decreased with subsequent injections.

In the SparkThera and SABRINA studies, the 1400 mg MabThera SC dose lead to higher systemic rituximab exposures compared to the intravenous MabThera 375 mg/m2 dose (see section 5.2 Pharmacokinetic properties). In SABRINA, a numerically higher number of adverse events (including ≥ Grade 3 and serious adverse events) were reported in MabThera SC arm, however the proportion of patients in each study arm experiencing such adverse events was comparable.

Preliminary analysis of safety results from pooled Stages 1 and 2 of SABRINA raises the possibility that neutropenia is more frequent with the use of fixed dose 1400 mg MabThera SC than with use of the IV formulation. In induction cycles 2 - 8 of the open-label SABRINA study, serious adverse events of neutropenia were reported in 1/210 (< 1%) in the IV arm vs. 5/197 (3%) in the SC arm; ≥ Grade 3 adverse events of neutropenia were reported in 14% vs. 21% respectively.

The safety profile of MabThera SC was otherwise comparable to that of intravenous MabThera.

Immunogenicity

Data from the MabThera SC development program indicate that the formation of anti-rituximab antibodies (HACAs) after SC administration is comparable with that observed after IV administration.

In the SABRINA study, the incidence of treatment-induced/enhanced anti-rituximab antibodies in the SC group was 1.5% IV vs 2% SC.

In the SAWYER study, the incidence of treatment-induced/enhanced anti-rituximab antibodies was similar in the two treatment arms; 6.7% IV vs. 2.4% SC.

The clinical relevance of the development of anti-rituximab or anti-vorhyaluronidase alfa antibodies after treatment with MabThera SC is not known.

Intravenous formulation

Information in this section reports data from the separate Product Information for intravenous MabThera.

Experience from Clinical Trials in Haemato-Oncology

The most common adverse reactions of MabThera (incidence ≥ 25%) observed in patients with NHL are infusion-related reactions, fever, chills, infection, asthenia and lymphopenia. The most important serious adverse reactions of MabThera are infusion-related reactions, tumour lysis syndrome, mucocutaneous toxicities, hepatitis B reactivation with fulminant hepatitis, PML, other viral infections, cardiac arrhythmias, renal toxicity, and bowel obstruction and perforation.

The frequencies of adverse drug reactions (ADRs) reported with MabThera alone or in combination with chemotherapy are summarised in the tables below and are based on data from clinical trials. These ADRs had either occurred in single arm studies or had occurred with at least a 2% difference compared to the control arm in at least one of the major randomised clinical trials. ADRs are added to the appropriate category in the tables below according to the highest incidence seen in any of the major clinical trials. Within each frequency grouping ADRs are listed in descending order of severity. Frequencies are defined as very common ≥ 1/10 (≥ 10%), common ≥ 1/100 to < 1/10 (≥ 1% to < 10%) and uncommon ≥ 1/1,000 to < 1/100 (≥ 0.1% to < 1%).

MabThera monotherapy/maintenance therapy

The ADRs in the table below are based on data from single-arm studies including 356 patients with low-grade or follicular lymphoma, treated with MabThera weekly as a single agent for the treatment or re-treatment of non-Hodgkin's lymphoma (see section 5.1 Pharmacodynamic properties, Clinical Trials). The table also contains ADRs based on data from 671 patients with follicular lymphoma who received MabThera as maintenance therapy for up to 2 years following response to initial induction with CHOP, R-CHOP, R-CVP or R-FCM (see section 5.1 Pharmacodynamic properties, Clinical Trials). The ADRs were reported up to 12 months after treatment with monotherapy and up to 1 month after treatment with MabThera maintenance.

Table 1 Summary of ADRs reported in patients with low-grade or follicular lymphoma receiving MabThera monotherapy (N = 356) or MabThera maintenance treatment (N = 671) in clinical trials

System Organ Class	**Very Common** (≥ 10%)	**Common** (≥1% - < 10%)	**Uncommon** (≥0.1% - < 1%)
Infections and infestations	bacterial infections, viral infections	sepsis, [+]pneumonia, [+]febrile infection, [+]herpes zoster, [+]respiratory tract infection, fungal infections, infections of unknown aetiology	
Blood and the lymphatic system disorders	neutropenia , leucopenia	anaemia, thrombocytopenia	coagulation disorders, transient aplastic anaemia, haemolytic anaemia, lymphadenopathy
Immune system disorders	angioedema	hypersensitivity	
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia	
Psychiatric disorders			depression, nervousness
Nervous system disorders		paresthesia, hypoesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	dysgeusia
Eye disorders		lacrimation disorder, conjunctivitis	
Ear and labyrinth disorders		tinnitus, ear pain	
Cardiac disorders		[+]myocardial infarction, arrhythmia, [+]atrial fibrillation, tachycardia, [+]cardiac disorder	[+]left ventricular failure, [+]supraventricular tachycardia, [+]ventricular tachycardia, [+]angina, [+]myocardial ischaemia, bradycardia
Vascular disorders		hypertension, orthostatic hypotension, hypotension	
Respiratory, thoracic and		bronchospasm , respiratory disease, chest	asthma , bronchiolitis obliterans, lung disorder, hypoxia

System Organ Class	**Very Common** (≥ 10%)	**Common** (≥1% - < 10%)	**Uncommon** (≥0.1% - < 1%)
mediastinal disorders		pain, dyspnoea , cough , rhinitis	
Gastrointestinal disorders	nausea	vomiting , diarrhoea, abdominal pain , dysphagia, stomatitis, constipation dyspepsia, anorexia, throat irritation	abdominal enlargement
Skin and subcutaneous tissue disorders	pruritus, rash	urticaria , +alopecia, sweating, night sweats	
Musculoskeletal, connective tissue and bone disorders		hypertonia, myalgia , arthralgia, back pain , neck pain, pain	
General disorders and administration site conditions	fever , chills , asthenia , headache	tumour pain, flushing, malaise, cold syndrome	infusion site pain
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 either trial is reported.

MabThera in combination with chemotherapy in NHL and CLL

The ADRs listed in the table below are based on rituximab-arm data from controlled clinical trials that occurred in addition to those seen with monotherapy/maintenance therapy and/or at a higher frequency grouping: 202 patients with diffuse large B-cell lymphoma (DLBCL) treated with R-CHOP, from 234 and 162 patients with follicular lymphoma treated with R-CHOP or R-CVP, respectively, and from 397 previously untreated CLL patients and 274 relapsed/refractory CLL patients treated with rituximab in combination with fludarabine and cyclophosphamide (R-FC) (see section 5.1 Pharmacodynamic properties, Clinical Trials).

The safety information of MabThera in combination with certain chemotherapy regimens is limited. When MabThera is used with other chemotherapy medicines, prescribers are advised to consider the adverse reaction profile of the component medicine(s).

Table 2: Summary of severe ADRs reported in patients receiving R-CHOP in DLBCL (N=202), R-CHOP in follicular lymphoma (N=234), R-CVP in follicular lymphoma (N=162) and R-FC in previously untreated (N=397) or relapsed/refractory (N=274) CLL

System Organ Class	Very Common (≥ 10%)	Common (≥ 1% - < 10%)
Infections and infestations	bronchitis	acute bronchitis, sinusitis, hepatitis B*
Blood and the lymphatic system disorders	neutropenia# febrile neutropenia, thrombocytopenia	pancytopenia, granulocytopenia
Skin and subcutaneous tissue disorders	alopecia	skin disorder
General disorders and administration site conditions	-	fatigue, shivering

*includes reactivation and primary infections; frequency based on R-FC regimen in relapsed/refractory CLL
Frequency count was based on only severe reactions defined in clinical trials as ≥ Grade 3 NCI common toxicity criteria. Only the highest frequency observed in any trial is reported.
#prolonged and/or delayed onset neutropenia after completion of an R-FC course in previously untreated or relapsed/refractory CLL

The following terms have been reported as adverse events, however, were reported at a similar (<2% difference between the groups) or lower incidence in the MabThera-arms compared to control arms: haematotoxicity, neutropenic infection, urinary tract infection, septic shock, superinfection lung, implant infection, septicaemia staphylococcal, lung infection, rhinorrhoea, pulmonary oedema, cardiac failure, sensory disturbance, venous thrombosis, mucosal inflammation nos, influenza-like illness, oedema lower limb, abnormal ejection fraction, pyrexia, general physical health deterioration, fall, multi-organ failure, venous thrombosis deep limb, positive blood culture, diabetes mellitus inadequate control.

Further information on selected, serious adverse drug reactions

Infusion/Administration-Related Reactions

Subcutaneous Formulation

The risk of acute administration-related reactions associated with MabThera SC was assessed in three clinical studies.

In SABRINA, severe administration-related reactions (Grade ≥ 3) were reported in six patients (3 %) following MabThera SC administration. These events were Grade 3 injection site rash, chest pain, dyspnoea, throat irritation, hypoxia, urine output decreased, tumour lysis syndrome and dry mouth.

In SparkThera, no severe administration related reactions were reported.

In SAWYER, severe administration-related reactions (Grade ≥ 3 were reported in four patients (5%) following MabThera SC administration. These events were Grade 4 thrombocytopenia and Grade 3 anxiety, injection-site erythema and urticaria.

Intravenous formulation

Information in this section reports data from the separate Product Information for intravenous MabThera.

Monotherapy – 4 weeks treatment

Signs and symptoms suggestive of an infusion-related reaction (IRR) were reported in more than 50% of patients in clinical trials, and were predominantly seen during the first infusion. Hypotension, fever, chills, rigors, urticaria, bronchospasm, sensation of tongue or throat swelling (angioedema), nausea, fatigue, headache, pruritus, dyspnoea, rhinitis, vomiting, flushing, and pain at disease sites have occurred in association with MabThera infusion as part of an infusion-related symptom complex. Some features of TLS have also been observed.

Maintenance Treatment (NHL) up to 2 years

Non-serious signs and symptoms suggestive of an infusion-related reaction were reported in 41% of patients for general disorders (mainly asthenia, pyrexia, influenza like illness, pain) and in 7% of patients for immune system disorders (hypersensitivity). Serious infusion-related reactions (defined as serious adverse events starting during or within one day of a rituximab infusion) occurred in < 1% of patients treated with MabThera maintenance.

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL; R-FC in CLL)

Severe IRRs occurred in up to 12% of all patients at the time of the first treatment cycle with MabThera in combination with chemotherapy. The incidence of infusion-related symptoms decreased substantially with subsequent infusions and occurred in <1% of patients by the eighth cycle. The signs and symptoms were consistent with those observed during monotherapy. Additional reactions reported were dyspepsia, rash, hypertension, tachycardia, and features of TLS. Isolated cases of myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia were also reported.

Information in the following sub-sections of section 4.0 Adverse effects (Undesirable effects) reports data from the separate Product Information for intravenous MabThera.

<u>Infections</u>

Monotherapy – 4 weeks treatment

MabThera induced B-cell depletion in 70% to 80% of patients and was associated with decreased serum immunoglobulins in only a minority of patients. Bacterial, viral, fungal and unknown etiology infections, irrespective of causal assessment, occurred in 30.3% of 356 patients. Severe infectious events (Grade 3 or 4), including sepsis occurred in 3.9% of patients.

Maintenance Treatment (NHL) up to 2 years

Higher frequencies of infections overall, including Grade 3 or 4 infections, were observed during MabThera treatment. The incidence of Grade 3 to 4 infections was 3% of patients on observation and 11% with MabThera maintenance. There was no cumulative toxicity in terms of infections reported over the 2-year maintenance period.

Data from clinical trials included cases of fatal PML in NHL patients that occurred after disease progression and retreatment (see Boxed Warning and section 4.4 Special warnings and precautions for use).

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL; R-FC in CLL)

No increase in the frequency of infections or infestations was observed in the MabThera arm of the R-CVP study. 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.

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.

In the R-CHOP study the overall incidence of Grade 2 to 4 infections was 45.5% in the R-CHOP group and 42.3% in the CHOP group. 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 was higher in the R-CHOP group (4.5%) than in the CHOP group (1.5%). 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.

In patients with CLL, the incidence of Grade 3 or 4 during treatment or within 28 days of the end of treatment was 18% with R-FC in the first-line setting and 19% in the relapsed/refractory setting and comparable with the FC group. The incidence of Grade 3 or 4 hepatitis B infection (reactivation and primary infection) was 2% with R-FC vs. 0% with FC.

Haematologic Events

Monotherapy – 4 weeks treatment

Severe (Grade 3 and 4) neutropenia was reported in 4.2% of patients, severe anaemia was reported in 1.1% of patients and severe thrombocytopenia was reported in 1.7% of patients. A single occurrence of transient aplastic anaemia (pure red cell aplasia) and two occurrences of haemolytic anaemia following MabThera therapy were reported.

Maintenance Treatment (NHL) up to 2 years

There was a higher incidence of Grade 3-4 neutropenia (observation 5%, MabThera 11%) and leucopenia (observation 2%, MabThera 5%) in the MabThera arm compared to the observation arm. The incidence of Grade 3 to 4 thrombocytopenia (observation 1%, MabThera < 1%) was low. In approximately half of the patients with available data on B-cell recovery after end of MabThera induction treatment, it took 12 months or more for their B-cell levels to return to normal values.

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL; R-FC in CLL)

During treatment in studies of MabThera in combination with chemotherapy, Grade 3 and 4 leucopenia (R-CHOP 88% vs. CHOP 79%; R-FC 23% vs. FC 12%), neutropenia (R-CVP 24% vs. CVP 14%; R-CHOP 97% vs. CHOP 88%; R-FC 30% vs. FC 19% in previously untreated CLL), 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. Studies in previously untreated and relapsed/refractory CLL have established that in some cases neutropenia was prolonged or with a late onset following treatment in the MabThera plus FC group.

No relevant difference between the treatment arms was observed with respect to Grade 3 and 4 anaemia or thrombocytopenia. In the CLL first-line study, Grade 3 or 4 anaemia was reported by 4% of patients treated with R-FC compared to 7% of patients receiving FC, and Grade 3 or 4 thrombocytopenia was reported by 7% of patients in the R-FC group compared to 10% of patients in the FC group. In the relapsed/refractory CLL study, adverse events of Grade 3 or 4 anaemia were reported in 12% of patients treated with R-FC compared to 13% of patients receiving FC and Grade 3 or 4 thrombocytopenia was reported by 11% of patients in the R-FC group compared to 9% of patients in the FC group.

Cardiovascular Event

Monotherapy – 4 weeks treatment

Cardiovascular events were reported in 18.8% of patients during the treatment period. The most frequently reported events were hypotension and hypertension. Cases of Grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris during a MabThera infusion were reported.

Maintenance Treatment (NHL) up to 2 years

The incidence of Grade 3 to 4 cardiac disorders was comparable between the two treatment groups (4% in observation, 5% in MabThera). Cardiac events were reported as serious adverse event in < 1 % of patients on observation and in 3% of patients on MabThera: atrial fibrillation (1%), myocardial infarction (1%), left ventricular failure (< 1%), myocardial ischaemia (< 1%), cardiomyopathy (<1%).

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL; R-FC in CLL)

In the R-CVP study the incidence of serious adverse events cardiac disorders was low (1% R-CVP, 2% CVP).

In the R-CHOP study 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 (6.9% of patients) as compared to the CHOP group (1.5% of patients). 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.

In CLL, the overall incidence of Grade 3 or 4 cardiac disorders was low both in the first-line study (4% R-FC vs. 3% FC) and in the relapsed/refractory study (4% R-FC vs. 4% FC).

Hypogammaglobulinaemia

Maintenance Treatment (NHL) up to 2 years

After induction treatment, median IgG levels were below the lower limit of normal (LLN) (< 7 g/L) 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 during MabThera treatment. 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). Monitoring of IgG levels should be considered for patients treated with MabThera. IV Ig substitution may be indicated for patients with decreased IgG levels.

Neurologic Events

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL; R-FC in CLL)

During the treatment period 2% of patients 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, 1.5% of patients had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period.

In CLL, the overall incidence of Grade 3 or 4 nervous system disorders was low both in the first-line study (4% R-FC vs. 4% FC) and in the relapsed/refractory study (3% R-FC vs. 3% FC).

Subpopulations

The adverse events described below are only those considered by the investigator to be related to treatment with MabThera.

Elderly patients (>65 years)

Monotherapy – 4 weeks treatment: The incidence of any ADR and of Grade 3 and 4 ADRs was similar in elderly and younger patients (88.3% versus 92.0% for any ADR and 16.0% versus 18.1% for Grade 3 and 4 ADR).

Combination Therapy: The incidence of Grade 3 or 4 blood and lymphatic adverse events was higher in elderly patients (≥ 65 years of age) compared to younger patients, with previously untreated or relapsed/refractory CLL.

Bulky disease: Patients with bulky disease had a higher incidence of Grade 3 and 4 ADRs than patients without bulky disease (25.6% versus 15.4%). The incidence of any ADR 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 ADRs upon re-treatment with further courses of MabThera was similar to the percentage of patients reporting any ADR and Grade 3 and 4 ADRs upon initial exposure (95.0% versus 89.7% for any ADR and 13.3% versus 14.8% for Grade 3 and 4 ADRs).

Post-Marketing Experience

Information in this section reports data from the separate Product Information for intravenous MabThera.

Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukaemia

The reporting frequencies in this section (rare, very rare) are based on estimated marketed exposures and largely on data derived from spontaneous reports.

Additional cases of severe infusion-related reactions have been reported during post-marketing use of intravenous MabThera.

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

Cardiovascular system: Severe including fatal cardiac events, such as heart failure and myocardial infarction have been observed, mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and mostly associated with infusion-related reactions. Vasculitis, predominantly cutaneous, such as leucocytoclastic vasculitis, has been reported very rarely.

Blood and lymphatic system: Rarely the onset of neutropenia has occurred more than four weeks after the last infusion of MabThera. Cases of infusion-related acute reversible thrombocytopenia have been reported.

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.

Respiratory system: Fatal bronchiolitis obliterans and pneumonitis (including interstitial pneumonitis) have been reported. Respiratory failure/insufficiency and lung infiltration in the context of IRRs. In addition to pulmonary events associated with infusions, interstitial lung disease, some with fatal outcome, has been reported.

Skin and appendages: Severe bullous skin reactions including some fatal cases of toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported rarely.

Nervous system: Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms include 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 recognised risk factors for PRES/RPLS, including the patients underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy. Cases of cranial neuropathy with or without peripheral neuropathy have been reported rarely. Signs and symptoms of cranial neuropathy, such as severe vision loss, hearing loss, loss of other senses and facial nerve palsy, occurred at various times up to several months after completion of MabThera therapy.

Body as a whole: Serum sickness-like reactions have been reported rarely.

Infections and infestations: Cases of hepatitis B reactivation have been reported in subjects receiving MabThera in combination with cytotoxic chemotherapy (see section 4.4 Special warnings and precautions for use). Other serious viral infections, either new, reactivation or exacerbation, some of which were fatal, have been reported with rituximab treatment. The majority of patients had received rituximab in combination with chemotherapy or as part of a haematopoietic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (cytomegalovirus (CMV), Varicella zoster virus and Herpes simplex virus), JC virus (progressive multifocal leukoencephalopathy (PML) see Boxed Warning) and Hepatitis C virus. Progression of Kaposi's sarcoma has been observed in rituximab-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV (Human Immunodeficiency Virus)-positive.

Gastro-intestinal system: Gastro-intestinal perforation, in some cases leading to death, has been observed in patients receiving rituximab in combination with chemotherapy for non-Hodgkin's lymphoma.

Renal and urinary system: Renal failure has been reported.

Use in Children

Hypogammaglobulinaemia has been observed in paediatric patients treated with MabThera (see section 4.4 Special warnings and precautions for use).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Intravenous and Subcutaneous Formulations

Limited experience with doses higher than the approved IV doses of MabThera is available from clinical trials in humans. The highest IV dose tested in humans to date is 5000 mg (2250 mg/m^2). 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 SC study, SABRINA were inadvertently administered SC formulation through the IV route up to a maximum dose of 2780 mg, with no untoward effect. Patients who experience overdose or medication error with MabThera SC should be closely monitored.

In the post-marketing setting 5 cases of intravenous 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 1800 mg and fatal respiratory failure, with a dose of 2000 mg.

Consideration should be given to the need for regular monitoring of blood cell count and for increased risk of infections while patients are B cell-depleted.

Treatment of overdose should also consist of general supportive measures.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Mechanism of Action

General: Rituximab binds specifically to the antigen CD20, a transmembrane molecule located on pre B and mature B lymphocytes. The antigen is expressed on > 95% of all B-cell non-Hodgkin's lymphomas. CD20 (human B lymphocyte-restricted differentiation antigen, Bp35) is a hydrophobic transmembrane protein with a molecular weight of approximately 35 kD. This non-glycosylated phosphoprotein is found on both normal and malignant B cells, but not on haematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissues. CD20 regulates (an) early step(s) in the activation process for cell cycle initiation and differentiation, and possibly functions as a calcium ion channel. CD20 does not internalise upon antibody binding and is not shed from the cell surface. This antigen does not circulate in the plasma. Thus, free antigen does not compete for rituximab binding.

In Vitro Mechanisms of Action: The Fab domain of rituximab binds to the CD20 antigen on B-lymphocytes and the Fc domain recruits immune effector functions to mediate B-cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and

antibody-dependent cellular cytotoxicity (ADCC). The antibody also induces apoptosis in the DHL 4 human B-cell lymphoma line. Finally, in vitro studies have demonstrated that rituximab sensitises drug-resistant human B cell lymphoma lines to the cytotoxic effects of some chemotherapeutic agents.

Binding specificity: In human tissue, the expression of the CD20 antigen is highly restricted; rituximab binding to CD20 was found only on lymphoid cells in the thymus, the white pulp of the spleen and a majority of B lymphocytes in peripheral blood and lymph nodes. Little or no non-specific binding was observed.

In Vivo: In cynomolgus monkeys, four or eight weekly doses of 269 mg/m2 of intravenous rituximab resulted in plasma concentrations of 161 to 386 µg/mL, approximately 24 hours after the first dose. Two weeks after the last dose, rituximab was still detected in the plasma of 3/6 monkeys treated for four weeks and in 4/6 monkeys treated for eight weeks.

B lymphocyte numbers were reduced by 99% or more in comparison with pre-test values in the peripheral blood of all monkeys, approximately 24 hours after the first dose. Two weeks after the last dose, B lymphocyte numbers were still reduced by more than 99% in 3/6 monkeys dosed for four weeks and in 4/6 monkeys dosed for eight weeks, and B lymphocyte numbers were also depleted in the mandibular lymph nodes and femoral bone marrow. A partial recovery of B lymphocyte numbers in the peripheral blood of some monkeys in both dose groups was correlated with the development of antibodies against rituximab.

Human Pharmacodynamics: A marked decline in median peripheral blood B-cell counts was seen beginning after the first dose of intravenous MabThera.

In patients treated for haematological malignancies, B-cell recovery began at approximately six months following the completion of treatment. Generally, B-cell levels returned to normal within twelve months following completion of treatment, although in some patients this may take longer. In one clinical trial in approximately half of the patients with available data on B-cell recovery after end of MabThera infusion induction treatment, it took 12 months or more for their B-cell levels to return to normal values (see section 4.8 Adverse effects (Undesirable effects)).

Clinical trials

Subcutaneous Formulation (1400 mg) for non-Hodgkin's Lymphoma

The clinical experience of MabThera SC in follicular NHL is based on data from a phase III clinical study (SABRINA) and a phase Ib dose-finding/dose-confirmation study (SparkThera).

SparkThera was a two-stage, randomised, open-label, multicenter adaptive phase Ib study to investigate the pharmacokinetics, safety and tolerability of MabThera SC in patients with follicular NHL as part of maintenance treatment. The primary objective was to select and confirm a MabThera SC dose that achieved non-inferior serum C_{trough} levels to that of intravenous MabThera. In stage 2, 157 patients who had previously responded to intravenous MabThera in induction and had received at least one cycle intravenous MabThera were randomised to receive MabThera SC at a fixed dose of 1400 mg (n = 78) or intravenous MabThera 375 mg/m^2 (n = 79). The maintenance dosing regimens were MabThera SC or IV administered once every three months or once every two months for a total of 8 or 12 cycles, respectively. Results from SparkThera are presented in section 5.2 Pharmacokinetic properties.

SABRINA was a two-stage phase III, international, multi-centre, randomised, controlled, open-label study conducted in patients with previously untreated follicular NHL. The study investigated the non-inferiority of the pharmacokinetic profile, together with efficacy and safety of MabThera SC in combination with CHOP or CVP versus intravenous MabThera in combination with CHOP or CVP followed by MabThera maintenance therapy.

The objective of the first stage was to establish the MabThera SC dose that resulted in comparable rituximab serum C_{trough} levels compared with intravenous MabThera, when given as part of induction treatment every 3 weeks (see section 5.2 Pharmacokinetic properties). Stage 1 enrolled 127 patients. In the second stage a greater number of patients were enrolled (n = 283) with the same study design as Stage 1, except for a less intensive PK sampling schedule. Stage 2 was intended to provide additional efficacy and safety data of MabThera SC compared with intravenous MabThera with the primary endpoint being overall response rate (ORR, comprising complete response [CR], complete response unconfirmed [CRu], and partial response [PR]) in each treatment arm at the end/completion of induction treatment. In Stages 1 and 2, previously untreated patients (n = 410) suffering from CD20 positive, follicular NHL grade 1, 2 or 3a were randomised into the following two treatment groups:

- MabThera SC (n = 205): 1st cycle intravenous MabThera plus 7 cycles of MabThera SC in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. Intravenous MabThera was used at the standard dose of 375 mg/m^2. MabThera SC was given at a dose of 1400 mg. Patients achieving at least PR were entered into the maintenance phase of the study receiving MabThera SC once every 8 weeks for 24 months.

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

MabThera Overall response rate (ORR, comprising complete response [CR], unconfirmed response [CRu], and partial response [PR]) at the end of induction treatment was calculated using investigator assessment of response in the ITT population based on pooled data from Stages 1 and 2. Additionally, ORR and complete response rate (CRR, comprising CR and CRu) at the end of maintenance treatment and time-to-event endpoints (progression-free survival [PFS] and overall survival [OS]) were analysed. Efficacy results are presented in Table 3 based on a median observation time of approximately 37 months.

Table 3: Efficacy Results for Study SABRINA/BO22334

	MabThera/Rituxan SC n=205	**MabThera/Rituxan IV** n=205
Overall Response Rate at End of Induction[a]		
Number of responders (CR/CRu, PR)	173	174
Overall response (CR/CRu, PR) rate (%, [95% CI])	84.4% [78.7;89.1]	84.9% [79.2;89.5]
Number of complete responders (CR/CRu)	66	66
Complete response (CR/CRu) rate (%, [95% CI])	32.2% [25.9;39.1]	32.2% [25.9;39.1]
Overall Response Rate at End of Maintenance		
Number of patients treated in maintenance (n)	172	178
Number of responders (CR/CRu, PR)	134	139
Overall response (CR/CRu, PR) rate (%, [95% CI])	77.9% [71.0;83.9]	78.1% [71.3;83.9]
Number of complete responders (CR/CRu)	87	100
Complete response (CR/CRu) rate (%, [95% CI])	50.6% [42.9;58.3]	56.2% [48.6;63.6]
Progression-free survival		
Number of patients with event	50 (24.4%)	57 (27.8%)
Hazard Ratio [95% CI] (unstratified Cox model)	0.84 [0.57;1.23]	
Overall survival		
Number of patients with event	16 (7.8%)	20 (9.8%)
Hazard Ratio [95% CI] (unstratified Cox model)	0.81 [0.42;1.57]	

[a] Stage 2 primary efficacy endpoint was ORR at the end of induction, however pooled results which were preplanned are presented in this Table.
Response rates based on investigator assessment.
Response rates at end of maintenance based on patients who received at least one cycle of maintenance treatment (n).

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

Subcutaneous Formulation (1600 mg) for Chronic Lymphocytic Leukaemia

The clinical experience of MabThera SC in CLL is based on data from the SAWYER study. This was a two-part phase Ib, multicentre, randomised, open-label, parallel-group study conducted in patients with previously untreated CLL, to investigate the non-inferiority of the pharmacokinetic profile, together with efficacy and safety of MabThera SC in combination with chemotherapy.

The objective of the Part 1 was to select a MabThera SC dose that resulted in comparable MabThera serum C_{trough} levels compared with intravenous MabThera. Previously untreated CLL patients (n = 64) were enrolled at any point during their treatment with intravenous

MabThera in combination with chemotherapy, the dose of 1600 mg of MabThera SC was selected for Part 2 of the study (see section 5.2 Pharmacokinetic properties).

The objective of the Part 2 was to establish the non-inferiority in observed C_{trough} levels between the confirmed MabThera SC dose and the reference intravenous MabThera dose. Previously untreated CLL patients (n = 176) were randomised into the following two treatment groups:

- MabThera SC (n = 88); 1st cycle of intravenous MabThera 375 mg/m^2 in combination with chemotherapy plus subsequent cycles (2 - 6) of MabThera SC 1600 mg in combination with chemotherapy.

- MabThera IV (n = 88): 1st cycle of intravenous MabThera 375 mg/m^2 in combination with chemotherapy followed by up to 5 cycles of intravenous MabThera 500 mg/m^2 in combination with chemotherapy.

SAWYER was an open –label study, with the primary endpoint of non-inferiority in observed C_{trough} levels. Secondary endpoints included overall response rate (ORR) and complete response rate (CRR). Response rates were similar for intravenous MabThera and SC, with an ORR of 80.7% (95% CI: 70.9; 88.3) and 85.2% (95% CI: 76.1; 91.9) in the IV and SC arms, respectively. CRR point estimates were 33.0% (95% CI: 23.3; 43.8) and 26.1% (95% CI: 17.3; 36.6) in the IV and SC arms, respectively.

Overall the results confirm that MabThera SC 1600 mg has a comparable benefit/risk profile to that of intravenous MabThera 500 mg/m^2. The data from the SAWYER study provides a pharmacokinetic and clinical bridge to previous data with intravenous MabThera and is consistent with data from the SABRINA study with MabThera SC in NHL which excludes major differences in efficacy and safety associated with the SC route of administration.

Intravenous MabThera

Information in this section reports data from the separate Product Information for intravenous MabThera.

Relapsed/Refractory Low Grade or Follicular non-Hodgkin's Lymphoma
Monotherapy

In the pivotal study, an open label, single arm trial of 166 patients with relapsed or refractory low-grade or follicular B-cell NHL, subjects received 375 mg/m^2 of MabThera as an IV infusion once a week for four weeks (4 doses). The overall response rate (ORR) in the intent-to-treat (ITT) population was 48% ($CI_{95\%}$ 41% – 56%), comprising a 6% complete response (CR) and 42% partial response (PR). The projected median time to progression (TTP) for responding patients was 13.0 months.

In a subgroup analysis, the ORR was significantly higher in patients with IWF B, C, and D histological subtypes as compared to IWF A subtype (58% vs. 12%) and in patients with prior autologous bone marrow transplantation (ABMT) compared to those with no prior ABMT (78% vs. 43%). Age, sex, lymphoma grade, years since initial diagnosis, presence or absence of bulky disease, normal or high LDH, or presence of extranodal disease did not have a significant effect (Fisher's exact test) on response to MabThera.

ORR was also significantly higher in patients with no bone marrow involvement compared to those with bone marrow involvement (59% vs. 40%). This finding was not supported by a

stepwise logistic regression analysis in which the following factors were identified as prognostic factors: histologic type, bcl-2 positivity at baseline, resistance to last chemotherapy and bulky disease.

Re-treatment

In a multicentre, single-arm study, 58 patients with relapsed or refractory 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 enrolment 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% (CR 10% and PR 28%) 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.

Bulky Disease

In pooled data from three studies, 39 patients with relapsed or refractory, bulky disease (single lesion ≥ 10cm in diameter), low-grade or follicular B-cell NHL received 375 mg/m^2 of MabThera given as an IV infusion once weekly for four doses). The overall response rate (ORR) was 36% (CR 3%, PR 33%) with a median TTP for responding patients of 9.6 months (range 4.5 to 26.8 months).

Clinical Laboratory Findings

*Molecular Genetic Markers**:*** Results from the exploratory analysis of the bcl-2 gene rearrangement showed that samples of peripheral blood obtained at baseline were positive for the bcl-2 rearrangement (bcl-2 positive) by nested Polymerase Chain Reaction (PCR) in 70 (42%) of the 166 enrolled patients. Of these 70 patients, 55 patients had a follow-up blood sample at 3 months and more than 60% showed a conversion to negative bcl-2 gene rearrangement.

With regard to bone marrow assessment, of 71 (45%) of the 166 enrolled patients who were bcl-2 positive in marrow at baseline, 22 were assessed for bcl-2 rearrangement at 3 months. Of these, 12 (55%) were bcl-2 negative at three months.

Of 67 patients evaluated for human anti-mouse antibody (HAMA), none were positive. Of 356 patients evaluated for HACA, 1.1% (4 patients) were positive.

Previously Untreated Follicular non-Hodgkin's Lymphoma

Combination with chemotherapy

In an open-label randomised study (M39021), a total of 322 previously untreated Stage III or IV 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.

The median follow-up of patients was 53 months. Addition of MabThera to CVP significantly increased time to treatment failure (the primary endpoint), tumour response, progression-free survival (PFS) and overall survival (OS) (Table 4).

Table 4 Summary of key results from study M39021

	CVP (N=159)	**R-CVP (N=162)**	**Hazard Ratio [95% CI] log-rank p**
Median Time to Treatment Failure (months)	6.6	27.0	0.34 [0.26, 0.44] p<0.0001
Median Progression-free Survival (months)	14.7	33.6	0.44 [0.33, 0.57] p<0.001
Overall Tumour Response[1] (%)	57	81	-
Overall Survival (%)	71	81	0.60 [0.38, 0.95] p=0.029[2]

[1] Tumour response = CR (complete response), CRu (complete response unconfirmed) and PR (partial response)
[2] Stratified by centre

Results from three other randomised studies using MabThera in combination with chemotherapy regimens other than CVP (CHOP, MCP, CHVP/interferon-alfa 2a) have also demonstrated significant improvements in response rates, time dependent parameters as well as in overall survival (Table 5).

Table 5: Summary of key results from three phase III randomised studies evaluating the benefit of MabThera with different chemotherapy regimens in follicular lymphoma

Study	**Treatment, n**	**Median follow up, months**	**ORR, %**	**CR, %**	**Outcome[1] (months)**	**OS rates, %**
GLSG'00	CHOP, 205 R-CHOP, 223	18	90 96	17 20	Median TTF: 31.2 Not reached p<0.001	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	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	84 91 p=0.029

Abbreviations: ORR – overall response rate; CR – complete response; OS rates – overall survival rates at the time of the analyses; R – MabThera; CHOP - cyclophosphamide, doxorubicin, vincristine, prednisone; MCP – mitoxantrone, chlorambucil, prednisolone; CHVP - cyclophosphamide, doxorubicin, etoposide, prednisolone ; IFN – interferon-alfa 2a.
[1]GLSG'00 outcome: TTF (time to treatment failure); OSHO-39: PFS (progression free survival); FL2000 outcome: EFS (event free survival)

Maintenance Therapy
Relapsed/Refractory follicular NHL

In a prospective, open label, international, multicentre, Phase III trial, 465 patients with relapsed/refractory follicular NHL 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), one dose of rituximab combined with each cycle of chemotherapy. 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 intravenous MabThera at 375 mg/m^2 body surface area given every 3 months until disease progression or for a maximum period of two years. Patients with hypogammaglobulinaemia (IgG <3g/L) or known HIV infection were excluded from the trial.

The final efficacy analysis included all patients randomised to both parts of the study. 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 NHL when compared to CHOP (see Table 6).

Table 6: 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
Secondary Efficacy				
OS (median)	NR	NR	0.0508	32%
PFS(median)	19.4 mo.	33.2 mo.	0.0001	38%

[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; NR, not reached; mo, months; ORR: overall response rate; CR: complete response; PR: partial response; OS : overall survival ; PFS : progression free survival

For patients randomised 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%).

The median time to new anti-lymphoma treatment was significantly longer with MabThera maintenance treatment than with observation (38.8 months vs. 20.1 months, $p< 0.0001$ log-rank test). The risk of starting a new treatment was reduced by 50% (95% CI; 30%-64%). In patients achieving a CR/CRu (complete response unconfirmed) as best response during induction treatment, MabThera maintenance treatment significantly prolonged the median disease free survival (DFS) compared to the observation group (53.7 vs. 16.5 months,

p=0.0003) log-rank test (Table 7). The risk of relapse in complete responders was reduced by 67% (95% CI; 39%-82%).

Table 7: 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**	**(95% CI)**
Progression-free survival (PFS)	14.3	42.2	<0.0001	61% (45-72%)
Overall Survival	NR	NR	0.0039	56% (22-75%)
Time to new lymphoma treatment	20.1	38.8	<0.0001	50% (30-64%)
Disease-free survival[a]	16.5	53.7	0.0003	67% (39-82%)
Subgroup Analysis				
PFS				
CHOP	11.6	37.5	<0.0001	71% (54-82%)
R-CHOP	22.1	51.9	0.0071	46% (15-65%)
CR	14.3	52.8	0.0008	64% (33-81%)
PR	14.3	37.8	<0.0001	54% (33-69%)
OS				
CHOP	NR	NR	0.0348	55% (4-79%)
R-CHOP	NR	NR	0.0482	56% (-2-81%)

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 7?). 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 analysed subgroups were small, and the median survival had not been reached after an overall median observation period of 47.2 months, a clinically meaningful benefit in terms of overall survival was observed for patients receiving MabThera maintenance treatment when compared to observation, in the overall population.

MabThera maintenance treatment provided consistent benefit in all subgroups tested [gender (male, female), age (≤ 60 years, > 60 years), stage (III, IV), WHO performance status (0 versus > 0), B symptoms (absent, present), bone marrow involvement (no versus yes), IPI (0-2 versus 3-5), FLIPI score (0-1, versus 2 versus 3-5), number of extra-nodal sites (0-1 versus > 1), number of nodal sites (< 5 versus ≥ 5), number of previous regimens (1 versus 2), best

response to prior therapy (CR/PR versus NC/PD), haemoglobin (< 12 g/dL versus ≥ 12 g/dL), β_2-microglobulin (< 3mg/L versus ≥ 3 mg/L), LDH (elevated, not elevated) except for the small subgroup of patients with bulky disease.

Previously untreated follicular NHL

In a prospective, open label, international, multi-centre, 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 randomised 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/m^2 body surface area given every 2 months until disease progression or for a maximum period of two years.

After a median observation time of 25 months from randomisation, 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 no maintenance therapy in patients with previously untreated follicular NHL (Table 8). This improvement in PFS was confirmed by an independent review committee (IRC) (Table 8).

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) (Table 8). Based on the limited number of deaths (58/513 patients (11%) in the observation arm and 59/505 patients (12%) in the rituximab maintenance arm), the current analysis did not show an advantage of maintenance treatment with MabThera in terms of overall survival (OS) HR 1.02 (95% CI: 0.71-1.47; p = 0.8959).

The updated analysis corresponding to a median observation time of 73 months from randomisation confirm the results of the primary analysis (Table 8).

Table 8: Overview of efficacy results for maintenance MabThera vs. observation (25 and 73 months median observation time)

Efficacy Parameter	**Primary Analysis[a]**		**Updated Analysis[b]**	
	Observation N = 513	**MabThera Maintenance N = 505**	**Observation N = 513**	**MabThera Maintenance N = 505**
Primary Endpoint				
Progression-free Survival[c]				
Median time to event (months)	NR	NR	49	NR
p value (stratified log-rank test)	p < 0.0001		p < 0.0001	
HR [95% CI] (stratified)	0.50 [0.39;0.64]		0.58 [0.48;0.69]	
Secondary Endpoints				
Overall Survival				

Efficacy Parameter	**Primary Analysis[a]**		**Updated Analysis[b]**	
	Observation N = 513	**MabThera Maintenance N = 505**	**Observation N = 513**	**MabThera Maintenance N = 505**
Median time to event (months)	NR	NR	NR	NR
p value (stratified log-rank test)	p = 0.7246		p = 0.8959	
HR [95% CI] (stratified)	0.89 [0.45;1.74]		1.02 [0.71;1.47]	
Overall Response Rate at End of Maintenance/Observation				
Patients assessed at end of treatment	398	389	509	500
Responders (CR/Cru, PR)	219/398 (55%)	288/389 (74%)	309/509 (61%)	395/500 (79%)
p value (χ^2 test)	p < 0.0001		p < 0.0001	
Non-responders	179/398 (45%)	101/389 (26%)	200/509 (40%)	105/500 (21%)
Patients with complete response (CR/CRu)	190 (48%)	260 (67%)	268 (53%)	361 (72%)
partial response (PR)	29 (7%)	28 (7%)	41 (8%)	34 (7%)
stable disease (SD)	1 (<1%)	0 (0%)	1 (<1%)	1 (<1%)
progressive disease (PD)	162 (41%)	79 (20%)	181 (36%)	86 (17%)
Event-free Survival				
Median time to event (months)	38	NR	48	NR
p value (stratified log-rank test)	p < 0.0001		p < 0.0001	
HR [95% CI] (stratified)	0.54 [0.43;0.69]		0.61 [0.51;0.72]	
Time to Next Anti-Lymphoma Treatment				
Median time to event (months)	NR	NR	71	NR
p value (stratified log-rank test)	p = 0.0003		p < 0.0001	
HR [95% CI] (stratified)	0.61 [0.46;0.80]		0.63 [0.52;0.76]	
Time to Next Chemotherapy Treatment				
Median time to event (months)	NR	NR	85	NR
p value (stratified log-rank test)	p = 0.0011		p = 0.0006	
HR [95% CI] (stratified)	0.60 [0.44;0.82]		0.70 [0.57;0.86]	
Transformation Rate at First Progression				
Patients with progression	173	91	278	186

Efficacy Parameter	Primary Analysis[a]		Updated Analysis[b]	
	Observation N = 513	**MabThera Maintenance N = 505**	**Observation N = 513**	**MabThera Maintenance N = 505**
Patients with transformation	19/513 (4%)	11/505 (2%)	24/114 (21%)	16/80 (20%)

HR: hazard ratio; NR: not reached. 1 month = 30.4375 days (ie, 365.25 days/12 months).
p values and hazard ratios for time-to-event endpoints were calculated using the stratified log-rank test and stratified Cox regression, respectively. Stratification factors were induction treatment received and response to induction treatment. p values for response rates were calculated using the χ^2 test, and odds ratios were calculated using logistic regression (response rate analyses were unadjusted).
[a] Clinical cut-off: January 14, 2009. Median observation time: 25.5 months.
[b] Clinical cut-off: January 31, 2013. Median observation time: 73 months.
[c] Based on investigator assessments

MabThera maintenance treatment provided consistent benefit in all 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 or PR).

There are currently no data to support superior efficacy for maintenance treatment given every 2 months over maintenance therapy given every 3 months, in either the relapsed/refractory or previously untreated setting.

Diffuse Large B-cell non-Hodgkin's Lymphoma

In a randomised, Phase III, open-label trial, a total of 399 previously untreated elderly ambulatory patients (age 60 to 80 years, ECOG performance status 0-2) with moderate to advanced (Ann Arbor stage II-IV) 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 intravenous MabThera 375 mg/m^2 administered as an intravenous infusion 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 characteristics and disease status. The final analysis confirmed that R-CHOP significantly increased 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 patient subgroups (gender, age, age-adjusted IPI, Ann Arbor stage, ECOG, Beta 2 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, although the benefit with R-CHOP was not always statistically significant.

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%.

Chronic Lymphocytic Leukaemia

In two open-label randomised studies, a total of 817 previously untreated patients and 552 patients with relapsed/refractory CLL were randomised to receive either fludarabine and cyclophosphamide (FC) chemotherapy (fludarabine 25 mg/m^2, cyclophosphamide 250 mg/m^2, days 1-3) every 4 weeks for 6 cycles or intravenous MabThera in combination with FC (R-FC). MabThera was administered at a dosage of 375 mg/m^2 during the first cycle one day prior to chemotherapy and at a dosage of 500 mg/m^2 on day 1 of cycles 2-6. A total of 810 patients (403 R-FC, 407 FC) from the first-line study (Table 9 and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study (Table 11) were analysed for efficacy.

In the first-line study, after a median observation time of 20.7 months, the primary endpoint of progression-free survival (PFS) was a median of 40 months in the R-FC group and a median of 32 months in the FC group (p<0.0001, log-rank test). The analysis of overall survival demonstrated improved survival in favour of the R-FC arm (p=0.0427). These results were confirmed with longer follow-up: after a median observation time of 48.1 months, the median PFS was 55 months in the R-FC group and 33 months in the FC group (p < 0.0001, log-rank test) and overall survival analyses continued to show a significant benefit of R-FC treatment over FC chemotherapy alone (p = 0.0319, log-rank test). The benefit in terms of PFS was consistently observed in most patient subgroups analysed according to disease risk at baseline (i.e. Binet stages A-C) and was confirmed with longer follow-up (Table 10).

Table 9: First-line treatment of Chronic Lymphocytic Leukaemia - overview of efficacy results for intravenous MabThera plus FC vs. FC alone (20.7 and 48.1 months median observation time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Median Follow-Up (Months)	Hazard Ratio R-FC vs. FC [95% CI]
	FC (N=407)	R-FC (N=403)	Log-Rank p value		
Progression-free survival	32.2	39.8	<0.0001	20.7	0.56 [0.43, 0.72]
	32.8	55.3	<0.0001	48.1***	0.55 [0.45, 0.66]
Overall Survival	NR	NR	0.0427	20.7	0.64 [0.41, 1.00]
	NR	NR	0.0319	48.1***	0.73 [0.54, 0.97]
Event Free Survival	31.1	39.8	<0.0001	20.7	0.55 [0.43, 0.70]

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Median Follow-Up (Months)	Hazard Ratio R-FC vs. FC [95% CI]
	FC (N=407)	R-FC (N=403)	Log-Rank p value		
	31.3	51.8	<0.0001	48.1***	0.56 [0.46, 0.67]
Response rate (CR, nPR, or PR)	72.7% 72.6%	86.1% 85.8%	<0.0001 <0.0001	20.7 48.1***	NA NA
CR rates	17.2% 16.9%	36.0% 36.0%	<0.0001 <0.0001	20.7 48.1***	NA NA
Duration of response*	34.7 36.2	40.2 57.3	0.0040 <0.0001	20.7 48.1***	0.61 [0.43, 0.85] 0.56 [0.45, 0.70]
Disease free survival**	NR 48.9	NR 60.3	0.7882 0.0520	20.7 48.1***	0.93 [0.44, 1.96] 0.69 [0.47, 1.01]
Time to new CLL treatment	NR 47.2	NR 69.7	0.0052 <0.0001	20.7 48.1***	0.65 [0.47, 0.90] 0.58 [0.47, 0.72]

Response rate and CR rates analysed using Chi-squared Test.
* only applicable to patients with CR, nPR or PR as end-of-treatment response
** only applicable to patients with CR as end-of-treatment response
*** ITT population: 409 FC, 408 R-FC
Abbreviations: CR: complete response; nPR: nodular partial response; PR: partial response; NA: not available; NR: not reached
Standard definitions and assessments for response were used in accordance with the National Cancer Institute-sponsored Working Group guidelines for CLL.

Table 10: Hazard ratios of PFS according to Binet stage (ITT) (20.7 and 48.1 months median observation time)

Progression-free survival	Number of patients		Median Follow-Up (Months)	Hazard Ratio R-FC vs. FC (95% CI)	Log-Rank p value
	FC	R-FC			
Binet Stage A	22 22	18 18	20.7 48.1*	0.13 [0.03, 0.61] 0.39 [0.15, 0.98)	0.0025 0.0370
Binet Stage B	257 259	259 263	20.7 48.1*	0.45 [0.32, 0.63) 0.52 [0.41, 0.66)	<0.0001 <0.0001
Binet Stage C	126 126	125 126	20.7 48.1*	0.88 [0.58, 1.33] 0.68 [0.49; 0.95]	0.5341 0.0215

* ITT population: 409 FC, 408 R-FC

In a case series of 30 previously untreated patients with CLL, an overall response rate of 97% was achieved with intravenous MabThera in combination with fludarabine, cyclophosphamide and mitoxantrone (FCM). Survival was not reported. In another case series of 64 previously untreated patients with CLL, an overall response rate of 91% and a median PFS of 32.6 months were achieved with intravenous MabThera in combination with pentostatin and cyclophosphamide (PC).

In the relapsed/refractory study, the median PFS (primary endpoint) was 30.6 months in the R-FC group and 20.6 months in the FC group (p=0.0002, log-rank test). The benefit in terms of PFS was observed in almost all patient subgroups analysed according to disease risk at baseline. A non-significant trend towards improvement in overall survival was reported in the R-FC arm compared to the FC arm.

Table 11: Treatment of relapsed/refractory Chronic Lymphocytic Leukaemia – overview of efficacy results for MabThera plus FC vs. FC alone (25.3 months median observation time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Hazard Ratio R-FC vs. FC [95% CI]
	FC (N=276)	R-FC (N=276)	Log-Rank p value	
Progression-free survival	20.6	30.6	0.0002	0.65 [0.51, 0.82]
Overall Survival	51.9	NR	0.2874	0.83 [0.59, 1.17]
Response rate (CR, nPR, or PR)	58.0%	69.9%	0.0034	NA
CR rates	13.0%	24.3%	0.0007	NA

Response rate and CR rates analysed using Chi-squared Test.
Abbreviations: CR: complete response; nPR: nodular partial response; PR: partial response; NA: not available; NR: not reached
Standard definitions and assessments for response were used in accordance with the National Cancer Institute-sponsored Working Group guidelines for CLL.

In relapsed/refractory CLL patients, response rates of 70% or greater have been reported in small studies of the following chemotherapy regimens with intravenous MabThera: FCM (fludarabine, cyclophosphamide, mitoxantrone), PC (pentostatin, cyclophosphamide), PCM (pentostatin, cyclophosphamide, mitoxantrone), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), bendamustine and cladribine.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Subcutaneous Formulation (1400 mg) for non -Hodgkin's Lymphoma

Study BP22333 (SparkThera) was a two-stage phase Ib study to investigate the pharmacokinetics, safety and tolerability of MabThera SC in patients with follicular NHL as part of maintenance treatment. In stage 2, MabThera SC was administered at a fixed dose of 1400 mg as subcutaneous injection during maintenance treatment. The subcutaneous injection was given after at least one cycle of intravenous MabThera formulation 375 mg/m^2 to patients who had previously responded to intravenous MabThera in induction. The predicted median C_{max} of rituximab following MabThera SC and intravenous MabThera

administered every two months (q2m) were comparable at 201 and 209 µg/mL, respectively. Similarly, for MabThera SC and intravenous MabThera administered every three months (q3m), the predicted median C_{max} were comparable at 189 and 184 µg/mL, respectively. The median T_{max} of rituximab administered subcutaneously was approximately 3 days compared to the T_{max} occurring at or close to the end of the infusion for IV administration.

In study BO22334 (SABRINA), previously untreated patients with follicular NHL were randomised 1:1 to receive MabThera SC as a 1400 mg subcutaneous injection (first cycle intravenous MabThera 375 mg/m^2 followed by 7 cycles of MabThera SC) or intravenous MabThera 375 mg/m^2 (8 cycles) in combination with up to 8 cycles of CHOP or CVP chemotherapy every three weeks as part of induction treatment (see section 5.1 Pharmacodynamic properties, Clinical Trials). Rituximab serum 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 IV and SC, respectively, with the resulting geometric mean ratio (C_{max} SC/C_{max} IV) of 0.941 (90% CI: 0.872, 1.015).

Subcutaneous Formulation (1600 mg) for Chronic Lymphocytic Leukaemia
Study BO25341 (SAWYER) was a phase Ib study to investigate the pharmacokinetics, safety and efficacy of MabThera SC in patients with CLL. MabThera SC at a fixed dose of 1600 mg was administered as a SC injection, in the abdomen, at 4-weekly intervals. Previously untreated patients with CD20+ CLL were randomized 1:1 to receive MabThera SC (first cycle intravenous MabThera followed by 5 cycles of MabThera SC) or intravenous MabThera (6 cycles) in combination with up to 6 cycles of chemotherapy [fludarabine and cyclophosphamide (FC)]. The serum Cmax at Cycle 6 was lower in the MabThera SC arm than the IV, with geometric mean (CV%) values of 202 (36.1) µg/mL and 280 (24.6) µg/mL with the resulting geometric mean ratio ($C_{max, SC}/C_{max, IV}$) of 0.719 (90% CI: 0.653, 0.792). The geometric mean t_{max} in the MabThera SC arm was approximately 3 days as compared to the t_{max} occurring at or close to the end of the infusion for the intravenous MabThera.

Distribution

Subcutaneous Formulation (1400 mg) for non -Hodgkin's Lymphoma
In the SparkThera study, the predicted mean and geometric mean rituximab C_{trough} values at cycle 2 were higher in the MabThera SC arm compared to the intravenous MabThera arm. The geometric mean values in the SC q2m and IV q2m arms were 32.2 and 25.9 µg/mL, respectively, and 12.1 and 10.9 µg/mL in the SC q3m and IV q3m arms, respectively. The $C_{trough(SC)}/C_{trough(IV)}$ geometric mean ratio (GMR) values were 1.24 and 1.12, respectively, for the q2m and q3m regimens. The lower boundaries of the two-sided 90% CI for the GMR of C_{trough} at cycle 2 were 1.02 for the q2m regimen and 0.86 for the q3m regimen. Both of these lower-limit values were greater than the pre-specified non-inferiority margin of 0.8. The results for the primary endpoint, C_{trough} at cycle 2, demonstrated that MabThera SC 1400 mg was non-inferior compared to intravenous MabThera 375 mg/m^2. The predicted mean and geometric mean rituximab AUC_{tau} values at cycle 2 were higher in the MabThera SC arm compared to the intravenous MabThera arm. The geometric mean values in the SC q2m and IV q2m arms were 5430 and 4012 µg•day/mL, respectively, and 5320 and 3947 µg•day/mL in the SC q3m and IV q3m arms, respectively.

In the SABRINA study, the mean and geometric mean rituximab C_{trough} values at pre-dose cycle 8 were higher in the MabThera SC arm compared to the intravenous MabThera arm. The geometric mean was 134.6 µg/mL for the SC arm compared to 83.1 µg/mL for the IV arm. The $C_{trough(SC)}/C_{trough(IV)}$ GMR value was 1.62 and the lower limit of the two-sided 90% CI was 1.36. The lower limit of the two-sided 90% CI was greater than the pre-specified non-

inferiority margin of 0.8. The results for the primary endpoint, C_{trough} pre-dose at cycle 8, demonstrated that MabThera SC 1400 mg was non-inferior compared to intravenous MabThera 375 mg/m^2. The mean and geometric mean AUC values at cycle 7 were higher in the SC arm compared to the IV arm. The geometric mean AUC was 3779 µg•day/mL for the SC group compared with 2734 µg•day/mL for the IV group.

In a population pharmacokinetic analysis in patients who received single or multiple infusions of MabThera as a single agent or in combination with chemotherapy, the population estimates of non-specific clearance (CL1), initial specific clearance (CL2) (likely contributed by B cells or tumour burden) and central compartment volume of distribution (V1) were 0.194 L/day, 0.535 L/day, and 4.37 L, respectively. The estimated median terminal elimination half-life of rituximab administered subcutaneously was 29.7 days (range, 9.9 to 91.2 days). Based on a population pharmacokinetic analysis an absolute bioavailability of 71% (95% CI: 70.0 – 72.1) was estimated.

In the final analysis dataset from 403 patients administered MabThera SC and/or intravenous MabThera in studies SparkThera (277 patients) and SABRINA (126 patients) the mean (range) weight and body surface area (BSA) were 74.4 kg (43.9 to 130 kg) and 1.83 m^2 (1.34 to 2.48 m^2), respectively. Mean (range) age was 57.4 years (23 to 87 years). There were no differences between demographic and laboratory parameters of the two studies. However, the baseline B-cell counts were markedly lower in SparkThera, than in SABRINA, as patients in SparkThera entered the study having received a minimum of four cycles of intravenous MabThera in induction and at least one cycle of intravenous MabThera maintenance, whereas patients in SABRINA had not received MabThera prior to study enrolment. Data on baseline tumour load was available only for patients in SABRINA.

BSA was identified as the main covariate. All clearance and volume parameters increased with the body size. Among other covariate dependencies, central volume increased with age and the absorption rate constant decreased with age (for patients aged > 60 years), but these age dependencies were shown to result in negligible changes in MabThera exposure. Anti-drug antibodies were detected in only 13 patients and did not result in any clinically relevant increase in clearance.

The model-based simulations indicated that body size had an effect on SC to IV exposure ratios. C_{trough} and AUC ratios for representative patients with low (1.4m^2), medium (1.9m^2) and high (2.4 m^2) BSA were simulated in Cycles 7, 10 and 18 of treatment, with the results shown in Table 12.

Table 12: Model–based simulations of C_{trough} and AUC_{tau} for Cycles 7, 10 and 18, by treatment and BSA

	BSA	**C_{trough} (µg/mL)**	**AUC_{tau} (µg•day/mL)**
		GMR (SC/IV)	GMR (SC/IV)
Cycle 7 (induction, q3w)	Low (1.4m^2)	2.25	1.96
	Medium (1.9m^2)	1.65	1.45
	High (2.4 m^2)	1.21	1.09
Cycle 10 (maintenance, q2m)	Low (1.4m^2)	2.09	1.92
	Medium (1.9m^2)	1.54	1.44
	High (2.4 m^2)	1.24	1.12
	Low (1.4m^2)	2.05	1.87

Cycle 18 (maintenance, q2m)	Medium (1.9m^2)	1.49	1.4
	High (2.4 m^2)	1.21	1.12

Subcutaneous Formulation (1600 mg) for Chronic Lymphocytic Leukaemia

In the SAWYER study, the geometric mean C_{trough} values at Cycle 5 (pre-dose Cycle 6) were higher among the MabThera SC group than the IV group (97.5 µg/mL versus 61.5 µg/mL respectively). Similarly, the geometric mean AUC values at Cycle 6 were higher among the MabThera SC group than the IV group (4088 µg•day/mL versus 3630 µg•day/mL respectively).

Intravenous formulation

Information in this section reports data from the separate Product Information for intravenous MabThera.

Non-Hodgkin's Lymphoma

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of rituximab as a single agent or in combination with CHOP therapy, the typical population estimates of nonspecific clearance (CL_1), specific clearance (CL_2) likely contributed by B cells or tumour burden, and central compartment volume of distribution (V_1) were 0.14 L/day, 0.59 L/day, and 2.7 L, respectively. The estimated median terminal elimination half-life of rituximab was 22 days (range, 6.1 to 52 days). Baseline CD19-positive cell counts and size of measurable tumour lesions contributed to some of the variability in CL_2 of rituximab in data from 161 patients given 375 mg/m^2 as an intravenous (IV) infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumour lesions had a higher CL_2. However, a large component of inter-individual variability remained for CL_2 after correction for CD19-positive cell counts and tumour lesion size. V_1 varied by body surface area (BSA) and CHOP therapy. The variability in V_1 caused by the range in BSA (1.53 to 2.32 m^2) and concurrent CHOP therapy was relatively small (27.1% and 19% respectively). Age, gender, race, and WHO (World Health Organisation) performance status had no effect on the pharmacokinetics of rituximab. This analysis suggests that dose adjustment of rituximab with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.

Rituximab at a dose of 375 mg/m^2 was administered as an IV infusion at weekly intervals for 4 doses to 203 patients with NHL naive to rituximab. The mean C_{max} following the fourth infusion was 486 µg/mL (range 77.5 - 996.6 µg/mL). The peak and trough serum levels of rituximab were inversely correlated with baseline values for the number of circulating CD19-positive B-cells and measures of disease burden. Median steady-state serum levels were higher for responders compared with non-responders. Serum levels were higher in patients with International Working Formulation (IWF) subtypes B, C, and D as compared with those with subtype A.

Rituximab was detectable in the serum of patients 3 – 6 months after completion of last treatment.

Rituximab at a dose of 375 mg/m^2 was administered as an IV infusion at weekly intervals for 8 doses to 37 patients with NHL. The mean C_{max} increased with each successive infusion, spanning from a mean of 243 µg/mL (range, 16 – 582 µg/mL) after the first infusion to 550 µg/mL (range 171 – 1177 µg/mL) after the eighth infusion.

The pharmacokinetic profile of rituximab when administered as 6 infusions of 375 mg/m^2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone.

Chronic Lymphocytic Leukaemia
Rituximab was administered as an IV infusion at a first-cycle dose of 375 mg/m^2 increased to 500 mg/m^2 each cycle for a further 5 doses in combination with FC in CLL patients. The mean C_{max} (N=15) was 408 μg/mL (range, 97 – 764 μg/mL) after the fifth 500 mg/m^2 infusion.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
The genotoxic potential of rituximab has not been investigated.

Carcinogenicity
The carcinogenic potential of rituximab has not been investigated.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

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

6.2 INCOMPATIBILITIES

No incompatibilities between the SC solution and polypropylene or polycarbonate syringe material or stainless steel transfer and injection needles have been observed.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2 to 8°C. Do not freeze.) Keep the container in the outer carton in order to protect from light.

Do not use beyond the expiry date stamped on the carton/vial.

Preparation of MabThera SC formulation
MabThera SC 1400 mg and 1600 mg vials are for single use in one patient only. Discard any residue.

Once transferred from the vial into a syringe, the solution of MabThera SC formulation is physically and chemically stable for 48 hours at 2 to 8 °C and subsequently for 8 hours at 30 °C in diffuse daylight. However, as MabThera SC formulation does not contain any antimicrobial agent or preservative, use the product as soon as practicable after preparation to reduce microbiological hazard. 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. If storage is necessary, hold at 2 to 8 °C for not more than 24 hours.

6.5 NATURE AND CONTENTS OF CONTAINER

MabThera SC 1400mg
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, pack of 1

MabThera SC 1600mg
Colourless type I glass vial with butyl rubber stopper with aluminium over seal and a blue plastic flip-off disk, containing 1600 mg/13.4 mL of rituximab, pack of 1. *
* *Not available*

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

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 disposable container).

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

MabThera (rituximab) is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The antibody is a glycosylated IgG_1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences (Fab domain) and human constant region sequences (Fc domain). Rituximab is composed of 1,328 amino acids and has an approximate molecular weight of 144 kD. Rituximab has a high binding affinity for the CD20 antigen of 5.2 to 11.0 nM.

The chimeric anti-CD20 antibody is produced by mammalian (Chinese hamster ovary) cell suspension culture in a nutrient medium containing 100 mg/mL of the antibiotic gentamicin. The antibiotic is not detectable in the final product. The anti-CD20 antibody is purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.

CAS number

174722-31-7

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine – Schedule 4

8. SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30-34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

6 October 1998

10. DATE OF REVISION

03 April 2020

Summary table of changes

Section Changed	Summary of new information
4.6	The statement on the potential risk of embryofetal toxicity resulting from exposure to rHuPH20 is removed based on updated clinical rationale.