NEW ZEALAND DATA SHEET
MabThera® SC (rituximab)

1. PRODUCT NAME
Mabthera 1400mg solution for subcutaneous injection (Mabthera SC 1400mg)

Mabthera 1600mg solution for subcutaneous injection (Mabthera SC 1600mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Rituximab 120mg/mL

Each vial of Mabthera SC 1400mg solution for subcutaneous injection contains 1400 mg/11.7mL rituximab.

Each vial of Mabthera SC 1600mg solution for subcutaneous injection contains 1600 mg/13.4mL of rituximab.

Excipients with known effect

Mabthera SC contains the excipient vorhyaluronidase alfa, an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously (see sections 4.4 and 4.6).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Mabthera solution for SC injection is a sterile, preservative-free non pyrogenic clear to opalescent, colourless to yellowish solution in a single-dose vial.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-Hodgkin's lymphoma
Mabthera SC 1400mg is indicated for the treatment of patients with:

- CD20 positive, previously untreated low-grade or follicular, B-cell non-Hodgkin's lymphoma in combination with chemotherapy,
- CD20 positive, relapsed or chemoresistant low-grade or follicular, B-cell non-Hodgkin's lymphoma,
- CD20 positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy.

Mabthera SC 1400mg is indicated for maintenance treatment of patients with CD20 positive, low grade or follicular, B-cell non-Hodgkin's lymphoma.

Chronic lymphocytic leukaemia
Mabthera SC 1600mg in combination with chemotherapy is indicated for the treatment of patients with chronic lymphocytic leukaemia.

4.2 Dose and method of administration

General
Substitution by any other biological medicinal product requires the consent of the prescribing physician.

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

Mabthera SC is not intended for intravenous (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 non-Hodgkin's lymphoma only.

Mabthera SC 1600mg is intended for use in chronic lymphocytic leukaemia only.

Premedication consisting of an analgesic/anti-pyretic and an antihistamine agent should always be given before each administration of Mabthera SC.

Premedication with glucocorticoids should also be considered, particularly if Mabthera SC is not given in combination with steroid-containing chemotherapy.

Use a sterile needle and syringe to prepare MabThera.

First intravenous administration
All patients must always receive their first dose of Mabthera by IV administration using the IV formulation. During their first cycle the patient is at the highest risk of experiencing an infusion/administration related reaction. Beginning therapy with Mabthera by IV infusion allows management of infusion / administration related reactions by slowing or stopping the intravenous infusion (see section 4.4, *Infusion /Administration-related reactions for*).

Subsequent subcutaneous administrations
The SC formulation must only be given at the second or subsequent cycles (See *Dose*).

Dose
Non-Hodgkin's lymphoma
Subcutaneous formulation (1400mg)

<u>First intravenous administration</u>
Before starting Mabthera SC injections, all patients must always receive beforehand, a full dose of Mabthera by IV infusion, using the intravenous Mabthera formulation (see section 4.4).

Please refer to the separate Data Sheet for intravenous Mabthera formulation for full instructions on dosing, method of administration, preparation and storage.

Subsequent subcutaneous administrations

If patients were not able to receive one full Mabthera IV infusion dose, they should continue the subsequent cycles with Mabthera IV until a full IV dose is successfully administered. For patients able to receive the full intravenous Mabthera dose, the second or subsequent Mabthera dose can be given subcutaneously using the Mabthera SC formulation.

Mabthera SC 1400mg injection should be administered over approximately 5 minutes. (see *Method of Administration*).

Low-grade or follicular non-Hodgkin's Lymphoma

Initial treatment

Monotherapy

The recommended dosage of Mabthera used as monotherapy for adult patients is first cycle with IV Mabthera 375 mg/m^2, administered as an IV infusion, followed by subsequent cycles with Mabthera SC at a fixed dose of 1400 mg per cycle once weekly. In total: 4 weeks

Combination therapy

The recommended dosage of Mabthera SC in combination with any chemotherapy is: first cycle with intravenous Mabthera 375 mg/m^2 administered as an IV infusion, followed by subsequent cycles with Mabthera SC as a fixed dose of 1400 mg per cycle for a total of:

- 8 cycles with R-CVP (cyclophosphamide, vincristine, prednisolone); 21 days/cycle.
- 8 cycles with R-MCP (mitoxantrone, chlorambucil, prednisolone); 28 days/cycle.
- 8 cycles with R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone); 21 days/cycle. 6 cycles if a complete remission is achieved after 4 cycles.
- 6 cycles with R-CHVP-interferon (cyclophosphamide, doxorubicin, etoposide, prednisolone); 21 days/cycle.

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

Re-treatment following relapse

Patients who have responded to Mabthera initially may be treated again with Mabthera SC at a fixed dose of 1400 mg, once weekly, following a first administration of IV Mabthera 375 mg/m^2 administered as an IV infusion (first week IV then 3 weeks SC for 4 weeks in total) (see section 5.1 *Pharmacodynamic Effect, Clinical efficacy and safety, Re-treatment, weekly for 4 doses*).

Maintenance treatment

Previously untreated patients after response to induction treatment may receive maintenance therapy with Mabthera SC given at a dose of 1400 mg once every 2 months until disease progression or for a maximum period of two years (12 administrations).

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

Diffuse large B-cell non-Hodgkin's lymphoma

Mabthera should be used in combination with CHOP (cyclophosphamide, doxorubicin, prednisone and vincristine) chemotherapy. The recommended dosage of Mabthera is: first dose with IV Mabthera 375 mg/m^2 administered as an IV infusion, followed by subsequent cycles with Mabthera SC injected at a fixed dose of 1400 mg per cycle. In total: 8 cycles.

Mabthera should be administered on day 1 of each chemotherapy cycle after IV administration of the glucocorticoid component of CHOP. The other components of CHOP should be given after the administration of Mabthera.

Chronic lymphocytic leukaemia

Subcutaneous formulation (1600 mg)
Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to 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 prednisone/prednisolone 100 mg intravenously shortly before administration with Mabthera to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

First intravenous administration
Before starting Mabthera SC injections, all patients must always receive beforehand, a full dose of Mabthera by IV infusion, using the intravenous Mabthera formulation (see section 4.4).

Please refer to the separate Data Sheet for intravenous Mabthera formulation for full instructions on dosing, method of administration, preparation and storage.

Subsequent subcutaneous administrations
Patients unable to receive one full Mabthera IV infusion dose should continue the subsequent cycles with IV Mabthera until a full IV dose is successfully administered. For patients able to receive the full IV Mabthera dose, the second or subsequent Mabthera dose can be given subcutaneously using the Mabthera SC formulation.

The recommended dose of Mabthera SC in combination with chemotherapy for CLL is a fixed dose of 1600mg, given as an SC injection, irrespective of the patient's body surface area, administered on day 1 of each chemotherapy cycle for 5 cycles over approximately 7 minutes (first cycle IV and 5 cycles SC, 6 cycles in total). (see section 5.1, *Clinical Efficacy and Safety*).The chemotherapy should be given after Mabthera administration.

Special populations

Paediatric Populations
The safety and effectiveness of Mabthera in paediatric patients has not been established *(see section 4.8 Paediatric patients).*

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

Special dosage instructions

Dosage adjustments during treatment for NHL or CLL
No dose reductions of Mabthera SC are recommended. When Mabthera SC is given in

combination with chemotherapy, standard dose reductions for the chemotherapeutic medicines should be applied.

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 1400mg should be injected over approximately 5 minutes for use in NHL.

Mabthera SC 1600mg should be injected over approximately 7 minutes for use in CLL.

The needle which will be used for the SC injection must only be attached to the syringe immediately prior to administration to avoid potential needle clogging.

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.

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 (see section 4.8 *Post-marketing experience*). The majority of patients had received Mabthera in combination with chemotherapy or as part of a haematopoietic stem cell transplant.

Infusion/Administration-related Reactions
Mabthera is associated with infusion/administration-related reactions (IRRs/ARRs), 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). 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 IV administration, using the IV 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. The subcutaneous formulation must only be given at the second or subsequent cycles.

Patients unable to receive one full Mabthera IV infusion dose should continue the subsequent cycles with Mabthera IVuntil a full IV dose is successfully administered. For patients who are able to receive the full Mabthera IV infusion dose, the second or subsequent Mabthera dose can be given subcutaneously using the Mabthera SC formulation (see section 4.2). 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).

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 IRRs with fatal outcome have been reported during post-marketing use. Severe IRRs 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, angioedema and other symptoms (see Undesirable Effects). 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 IRRs. Infusion reaction symptoms are usually reversible with interruption of the infusion. Treatment of infusion-related symptoms with an anti-histamine and 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 IRRs 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 IRRs.

Patients with a high number (> 25 x 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 IRRs, should only be treated with extreme caution. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients, or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still > 25 x 10^9/L.

Hypersensitivity Reactions/Anaphylaxis

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. Epinephrine, antihistamines and glucocorticoids 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 1 or 2 hours of initiating the first infusion. Patients who experience severe pulmonary events should have their Mabthera IV or SC administration interrupted immediately (see section 4.2) and should receive aggressive symptomatic treatment.

Rapid Tumour Lysis

Mabthera mediates the rapid lysis of benign and malignant CD20 positive cells. Signs and symptoms (e.g., hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, acute renal failure, elevated LDH) consistent with tumour lysis syndrome (TLS) have been reported to occur after the first Mabthera 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 CLL or 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 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, cardiac arrhythmia, such as atrial flutter and fibrillation, heart failure and myocardial infarction have occurred in patients treated with Mabthera. Therefore patients with a history of cardiac disease should be monitored closely.

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.

Hepatitis B Infections
Cases of hepatitis B (HB) reactivation including reports of fulminant hepatitis, some of which were fatal, have been reported in subjects receiving intravenous Mabthera, although the majority of these subjects were also exposed to cytotoxic chemotherapy. The reports are confounded by both the underlying disease state, and the cytotoxic chemotherapy.

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with Mabthera. At a minimum this should include HB surface antigen status and anti-HB core antibody status. These can be complemented with other appropriate markers as per local guidelines. Patients with active HB disease should not be treated with Mabthera. 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.

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, *Post-marketing experience*). If signs and symptoms suggestive of a severe skin reaction occur, with a suspected relationship to Mabthera, treatment should be permanently discontinued.

Immunisation
The safety of immunisation with live viral vaccines following Mabthera therapy has not been studied and vaccination with live viral 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 titre).

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

General
In order to improve traceability of biological medicinal products, the trade name and batch number of the administered product should be clearly recorded in the patient's medical record.

4.5 Interaction with other medicines and other forms of interaction

At present, there are limited data on possible interactions with Mabthera.

In CLL patients, co-administration with Mabthera did not appear to have an effect on the pharmacokinetics of fludarabine or cyclophosphamide. In addition; there were no apparent effects of fludarabine and cyclophosphamide on the pharmacokinetics of Mabthera.

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

4.6 Fertility, pregnancy and lactation

Contraception in males and females
Women of childbearing age must use effective contraceptive methods during and for 12 months after treatment with Mabthera.

Pregnancy
IgG immunoglobulins are known to cross the placental barrier.

B-cell levels in human neonates following maternal exposure to Mabthera have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women. However transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to rituximab during pregnancy. For these reasons Mabthera should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

Mabthera SC contains vorhyaluronidase alfa (see sections 2 and 6.1). Pharmacokinetic and toxicology studies in animals demonstrate reductions in foetal weight and increases in the number of resorptions following injection of vorhyaluronidase alfa , at maternal systemic exposure levels comparable to those that could occur after accidental bolus IV administration of a single vial of the Mabthera SC in humans, based on the most conservative assumptions possible.

There is no evidence of dysmorphogenesis (i.e. teratogenesis) resulting from systemic exposure to vorhyaluronidase alfa.

Systemic absorption of vorhyaluronidase alfa after subcutaneous administration is unlikely to occur.

Breast-feeding

Limited data on rituximab excretion into breast milk suggest very low rituximab concentrations in milk (relative infant dose less than 0.4%). In the few cases where breastfed infants were followed-up, infants showed normal growth and development up to 2 years. However, as these data are limited and the long-term outcomes of breastfed infants remain

unknown, breast-feeding is not recommended while being treated with MabThera SC and, optimally, also for 6 months following MabThera SC treatment.

4.7 Effects on ability to drive and use machines

MabThera has no or negligible effect on the ability to drive and use machines.

4.8 Undesirable effects

Clinical trials

Subcutaneous Formulation
Local cutaneous reactions, including injection site reactions, were very common (≥ 1/10%) in patients receiving Mabthera SC. In the phase III SABRINA study (BO22334), local cutaneous reactions were reported in up to 23% of patients receiving Mabthera SC. The most common local cutaneous reactions in the Mabthera SC arm were injection site erythema (13%), injection site pain (8%), and injection site oedema (4%). 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.

The safety profile of Mabthera SC was otherwise comparable to that of the IV formulation.

No cases of anaphylaxis or severe hypersensitivity reactions, cytokine release syndrome or tumour lysis syndrome were observed following SC administration during the SC development program.

Intravenous Formulation
Information in this section reports data from the separate Data Sheet for intravenous Mabthera.

Experience from clinical trials in haemato-oncology
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, Clinical Efficacy and Safety*). 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, *Clinical Efficacy and Safety*). 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	angiooedema	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	

System Organ Class	Very Common (≥ 10%)	Common (≥ 1% - < 10%)	Uncommon (≥ 0.1% - < 1%)
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 mediastinal disorders		bronchospasm, respiratory disease, chest pain, dyspnoea, cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia
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.

<u>Mabthera in combination with chemotherapy in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia (CLL)</u>

The ADRs listed in the table below are based on Mabthera-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 Mabthera in combination with fludarabine and cyclophosphamide (R-FC) (see section 5.1, *Clinical Efficacy and Safety*).

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.

The safety profile for Mabthera in combination with other chemotherapies (e.g. MCP, CHVP-IFN) is comparable to the safety profile as described for the combination of Mabthera and CVP, CHOP or FC in equivalent populations.

Further information on selected, serious adverse drug reactions

Infusion/Administration-related reactions (IRRs/ARRs)

Subcutaneous Formulation
The risk of acute reactions associated with the Mabthera SC was assessed in three clinical studies.

In SparkThera, no severe administration-related reactions were reported.

In SABRINA, severe administration-related reactions (Grade ≥ 3) were reported in two patients (2%) following Mabthera SC administration. These events were Grade 3 injection site rash and dry mouth.

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 Data Sheet for intravenous Mabthera.

Monotherapy - 4 weeks treatment
Signs and symptoms suggestive of an 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 tumour lysis syndrome have also been observed.

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. Additional reactions reported were dyspepsia, rash, hypertension, tachycardia, features of tumour lysis syndrome. Isolated cases of myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia were also reported.

Information from the following sub-sections of the Adverse Effects section reports data from the separate Data Sheet for intravenous Mabthera.

Infections
Monotherapy - 4 weeks treatment
Mabthera induced B-cell depletion in 70% to 80% of patients but 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 3/4), including sepsis occurred in 3.9% of patients.

Maintenance Treatment (NHL) up to 2 years
Higher frequencies of infections overall, including Grade 3/4 infections, were observed during Mabthera treatment. 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 section 4.4).

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)
In the R-CVP study no increase in the frequency of infections or infestations was observed. 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 3/4 hepatitis B infection (reactivation and primary infection) was 2% R-FC vs 0% FC.

Haematologic Events

Monotherapy - 4 weeks treatment

Severe (Grade 3/4) 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.

Maintenance Treatment (NHL) up to 2 years

There was a higher incidence of Grade 3/4 leucopenia (observation 2%, Mabthera 5%) and neutropenia (observation 4%, Mabthera 10%) in the Mabthera arm compared to the observation arm. The incidence of Grade 3/4 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 with Mabthera in combination with chemotherapy in clinical studies, Grade 3/4 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 3/4 anaemia or thrombocytopenia. In the CLL first-line study, Grade 3/4 anaemia was reported by 4% of patients treated with R-FC compared to 7% of patients receiving FC, and Grade 3/4 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 3/4 anaemia were reported in 12% of patients treated with R-FC compared to 13% of patients receiving FC and Grade 3/4 thrombocytopenia was reported by 11% of patients in the R-FC group compared to 9% of patients in the FC group.

Cardiovascular Events

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 3/4 cardiac disorders was comparable between the two treatment groups. Cardiac events were reported as serious adverse events 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%).

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)
In the R-CHOP study the incidence of Grade 3/4 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 (see section 4.4). No difference between the R-CHOP and CHOP group was observed in the incidence of other Grade 3/4 cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease.

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

IgG Levels
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).

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 group 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 3/4 nervous system disorders was low both in previously untreated patients (4% R-FC vs 4% FC) and in relapsed/refractory patients (3% R-FC vs 3% FC).

Special populations
Elderly patients (≥ 65 years)
Monotherapy - 4 weeks treatment: The incidence of any ADR and of Grade 3/4 ADRs was similar in elderly and younger patients (88.3% vs 92.0% for any ADR and 16.0% vs 18.1% for Grade 3/4 ADRs).

Combination Therapy: The incidence of Grade 3/4 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.

Paediatric patients
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.

Bulky disease
Patients with bulky disease had a higher incidence of Grade 3/4 ADRs than patients without bulky disease (25.6% vs 15.4%). The incidence of any ADR was similar in these two groups (92.3% in bulky disease vs 89.2% in non-bulky disease).

Re-treatment with monotherapy
The percentage of patients reporting any ADR and Grade 3/4 ADRs upon re-treatment with further courses of Mabthera was similar to the percentage of patients reporting any ADR and Grade 3/4 ADRs upon initial exposure (95.0% vs 89.7% for any ADR and 13.3% vs 14.8% for Grade 3/4 ADRs).

Post-marketing experience
Information in this section reports data from the separate Data Sheet 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 Mabthera (see section 4.4).

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

- *Cardiovascular system*: Severe cardiac events, including 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 leukocytoclastic 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. Studies of Mabthera in patients with Waldenstrom's macroglobulinaemia, transient increases in serum IgM levels have been observed following treatment initiation, which may be associated with hyperviscosity and related symptoms. The transient IgM increase usually returned to at least baseline level within 4 months.

- *Respiratory system:* Respiratory failure/insufficiency and lung infiltration in the context of infusion- related reactions (see section 4.4). 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 included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had 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, the majority of which were in subjects receiving rituximab in combination with cytotoxic chemotherapy (see section 4.4).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 section 4.4) 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 positive.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions
https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Intravenous and Subcutaneous Formulations
Limited experience with doses higher than the approved intravenous doses of Mabthera is available from clinical trials in humans. The highest intravenous dose tested to date is 5000 mg (2250 mg/m^2) tested in a dose escalation study in patients with chronic lymphocytic leukaemia. 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 trial SABRINA inadvertently received a 2280 mg SC formulation dose via the IV route with no untoward effect. Patients who experience overdose or medication error should be closely monitored.

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies, ATC code: L01FA01

Mechanism of action
Rituximab is a chimeric mouse/human monoclonal antibody that binds specifically to the transmembrane antigen CD20. This antigen is located on pre-B- and mature B-lymphocytes, but not on haemopoietic stem cells, pro–B-cells, normal plasma cells or other normal tissue. The antigen is expressed on > 95% of all B–cell non-Hodgkin's lymphomas (NHLs). Following antibody binding, CD20 is not internalised or shed from the cell membrane into the environment. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding.

Rituximab binds to the CD20 antigen on B-lymphocytes and initiates immunologic reactions that mediate B-cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and induction of apoptosis. Finally, in–vitro studies have demonstrated that rituximab sensitises drug-resistant human B–cell lymphoma lines to the cytotoxic effects of some chemotherapeutic agents.

Peripheral B–cell counts declined to levels below normal following the first dose of Mabthera. In patients treated for haematological malignancies, B-cell recovery began within 6 months of treatment and generally returning to normal levels within 12 months after completion of therapy, although in some patients this may take longer (see Undesirable Effects - Experience from clinical trials in haemato-oncology).

Of 67 patients evaluated for human anti-mouse antibody (HAMA), none were positive. Of 356 non- Hodgkin's lymphoma patients evaluated for human anti-chimeric antibody (HACA), 1.1% (4 patients) were positive.

Pharmacodynamic effect
Clinical efficacy and safety
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). Results from SparkThera are presented under the section Pharmacokinetic Properties.

SABRINA was a two-stage phase III, international, multi-centre, randomized, 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 Mabthera IV 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 Ctrough levels compared with intravenous Mabthera, when given as part of induction treatment every 3 weeks (see section 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 randomized into the following two treatment groups:

- Mabthera SC (n = 205): 1st cycle Mabthera IV plus 7 cycles of Mabthera SC in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. Mabthera IV was used at the standard dose of 375 mg/m2. 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 Mabthera IV in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. Mabthera IV was used at the standard dose of 375 mg/m2. Patients achieving at least PR were entered into the maintenance phase of the study receiving Mabthera IV once every 8 weeks for 24 months.

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 the pooled data from Stages 1 and 2. Additionally, ORR and complete response (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. Key efficacy results are presented in Table 3 based on a median follow-up of 58 months.

Table 3: Efficacy Results for Study SABRINA/BO22334

	MabThera SC N=205	**MabThera 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	65
Complete response (CR/CRu) rate (%, [95% CI])	32.2% [25.9; 39.1]	31.7% [25.4; 38.6]
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	103
Complete response (CR/CRu) rate (%, [95% CI])	50.6% [42.9; 58.3]	57.9% [50.3; 65.2]
Progression-free survival		
Number of patients with event	65 (31.7%)	71 (34.6%)
Hazard Ratio [95% CI] (unstratified Cox model)	0.90 [0.64%, 1.26%]	
Overall survival		
Number of patients with event	18 (8.8%)	26 (12.7%)
Hazard Ratio [95% CI] (unstratified Cox model)	0.70 [0.38; 1.27]	

[a] at end of Induction
[b] at time of final analysis (median follow-up 58 months)
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 was 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 Ctrough levels compared with Mabthera IV. Previously untreated CLL patients (n = 64) were enrolled at any point during their treatment with Mabthera IV in combination with chemotherapy, The dose of 1600 mg of Mabthera SC was selected for the Part 2 of the study.

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

- Mabthera SC (n = 88); 1st cycle of Mabthera IV 375 mg/m2 in combination with chemotherapy plus subsequent cycles (Cycle 2 to 6) of MabThera SC 1600mg in combination with chemotherapy.
- MabThera IV (n = 88): 1st cycle of Mabthera IV 375 mg/m2 in combination with chemotherapy followed by up to 5 cycles of MabThera IV 500 mg/m2 in combination with chemotherapy.

Table 4: Efficacy Results for Study SAWYER/BO25341

		Part 2 N = 176	
		MabThera/Rituxan IV (n = 88)	**MabThera/Rituxan SC** (n = 88)
ORR[a]	Point estimate	80.7% (n = 71)	85.2% (n = 75)
	95% CI	[70.9%, 88.3%]	[76.1%, 91.9%]
CRR[a]	Point estimate	31.8% (n = 28)	27.3% (n = 24)
	95% CI	[22.3%, 42.6%]	[18.3%, 37.8%]
PFS[b]	Proportion with PFS event	42.0% (n = 37)	34.1% (n = 30)
	HR 95% CI	0.76 [0.47%, 1.23%]	

ORR – Overall Response Rate
CRR – Complete Response Rate
PFS – Progression-Free Survival (proportion with event, disease progression/relapse or death from any cause)
[a] – at 3 month follow-up visit (Part 2)
[b] – at time of final analysis (median follow-up 53 months)

Overall the results confirm that Mabthera SC 1600 mg has a comparable benefit/risk profile to that of Mabthera IV 500 mg/m^2.

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 low and similar to that observed in the IV group (1.9% IV vs 2% SC). The incidence of treatment-induced/enhanced anti-vorhyaluronidase alfa antibodies was 8% in the IV group compared with 15% in the SC group, and none of the patients who tested positive for anti-vorhyaluronidase alfa antibodies tested positive for neutralising antibodies. The overall proportion of patients found to have anti-vorhyaluronidase alfa antibodies remained generally constant over the follow-up period in both cohorts.

In the SAWYER study (BO25341) the incidence of treatment-induced/enhanced anti-rituximab antibodies was similar in the two treatment arms; 15% IV vs. 12% SC. The incidence of treatment- induced/enhanced anti-vorhyaluronidase alfa antibodies, only measured in patients in the SC arm was 12%. None of the patients who tested positive for anti-vorhyaluronidase alfa antibodies tested positive for neutralising antibodies.

The clinical relevance of the development of anti-rituximab or anti-vorhyaluronidase alfa antibodies after treatment with Mabthera SC is not known. There was no impact of the presence of anti-rituximab or anti-vorhyaluronidase alfa antibodies on safety or efficacy in both studies.

Intravenous formulation
Information in this section reports data from the separate Data Sheet for intravenous Mabthera.

Low-grade or follicular non-Hodgkin's lymphoma
Monotherapy
Initial treatment, weekly for 4 doses
In the pivotal study, 166 patients with relapsed or chemoresistant low-grade or follicular B–cell NHL received 375 mg/m2 of Mabthera as an IV infusion weekly for four doses. The overall response rate (ORR) in the intent-to-treat (ITT) population was 48% (CI95% 41% - 56%) with a 6% complete response (CR) and a 42% partial response (PR) rate. The projected median time to progression (TTP) for responding patients was 13.0 months.

In a subgroup analysis, the ORR was higher in patients with IWF B, C, and D histologic subtypes as compared to IWF A subtype (58% vs 12%), higher in patients whose largest lesion was < 5 cm vs > 7 cm in greatest diameter (53% vs 38%), and higher in patients with chemosensitive relapse as compared to chemoresistant (defined as duration of response < 3 months) relapse (50% vs 22%). ORR in patients previously treated with autologous bone marrow transplant (ABMT) was 78% versus 43% in patients with no ABMT. Neither age, sex, lymphoma grade, initial diagnosis, presence or absence of bulky disease, normal or high LDH nor presence of extranodal disease had a statistically significant effect (Fisher's exact test) on response to Mabthera.

A statistically significant correlation was noted between response rates and bone marrow involvement. 40% of patients with bone marrow involvement responded compared to 59% of

patients with no bone marrow involvement (p = 0.0186). This finding was not supported by a stepwise logistic regression analysis in which the following factors were identified as prognostic factors: histologic type, bcl-2 positivity at baseline, resistance to last chemotherapy and bulky disease.

Initial treatment, weekly for 8 doses
In a multi-centre, single-arm study, 37 patients with relapsed or chemoresistant, low grade or follicular B–cell NHL received 375 mg/m2 of Mabthera as IV infusion weekly for eight doses. The ORR was 57% (CI95% 41% – 73%; CR 14%, PR 43%) with a projected median TTP for responding patients of 19.4 months (range 5.3 to 38.9 months).

Initial treatment, bulky disease, weekly for 4 doses
In pooled data from three studies, 39 patients with relapsed or chemoresistant, bulky disease (single lesion 2 10 cm in diameter), low grade or follicular B–cell NHL received 375 mg/m2 of Mabthera as IV infusion weekly for four doses. The ORR was 36% (CI95% 21% – 51%; CR 3%, PR 33%) with a median TTP for responding patients of 9.6 months (range 4.5 to 26.8 months).

Re-treatment, weekly for 4 doses
In a multi-centre, single-arm study, 58 patients with relapsed or chemoresistant low grade or follicular B–cell NHL, who had achieved an objective clinical response to a prior course of Mabthera, were re- treated with 375 mg/m2 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% (CI95% 26% – 51%; 10% CR, 28% PR) with a projected median TTP for responding patients of 17.8 months (range 5.4 – 26.6). This compares favourably with the TTP achieved after the prior course of Mabthera (12.4 months).

In combination with chemotherapy

Initial treatment
In an open-label randomised trial, a total of 322 previously untreated patients with follicular lymphoma were randomised to receive either CVP chemotherapy (cyclophosphamide 750 mg/m2, vincristine 1.4 mg/m2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m2/day on days 1-5) every 3 weeks for 8 cycles or Mabthera 375 mg/m2 in combination with CVP (R-CVP). Mabthera was administered on the first day of each treatment cycle. A total of 321 patients (162 R-CVP, 159 CVP) received therapy and were analysed for efficacy.

The median follow-up of patients was 53 months. R-CVP led to a significant benefit over CVP for the primary endpoint, time to treatment failure (27 months vs. 6.6 months, p < 0.0001, log-rank test). The proportion of patients with a tumour response (CR, CRu, PR) was significantly higher (p<0.0001 Chi- Square test) in the R-CVP group (80.9%) than the CVP group (57.2%). Treatment with R-CVP significantly prolonged the time to disease progression or death compared to CVP, 33.6 months and 14.7 months, respectively (p<0.0001, log-rank test). The median duration of response was 37.7 months in the R-CVP group and was 13.5 months in the CVP group (p < 0.0001, log-rank test). The difference between the treatment groups with respect to overall survival showed a strong clinical benefit (p=0.029, log-rank test stratified by centre). Survival rates at 53 months were 80.9% for patients in the R-CVP group compared to 71.1% for patients in the CVP group.

Results from three other randomised trials 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. Key results from all four studies are summarised in the table below.

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

Study	Treatment, n	Median FU, months	ORR, %	CR, %	Median TTF/PFS/ EFS mo	OS rates, %
M39021	CVP, 159 R-CVP, 162	53	57 81	10 41	Median TTP: 14.7 33.6 P<0.0001	71.1 80.9 p=0.029
GLSG'00	CHOP, 205 R-CHOP, 223	18	90 96	17 20	Median TTF: 2.6 years Not reached p < 0.001	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; CVP – cyclophosphamide, vincristine, prednisolone; CHOP - cyclophosphamide, doxorubicin, vincristine, prednisone; MCP – mitoxantrone, chlorambucil, prednisolone; CHVP - cyclophosphamide, doxorubicin, etoposide, prednisolone ; IFN – interferon-alfa 2a.
1M39021 outcome: TTP (time to progression or death); GLSG'00 outcome: TTF (time to treatment failure); OSHO- 39: PFS (progression free survival); FL2000 outcome: EFS (event free survival).

Maintenance therapy - previously untreated follicular NHL
In a prospective, open label, international, multi-center, phase III trial 1193 patients with previously untreated advanced follicular lymphoma received induction therapy with R-CHOP (n=881), R-CVP (n=268) or R-FCM (n=44), according to the investigators' choice. A total of 1078 patients responded to induction therapy, of which 1018 were 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 two months until disease progression or for a maximum period of two years.

The pre-specified primary analysis was conducted at a median observation time of 25 months from 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 observation in patients with previously untreated follicular NHL (Table 5). This improvement in PFS was confirmed by an independent review committee (IRC).

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 6).

Data from extended follow-up of patients in the study (median follow-up 9 years) confirmed the long-term benefit of MabThera maintenance therapy in terms of PFS, EFS, TNLT and TNCT (Table 6).

Table 6: Overview of efficacy results for maintenance MabThera vs. observation (25 months and 9 years median follow-up - final analysis)

	Primary analysis (median FU: 25 months)		**Final analysis (median FU: 9.0 years)**	
	Observation N=513	**MabThera N=505**	**Observation N=513**	**MabThera N=505**
Primary efficacy				
Progression-free survival (median)	NR	NR	4.06 years	10.49 years
log-rank p value	<0.0001		<0.0001	
hazard ratio (95% CI)	0.50 (0.39, 0.64)		0.61 (0.52, 0.73)	
risk reduction	50%		39%	
Secondary efficacy				
Overall survival (median)	NR	NR	NR	NR
log-rank p value	0.7246		0.7953	
hazard ratio (95% CI)	0.89 (0.45, 1.74)		1.04 (0.77, 1.40)	
risk reduction	11%		-6%	
Event-free survival (median)	38 months	NR	4.04 years	9.25 years
log-rank p value	<0.0001		<0.0001	
hazard ratio (95% CI)	0.54 (0.43, 0.69)		0.64 (0.54, 0.76)	
risk reduction	46%		36%	
TNLT (median)	NR	NR	6.11 years	NR
log-rank p value	0.0003		<0.0001	
hazard ratio (95% CI)	0.61 (0.46, 0.80)		0.66 (0.55, 0.78)	
risk reduction	39%		34%	
TNCT (median)	NR	NR	9.32 years	NR
log-rank p value	0.0011		0.0004	
hazard ratio (95% CI)	0.60 (0.44, 0.82)		0.71 (0.59, 0.86)	
risk reduction	40%		39%	
Overall response rate*	55%	74%	61%	79%
chi-squared test p value	<0.0001		<0.0001	
odds ratio (95% CI)	2.33 (1.73, 3.15)		2.43 (1.84, 3.22)	
Complete response (CR/CRu) rate*	48%	67%	53%	67%
chi-squared test p value	<0.0001		<0.0001	
odds ratio (95% CI)	2.21 (1.65, 2.94)		2.34 (1.80, 3.03)	

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

Mabthera maintenance treatment provided consistent benefit in all 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).

Maintenance therapy - relapsed/refractory follicular NHL
In a prospective, open label, international, multi-centre, 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). The two treatment groups were well balanced with regard to

baseline characteristics and disease status. A total of 334 patients achieving a complete or partial remission following induction therapy were randomised in a second step to Mabthera maintenance therapy (n=167) or observation (n=167). Mabthera maintenance treatment consisted of a single infusion of Mabthera at 375 mg/m2 body surface area given every 3 months until disease progression or for a maximum period of two years.

The final efficacy analysis included all patients 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 7).

Table 7: 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 vs PR vs 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 8). The risk of relapse in complete responders was reduced by 67% (95% CI; 39% - 82%).

Table 8: Maintenance Phase: Overview of Efficacy Results Mabthera vs. observation (28 months median observation time)

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

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

The benefit of Mabthera maintenance treatment was confirmed in all subgroups analysed, regardless of induction regimen (CHOP or R-CHOP) or quality of response to induction treatment (CR or PR) (Table 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, $p=0.0071$). Mabthera maintenance treatment also provided a clinically meaningful benefit in terms of overall survival for both patients responding to CHOP and patients responding to R-CHOP in the induction phase of the study, although longer follow-up is required to confirm this observation.

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 vs > 0), B symptoms (absent, present), bone marrow involvement (no vs yes), IPI (0-2 vs 3-5), FLIPI score (0 - 1, vs 2 vs 3 - 5), number of extra-nodal sites (0 - 1 vs > 1), number of nodal sites (< 5 vs 2 5), number of previous regimens (1 vs 2), best response to prior therapy (CR/PR vs NC/PD), haemoglobin (< 12 g/dL vs 2 12 g/dL), p2-microglobulin (< 3mg/L vs 2 3 mg/L), LDH (elevated, not elevated) except for the small subgroup of patients with bulky disease.

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

The final efficacy analysis included all randomised patients (197 CHOP, 202 R-CHOP), and had a median follow-up duration of approximately 31 months. The two treatment groups were well balanced in baseline 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 60 months, confirmed the benefit of R-CHOP over CHOP treatment (p=0.0071), representing a risk reduction of 32%.

The analysis of all secondary parameters (response rates, progression-free survival, disease-free survival, duration of response) verified the treatment effect of R-CHOP compared to CHOP. The complete response rate after cycle 8 was 76.2% in the R-CHOP group and 62.4% in the CHOP group (p = 0.0028). The risk of disease progression was reduced by 46% and the risk of relapse by 51%.

In all 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. R-CHOP was associated with improvements in outcome for both high- and low- risk patients according to age adjusted IPI.

Chronic lymphocytic leukaemia
In two open-label randomised trials, a total of 817 previously untreated patients and 552 patients with relapsed/refractory CLL were randomised to receive either FC chemotherapy (fludarabine 25 mg/m2, cyclophosphamide 250 mg/m2, days 1-3) every 4 weeks for 6 cycles or Mabthera in combination with FC (R-FC). Mabthera was administered at a dosage of 375 mg/m2 during the first cycle one day prior to chemotherapy and at a dosage of 500 mg/m2 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 Table 10) 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 median progression-free survival (PFS; primary endpoint) 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, log-rank test). 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 Mabthera plus FC vs. FC alone (20.7 months median observation time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Hazard Ratio
	FC (n=407)	R-FC (n=403)	Log-Rank p-value	
Progression-free survival (PFS)	32.2 (32.8)***	39.8 (55.3)***	<0.0001 (<0.0001)***	0.56 (0.55)***
Overall Survival	NR (NR)***	NR (NR)***	0.0427 (0.0319)***	0.64 (0.73)***
Event Free Survival	31.1 (31.3)***	39.8 (51.8)***	<0.0001 (<0.0001)***	0.55 (0.56)***
Response rate (CR, nPR, or PR)	72.7%	86.1%	<0.0001	n.a.
CR rates	17.2%	36.0%	<0.0001	n.a.
Duration of response*	34.7 (36.2)***	40.2 (57.3)***	0.0040 (<0.0001)***	0.61 (0.56)***
Disease free survival (DFS)**	NR (48.9)***	NR (60.3)***	0.7882 (0.0520)***	0.93 (0.69)***
Time to new CLL treatment	NR (47.2)***	NR (69.7)***	0.0052 (<0.0001)***	0.65 (0.58)***

Response rate and CR rates analysed using Chi-squared Test.
*: only applicable to patients with CR (complete response), nPR (nodular partial response) or PR (partial response) as end of treatment response
**: only applicable to patients with CR as end of treatment response
***: values in brackets correspond to 48.1 months median observation time (ITT population – 409 FC, 408 R-FC) NR: not reached; n.a. not applicable.

Table 10: Hazard Ratios of Progression –Free Survival According to Binet Stage (ITT) (20.7 Months Median Observation Time)

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

CI: Confidence Interval
*: values correspond to 48.1 months median observation time (ITT population – 409 FC, 408 R-FC)

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)			Risk Reduction
	FC (n=276)	R-FC (n=276)	Log-Rank p-value	
Progression-free survival (PFS)	20.6	30.6	0.0002	35%
Overall Survival	51.9	NR	0.2874	17%
Event Free Survival	19.3	28.7	0.0002	36%
Response rate (CR, nPR, or PR)	58.0%	69.9%	0.0034	n.a.
CR rates	13.0%	24.3%	0.0007	n.a.
Duration of response *	27.6	39.6	0.0252	31%
Disease free survival (DFS)**	42.2	39.6	0.8842	-6%
Time to new CLL treatment	34.2	NR	0.0024	35%

Response rate and CR rates analysed using Chi-squared Test
*: only applicable to patients with CR (complete response), nPR (nodular partial response), PR (partial response) as best overall response
**: only applicable to patients with CR as best overall response
NR: not reached; n.a. not applicable.

Results from other supportive studies using Mabthera in combination with other chemotherapy regimens (including CHOP, FCM (fludarabine, cyclophosphamide, mitoxantrone), PC (pentostatin, cyclophosphamide), PCM (pentostatin, cyclophosphamide, mitoxantrone), bendamustine and cladribine) for the treatment of CLL patients have also demonstrated high overall response rates with promising PFS rates without adding relevant toxicity to the treatment.

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 SC injection was given after at least one cycle of intravenous Mabthera 375 mg/m^2 to patients who had previously responded to intravenous Mabthera formulation in induction.

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

In study BO22334 (SABRINA), previously untreated patients with follicular NHL were randomized 1:1 to receive Mabthera SC as a 1400 mg subcutaneous injection (first cycle

Mabthera IV formulation 375 mg/m^2 followed by 7 cycles of Mabthera SC) or intravenous Mabthera 375 mg/m2 (8 cycles) in combination with up to 8 cycles of CHOP or CVP chemotherapy every three weeks as part of induction treatment (see also Clinical/efficacy studies). Rituximab serum Cmax 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 (Cmax SC/Cmax IV) of 0.941 (90% CI: 0.872, 1.015).

Based on a population pharmacokinetic analysis an absolute bioavailability of 71% (95%CI: 70.0 – 72.1) was estimated.

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 for 5 cycles SC at 4-weekly intervals, following the first cycle of Mabthera IV, in previously untreated CLL patients in combination with chemotherapy [fludarabine and cyclophosphamide (FC)]. The serum Mabthera 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 (Cmax, SC/Cmax, IV) of 0.719 (90% CI: 0.653, 0.792). The geometric mean Tmax in the Mabthera SC was approximately 3 days as compared to the Tmax occuring at or close to the end of the infusion for the Mabthera IV.

Distribution
Subcutaneous formulation (1400mg) for non-Hogkin's lymphoma
In the SparkThera study, the predicted mean and geometric mean rituximab Ctrough 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. Similarly, the predicted mean and geometric mean rituximab AUCtau 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 Ctrough 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. Similarly, 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 3778 µg•day/mL for the SC group compared with 2733 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).

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 m2 (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 enrollment. 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.

Subcutaneous formulation (1600 mg) for chronic lymphocytic leukaemia
In the SAWYER study, the geometric mean Ctrough values at Cycle 5 (pre-dose Cycle 6) were higher among the MabThera SC group than the MabThera 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 MabThera IV group (4088 μg•day/mL versus 3630 μg•day/mL respectively).

Intravenous formulation
Information in this section reports data from the separate Data Sheet for Mabthera IV formulation.

Distribution and elimination
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 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. This variability in V_1 (27.1% and 19.0%) contributed by the range in BSA (1.53 to 2.32 m^2) and concurrent CHOP therapy, respectively, were relatively small. Age, gender, race, and WHO 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 Cmax following the fourth infusion was 486 μg/mL (range 77.5 to 996.6 mcg/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 mcg/mL (range 16 – 582 mcg/mL) after the first infusion to 550 mcg/mL (range 171 – 1177 mcg/mL) after the eighth infusion.

The pharmacokinetic profile of rituximab when administered as 6 infusions of 375 mg/m2 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/m2 increased to 500 mg/m2 each cycle for 5 doses in combination with fludarabine and cyclophosphamide in CLL patients. The mean C_{max} (n = 15) was 408 mcg/mL (range, 97 – 764 mcg/mL) after the fifth 500 mg/m^2 infusion.

Pharmacokinetics in special populations
No pharmacokinetic data are available in patients with hepatic or renal impairment.

5.3 Preclinical safety data

Developmental toxicity studies performed in cynomolgus monkeys revealed no evidence of embryotoxicity in utero. New born offspring of maternal animals exposed to Mabthera were noted to have depleted B-cell populations during the post natal phase.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Mabthera SC 1400mg and 1600mg

vorhyaluronidase alfa
histidine
histidine hydrochloride
trehalose dihydrate
methionine
Polysorbate 80
Water for injections (pH adjusted to 5.5).

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

6.3 Shelf life
From a microbiological point of view, the solution should be used immediately. If not used immediately, preparation should take place in controlled and validated aseptic conditions. In-use storage times and conditions for the solution in the syringe prior to use are the

responsibility of the user and would normally not be longer than 48 hours at 2°C to 8°C and subsequent 8 hours at 30°C in diffuse daylight.

This medicine should not be used after the expiry date shown on the pack.

Mabthera SC 1400mg: 36 months shelf life (see section 6.4)

Mabthera SC 1600mg: 36 months shelf life (see section 6.4)

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Packs of 1:

- Single use 15mL vials containing 1400mg in 11.7mL
- Single dose 20mL vials containing 1600mg rituximab in 13.4mL

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Mabthera SC is a ready-to-use solution. The full contents of the vial should be drawn up into a syringe for subcutaneous injection for a single patient.

The needle which will be used for the SC injection must only be attached to the syringe immediately prior to administration to avoid potential needle clogging.

Mabthera SC does not contain an antimicrobial agent or preservative; therefore, care must be taken to ensure the sterility of the vials. Each vial and syringe should be used once only and any residue discarded.

Mabthera SC solution (once transferred from the vial into the syringe) is physically and chemically stable for 48 hours at 2°C to 8°C and subsequent 8 hours at 30°C in diffuse daylight.

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).

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Roche Products (New Zealand) Limited
PO Box 109113 Newmarket
Auckland 1149
NEW ZEALAND

Medical enquiries: 0800 276 243

9. DATE OF FIRST APPROVAL

25 June 2015 (Mabthera SC 1400mg/11.7mL)

13 July 2017 (Mabthera SC 1600mg/13.4mL)

10. DATE OF REVISION OF THE TEXT

1 February 2023

Summary of Changes Table

Section Changed	Summary of new information
4.6	Additional safety information on breast-feeding
5.1	Change of ATC code