Australian Government

Department of Health and Ageing

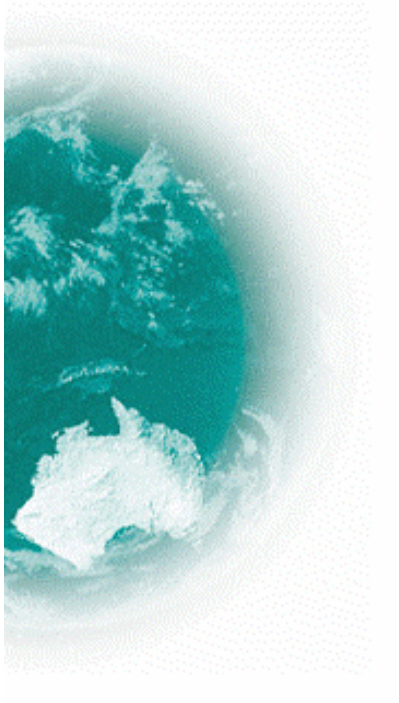
Therapeutic Goods Administration

Australian Public Assessment Report
for
Rituximab

Proprietary Product Name: MabThera

Submission No: PM-2009-00656-3-4

Sponsor: Roche Products Pty Ltd



February 2010

Contents

I. Introduction to Product Submission

Product Details

Type of Submission	Extension of Indications
Decision:	Approved
Date of Decision	8 January 2010
Active ingredient(s):	Rituximab
Product Name(s):	MabThera
Sponsor's Name and Address	Roche Products Pty Ltd 4-10 Inman Road Dee Why NSW 2099
Dose form(s):	Intravenous solution
Strength(s):	100 mg/10 mL and 500 mg/50 mL
Container(s):	Single-use vial
Pack size(s):	Pack of 1 - single-use vial containing concentrated solution for dilution and intravenous infusion 500 mg/50 mL Packs of 2 - single-use vials containing concentrated solution for dilution and intravenous infusion 100 mg/10 mL
Approved Therapeutic use:	for the treatment of patients with CD20 positive chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.
Route(s) of administration:	Intravenous
Dosage:	The recommended dosage in combination with chemotherapy is 375 mg/m^2 administered on day 1 of the first treatment cycle followed by 500 mg/m^2 administered on day 1 of each subsequent cycle, for a total of 6 cycles

Product Background

MabThera has been registered in Australia since 1998 and is currently registered for the following indications:

- treatment of patients with CD-20 positive, previously untreated, Stage III/IV follicular, B-cell non-Hodgkin's lymphoma,
- treatment of patients with CD-20 positive, relapsed or refractory low grade or follicular, B-cell non-Hodgkin's lymphoma,
- treatment of patients with CD-20 positive, diffuse large B-cell lymphoma in combination with chemotherapy,
- in combination with methotrexate to reduce signs and symptoms in adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to at least one tumour necrosis factor (TNF) antagonist therapy.

The drug causes a marked decline in peripheral blood B lymphocytes. Recovery in lymphocyte count begins approximately 6 months after completing treatment and takes 3-6 months. The median

elimination half-life of rituximab is 22 days, range 6-52 days. Major adverse reactions are hypersensitivity, immunosuppression, viral infection and pulmonary effects. Pre-medication with an analgesic and an antihistamine is recommended.

In this application Roche Products Pty Ltd is seeking to register an additional indication for MabThera (rituximab) for the treatment of patients with relapsed/refractory chronic lymphocytic leukaemia (CLL). Currently MabThera is approved for the first line treatment of patients with CLL. With this submission the sponsor is seeking to add relapsed/refractory patients to the proposed first line indication.

In addition, and separate to the extension of indication outlined above, the sponsor also seeks to amend the Product Information but this consideration will not be discussed in the current AusPAR.

Regulatory Status at the Time of Submission

The product received initial ARTG Registration in 1998.

A similar application, with a similar dataset, has been approved in the European Union (21 August 2009), New Zealand (27 August 2009) and Switzerland (22 June 2009) as well as in Iceland and Norway. An application has been submitted in the US (15 May 2009) and Canada (16 January 2009) where it is under evaluation.

Product Information

The approved product information current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The antibody is a glycosylated IgG1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences (Fab domain) and human constant region sequences (Fc domain). Rituximab is composed of 1,328 amino acids and has an approximate molecular weight of 144 kD.

Rituximab has a high binding affinity for the CD20 antigen of 5.2 to 11.0 nM.

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

Drug Product

MabThera is a sterile, clear, colourless, preservative-free, concentrated solution for intravenous (IV) infusion.

MabThera is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated in 7.35 mg/mL sodium citrate buffer containing 0.7 mg/mL polysorbate 80, 9.0 mg/mL sodium chloride and sterile water for injection. The pH is adjusted to 6.5 with sodium hydroxide or hydrochloric acid.

Quality Summary and Conclusions

There was no requirement for a quality evaluation in an application of this type.

III. Non-Clinical Findings

Non-Clinical Summary and Conclusions

There was no requirement for a non-clinical evaluation in an application of this type.

IV. Clinical Findings

Introduction

The clinical development program to support registration of rituximab for treatment of patients with CLL consisted of one pivotal study comparing fludarabine and cyclophosphamide (FC) to rituximab in combination with fludarabine and cyclophosphamide (R-FC) in patients with relapsed/refractory chronic lymphocytic leukaemia (CLL) (study BO17072 or REACH).

This application to obtain a marketing authorisation for rituximab in combination with chemotherapy for the treatment of patients with relapsed/refractory CLL was also supported by additional information from a number of phase II studies and by one retrospective cohort analysis published as papers in peer-reviewed journals or as abstracts at recent international oncology conferences (American Society of Clinical Oncology [ASCO] or American Society of Hematology [ASH]).

Overall, a total of 8 publications on phase II studies and one historical comparison, including between them more than 460 patients who received rituximab in combination with chemotherapy, provided data relevant to assessing efficacy and safety of rituximab used in combination with various therapies in patients with relapsed/refractory CLL. Ideally, full clinical study reports (CSR) evaluating different chemotherapy regimens should be submitted in support of a marketing authorisation application for rituximab in combination with chemotherapy for patients with relapsed/refractory CLL; however, due to the heterogeneity in the choice of chemotherapy for second/third-line treatment of this disease, the initiation of multiple company sponsored trials in this setting using different chemotherapy regimens in combination with rituximab was not considered feasible at the time the registration program was designed. Trials evaluating rituximab in combination with chemotherapy regimens other than FC were mostly initiated by independent national leukaemia groups. The majority of these studies evaluated nucleoside analogue based therapies (such as fludarabine), which are currently considered the most effective induction regimens in CLL.

In addition to study BO17072, supportive efficacy data from the following studies in patients with recurrent/refractory CLL were provided:

- A phase II study of efficacy, toxicity and tolerability of R-FC [Ref 8597], and a retrospective comparison [8599] of three sequential groups of patients with recurrent/refractory CLL treated with fludarabine (F) alone, FC or R-FC (including 143/177 patients of the phase II study by Wierda e tal. [8597]).
- A randomised phase II study of fludarabine, cyclophosphamide and mitoxantrone, with and without rituximab (R ± FCM) [8626].
- A single-arm phase II study investigating rituximab in combination with pentostatin and cyclophosphamide (R-PC) [8627].
- A single-arm phase II study of rituximab in combination with pentostatin, cyclophosphamide and mitoxantrone (R-PCM) [8628].
- A randomised phase II study of rituximab plus cladribine, with or without cyclophosphamide (R-Cl ±C) [8629].
- A single-arm, multicenter phase II study of rituximab in combination with bendamustine (R-B) [8630].
- A single-arm, multicentre phase II study of rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) in patients with fludarabine-refractory CLL or CLL with autoimmune haemolytic anaemia or Richter's transformation [8631].

- A retrospective study investigating salvage therapy following failure or relapse after R-FC chemo-immunotherapy as initial treatment for patients with CLL [8814].

Pharmacokinetics

There were no pharmacokinetics data submitted with the application.

Pharmacodynamics

There were no pharmacodynamics data submitted with the application

Efficacy

Pivotal Study BO17072 was a randomised (1:1), multicentre, open-label, comparative, parallel group, two-arm study of R-FC versus FC in patients with relapsed/refractory CD20-positive CLL (according to NCI IWGG criteria). Patients randomised to the FC arm were scheduled to receive 6 cycles of FC chemotherapy (fludarabine [25 mg/m^2] and cyclophosphamide [250 mg/m^2] intravenously (IV) on days 1, 2 and 3 of each cycle) at intervals of 28 days. Patients randomised to the R-FC arm received FC in combination with rituximab (375 mg/m^2 IV on day 1 of cycle 1 [with FC on days 2-4], and 500 mg/m^2 on day 1 of cycles 2-6 [with FC on days 1-3]). Placebo/sham infusions of rituximab were not given for practical reasons and because of the difficulty maintaining a blind in the face of probable infusion-related reactions with rituximab.

Patients were randomly assigned to treatment groups through a central randomisation process, with patients stratified according to country, previous treatment, time from first diagnosis and β2-microglobulin. The study design chosen for study BO17072 was similar with regards to treatment regimens, response assessments and inclusion/exclusion criteria to a large, randomised phase III study in 817 patients with previously untreated CLL (ML17102).

The primary objective of study BO17072 was:

- To demonstrate a clinically relevant statistical superiority in progression free survival (PFS) with rituximab when used in combination with fludarabine and cyclophosphamide (R-FC) compared with fludarabine and cyclophosphamide alone (FC) for the treatment of previously treated patients with CLL.

Secondary objectives of study BO17072 were:

- To evaluate and compare, in each study arm, event free survival (EFS), disease free survival (DFS) in complete response (CR) patients, duration of response and overall response rate (ORR), (CR, nodal partial response [nPR], partial response [PR])
- To determine and compare overall survival (OS) for each study arm
- To evaluate and compare the proportion of patients with molecular remission
- To evaluate and compare the safety profile of patients treated with the combination of R-FC versus FC
- To characterise the pharmacokinetics of rituximab, fludarabine and cyclophosphamide
- To evaluate the relationship between various baseline markers and clinical outcome parameters in a subset of patients in each study arm
- To analyse pharmacoeconomics (medical resource utilisation) in both treatment arms
- To assess quality of life (QoL) in the two treatment arms.

From a total of 571 patients screened, 552 patients were enrolled and randomised: 276 patients per arm. Only 19 patients did not meet screening criteria and this was due mainly to their first line treatment which made them ineligible for the study.

Patients were recruited at 88 centres in 17 countries: Australia, Belgium, Canada, Denmark, France, Hungary, Italy, Netherlands, New Zealand, Norway, Poland, Romania, Russia, Spain, Sweden, UK, USA. The majority of the patients were enrolled in France (87 patients, 16% of the total), Russia (78 patients, 14%), Poland (74 patients, 13%) and Canada (56 patients, 10%). All other countries recruited between 16 and 36 patients (3%-7% of the total) apart from Sweden, the US and Norway, where 6 (1%), 2 (< 1%) and one (< 1%), patient were recruited, respectively. The first patient was randomised on July 31, 2003 and the last on August 10, 2007.

A total of 6 randomised patients (4 patients FC, 2 patients R-FC) did not receive any study treatment. In the FC arm, 3 patients refused treatment, and 1 patient did not meet one of the entry criteria (had more than one previous line of chemotherapy). In the R-FC arm, one patient became ill before receiving any treatment, and the other patient had violations of entry criteria (creatinine clearance and neutrophil count). A slightly lower number of patients in the FC arm than in the R-FC arm completed 6 cycles of treatment, 167 FC versus 181 R-FC, and fewer patients in the FC arm than in the R-FC arm are still being followed for progression and survival (overall 96 patients in 7 patients in R-FC).

The Intention-to-Treat (ITT) population included all 552 randomised patients, 276 patients in each treatment arm. All efficacy statistical outputs described in this report are based on the ITT population.

The per Protocol (PPS) population consisted of all patients who received at least 3 cycles of randomised treatment and patients who terminated treatment before 3 cycles because of progression or death. Patients in this analysis population were to have at least one complete post-baseline tumour/disease assessment during or after treatment and no major protocol violation. A total of 458 patients were included in the PPS population, 223 on FC (81% based on ITT) and 235 (85% based on ITT) on R-FC.

The safety population (SAP) included all patients who had received at least one dose of trial treatment, whether withdrawn prematurely or not, who had at least one safety follow-up (N=546). A total of 6 patients (4 on FC, 2 on R-FC) were excluded from the SAP, because they did not receive any study medication. No patient randomised to FC received R-FC or vice versa. However, 3 patients in the FC arm received rituximab (non-study treatment) as treatment for autoimmune complications after commencement of FC. These patients were kept in the FC arm for the SAP analyses.

Patient demographic characteristics were well balanced across the two treatment arms. The overall study population comprised more male than female patients (67% versus 33%, respectively) as would be expected in a CLL patient population, and had a median age of 63 years. The majority of patients (57%) were below the age of 65 years, 26% were 65 and 70 years old, 17% were > 70 years old. The majority of patients were Caucasian, a reflection of the countries in which the study was conducted.

Both treatment arms were well balanced with respect to disease stage and Eastern Cooperative Oncology Group (ECOG) status. At baseline, 10% of patients had Binet stage A disease, the majority of patients (59%) had Binet stage B disease and 31% had Binet stage C disease. At pre-therapeutic staging, 60% of patients had an ECOG performance status of 0, 40% of patients had an ECOG of 1. Slightly more patients in the FC arm than in the R-FC arm had B symptoms at baseline (31% FC versus 26% R-FC).

The median time from first diagnosis was nearly 4 years, as would be expected in patients with CLL, a disease that generally follows a chronic course. Time from diagnosis was similar in the two treatment arms; FC median 3.7 years (range 0.1-23.4 years) and R-FC median 3.8 years (range 0.1-25.2 years). At the time of the first diagnosis, 138 patients [50%] in the FC group and 132 patients

[48%] in the R-FC group had Binet stage A disease. The median time from last progression was 1.64 months (range 0.1-46.2 months) for the FC arm and 1.61 months (range 0-28.9 months) for the R-FC arm.

At baseline, more patients in the FC arm (83/274 [30%] versus 66/275 patients [24%] in the R-FC arm) had hepatomegaly. At baseline, the majority of patients in both groups had splenomegaly (175/275 [64%] FC versus 191/274 [70%] R-FC). In both arms, 20/276 patients (7%) had extranodal disease and 21/276 (8%) had bulky disease. The baseline haematology values were well balanced between both treatment arms.

Most patients in each treatment group were recorded to have a previous or concurrent disease (84% FC versus 83% R-FC) in addition to CLL. The types and frequencies of diseases were similar in the two treatment arms.

Patients were categorised by the investigator at study entry according to their response/resistance to prior therapy and these categories were used for stratification. Overall, the use of anti-CLL treatment prior to study entry was balanced between the treatment arms. The majority of patients (56%) were classified as alkylator-sensitive by the investigator, 26% were classified as alkylator refractory, 16% as having received prior fludarabine, and 1% as having received sequential fludarabine and alkylating agents.

The majority of patients (452/552 [82%]) had had prior monotherapy: 363/552 patients (66%; 178 patients [32%] R-FC, 185 patients [34%] FC) had been treated with chorambucil, cyclophosphamide or another alkylating agent (including bendamustine and prednimustine) and 87/552 patients (16%; 40 patients [7%] R-FC, 47 patients [9%] FC) had been treated with fludarabine, cladribine or both. Only 100/552 patients (18%; 58 patients [10%] R-FC, 44 patients [8%] FC) had had prior multi-agent chemotherapy, including 14/552 (2.5%) who had been treated with fludarabine/cladribine combinations and 88/552 (16%) who had been treated with “other” agents.

Efficacy Variables

Primary Variable: Progression-free survival (PFS)

Secondary Variables: Event free survival, disease free survival in complete response (CR) patients, duration of response, overall response rate (CR, nodal partial response [nPR], partial response [PR]), overall survival (OS), proportion of patients with molecular remission.

Efficacy Results

Progression-free Survival

The primary efficacy analysis was based on a non-stratified, two-sided log-rank test of investigator assessed PFS. Progression-free survival was determined for the ITT population and for the PPS population. A tabular summary of results is provided in Table 1.

Table 1: Study BO17072 - Summary of Composition of Progression-free Survival Events (ITT, Investigator Assessment)

	FC N=276 No. (%)	R-FC N=276 No. (%)
Total number of events	158 (57.2%)	132 (47.8%)
Death	25 (9.1%)	30 (10.9%)
Progression	133 (48.2%)	102 (37.0%)

PFS - day of randomization until first documented disease progression, or death from any cause - investigator assessment

At the time of the analysis (clinical cut-off date of July 23, 2008), approximately 9% more patients in the FC arm than in the R-FC arm had experienced an event (progression or death; 158 patients [57%] on FC versus 132 patients [48%] on R-FC). More patients in the FC arm than in the R-FC arm had a progression as a first PFS event (48% FC versus 37% R-FC), whereas slightly more patients in the rituximab containing arm had died (9% FC versus 11% R-FC).

The addition of rituximab to the FC regimen significantly prolonged the median PFS when compared to the FC regimen alone (p=0.0002, Log-Rank test). The Kaplan-Meier estimated median PFS was 20.6 months (627 days) with FC and 30.6 months (932 days) with R-FC. The risk of having a PFS event (progression or death, whichever occurred first) was statistically significantly decreased by 35% (unadjusted HR = 0.65; 95% CI: 0.51, 0.82; p=0002, Wald test) for patients in the rituximab arm compared to the FC arm. Forty-four percent of the patients in the FC arm, and 60% of those in the R-FC arm, were progression-free at two years using Kaplan-Meier estimates. The Kaplan-Meier curves for duration of PFS show a separation of the curves already at the first time progression was assessed, ie approximately 3 months after study start.

The results of the analysis of PFS based on the PPS were consistent with the ITT analysis and demonstrated that the risk of progression was reduced by 38% (unadjusted HR = 0.62; 95% CI: 0.48, 0.81) compared to the FC arm.

Overall Survival

A tabular summary of results for overall survival (OS) is provided in Table 2. At the time of the analysis (clinical cut-off July 23, 2008), a total of 130 randomised patients had died: 68 patients (25%) in the FC arm and 62 patients (23%) in the R-FC arm. The median survival time was 1580 days (51.9 months) for patients in the FC arm and could not be estimated for patients in the R-FC arm. Treatment with R-FC reduced the risk of death by 17% when compared to FC alone, a difference which was not statistically significant (unadjusted HR 0.83; 95% CI: 0.59, 1.17; p = 0.2871, Wald test). At clinical cut-off, the data were still relatively immature, with the majority of patients still alive in both treatment arms.

The Kaplan-Meier curves for FC and R-FC overlap for a period of about 30 months (900 days), after which the curves start to separate with better survival for patients in the R-FC arm than in the FC arm. This is in contrast to the effects on PFS where the benefits of rituximab were seen already at 3 months, an important benefit in patients whose time without additional treatment may be as important as OS.

Overall survival was also analysed in the PPS population. In this population, treatment with R-FC reduced the risk of death by 27% when compared to FC alone, which was statistically not significant (unadjusted HR 0.73; 95% CI: 0.50, 1.06; p = 0.0986, Wald test).

Table 2: Study BO17072 - Summary of Overall Survival (ITT, Non-stratified Analysis)

	FC (N=276)		R-FC (N=276)
Patients with event	68 (24.6 %)		62 (22.5 %)
Patients without events*	208 (75.4 %)		214 (77.5 %)
Time to event (days)			
Median#	1580.0		.
95% CI for Median#	[1408;.]		[1552;.]
25% and 75%-ile	921;.		1117;.
Range##	1 to 1703		8 to 1720
p-Value (Log-Rank Test)		0.2874	
Hazard Ratio		0.83	
95% CI		[0.59;1.17]	
p-Value (Wald Test)		0.2871	
2 years duration			
Number left	141		154
Event Free Rate#	0.82		0.82
95% CI for Rate#	[0.77;0.87]		[0.77;0.87]

Days From Randomization To Event/Censoring (OS) (TTOS) - Censoring: Event (OS) (CSOS)
* censored
# Kaplan-Meier estimate
including censored observations

OS - day of randomization until death from any cause. Censoring occurs at date of last contact
2 years duration is defined as 728 days.

Overall Response Rates

Two categories of response rates were calculated for each patient, best overall response (BOR) and end of treatment response (ETR). Best overall response considers response at any time and allows for the sometimes slow recovery of cytopenias after fludarabine-based therapy. This response category is provided in this section.

The proportion of patients with a response (CR/(n)PR) was significantly higher in the RFC arm (69.9%) compared to the FC arm (58.0%, p=0.0034, Chi-square test) and this was mostly due to a significantly higher CR rate (13.0% FC versus 24.3% R-FC, p=0.0007, Chi-square test). Results are summarised in Table 3. Forty patients (14.5%) in the FC group and 29 patients (10.5%) in the R-FC group had a BOR of 'not evaluable'. Most of these patients were considered not evaluable because they had no response assessment documented at all or no response assessment documented before initiation of an alternative treatment for CLL (31 patients FC, 21 RFC). The remaining patients (9 in the FC arm, 8 in the R-FC arm) were considered non-evaluable because they had an unconfirmed PR.

Table 3: Study BO17072 - Summary of Best Overall Response (ITT, Investigator Assessment)

	FC (N=276)		R-FC (N=276)
Responders$	160 (58.0 %)		193 (69.9 %)
Non-Responders	116 (42.0 %)		83 (30.1 %)
95% CI for Response Rates*	[51.9; 63.9]		[64.1; 75.3]
Difference in Response Rates		11.96	
95% CI for Difference in Response Rates#		[3.8; 20.1]	
p-Value (Chi-squared Test)		0.0034	
Odds Ratio		1.69	
95% CI for Odds Ratio		[1.19;2.40]	
Complete Response (CR)	36 (13.0 %)		67 (24.3 %)
95% CI for CR Rates*	[9.3; 17.6]		[19.3; 29.8]
Difference in CR Rates		11.23	
95% CI for Difference in CR Rates#		[4.6; 17.9]	
p-Value (Chi-squared Test)		0.0007	
Odds Ratio		2.14	
95% CI for Odds Ratio		[1.37;3.34]	
Partial Response (PR and nPR)	124 (44.9 %)		126 (45.7 %)
95% CI for PR and nPR Rates*	[39.0; 51.0]		[39.7; 51.7]
Difference in PR and nPR Rates		0.72	
95% CI for Difference in PR and nPR Rates#		[-7.8; 9.2]	
p-Value (Chi-squared Test)		0.8642	
Odds Ratio		1.03	
95% CI for Odds Ratio		[0.74;1.44]	
Stable Disease (SD)	61 (22.1 %)		47 (17.0 %)
95% CI for SD Rates*	[17.3; 27.5]		[12.8; 22.0]
Progressive Disease (PD)	15 (5.4 %)		7 (2.5 %)
95% CI for PD Rates*	[3.1; 8.8]		[1.0; 5.2]
Missing (not evaluable)	40 (14.5 %)		29 (10.5 %)

Value Of RSBOR But nPR Recoded To PR (RSBOR2)

BOR - best overall response based on investigator response assessment.
* 95% CI for one sample binomial using Pearson-Clopper
# Approximate 95% CI for difference of two rates using Hauck-Anderson method
$ Patients with best overall response of CR, PR or nPR

A robustness analysis considering patients with missing/not evaluable BORs as complete responders for both arms was performed. In this analysis, the proportion of patients with a PR or CR was higher in the R-FC arm than in the FC arm (80.4% and 72.5%, respectively). This treatment difference was statistically significant (p=0.0273, Chi-squared Test).

Minimal residual disease (MRD) assessment was only scheduled in patients achieving a CR in this study. As a result, information on molecular response in blood is available for only a limited number of patients (FC 32/276 [12%]; R-FC 37/276 [13%]), because of the relatively low CR rate in this study. Of the patients with available information, the percentage of patients who achieved a high quality response (MRD-negative) in blood was lower in patients who had received FC compared with patients who had received RFC (31% FC vs 43% R-FC).

Secondary Time to Event Endpoints

The following secondary time to event endpoints based on the investigator assessment had been pre-specified in the protocol and were analysed in study BO17072:

- Event-free survival, defined as time to disease progression, relapse, death or start of a new CLL treatment
- Duration of response (assessed in patients with a BOR of CR or PR)
- Disease-free survival (DFS), defined as the interval from first documented BOR of CR to disease progression or death
- Time-to-new-CLL treatment (defined as time to death or start of a new CLL treatment).

The median time to event was significantly increased for patients in the rituximab containing arm compared to patients in the FC arm for almost all secondary endpoints with the exception of DFS, as summarised in Table 4. The lack of difference in DFS between the treatment arms suggests that patients with relapsed/refractory CLL who achieve a CR have a similar outcome, regardless of how the CR was achieved. Although the duration of CR was similar in the two arms, nearly twice as many patients in the R-FC arm achieved a CR.

Table 4: Study BO17072 - Summary of Secondary Endpoints (ITT)

	FC N=276	R-FC N=276
Event-free survival		
median	19.3 months	28.7 months
p-value (Log-Rank)	0.0002	
unadjusted HR (95% CI)	0.64 (0.51; 0.81)	
Duration of response		
n	160	193
median	27.6 months	39.6 months
p-value (Log-Rank)	0.0252	
unadjusted HR (95% CI)	0.69 (0.50; 0.96)	
Disease-free survival[1)]		
n	36	67
median	42.2 months	39.6 months
p-value (Log-Rank)	0.8842	
unadjusted HR (95% CI)	1.06 (0.49; 2.28)	
Time to new CLL treatment		
median	34.2 months	nr
p-value (Log-Rank)	0.0024	
unadjusted HR (95% CI)	0.65 (0.49; 0.86)	

[1)] Only Patients with a BOR of CR were included in this analysis
Abbreviations: nr, not reached. For other abbreviations see Glossary of Abbreviations

More patients in the FC arm than in the R-FC arm started a new treatment for CLL subsequent to study treatment (25% on FC versus 17% on R-FC). Out of 69 patients in the FC arm who relapsed

and received subsequent therapy, 49% received rituximab as part of the subsequent treatment. Out of 47 patients in the R-FC arm who relapsed and received subsequent therapy, 30% received rituximab as part of the subsequent treatment.

Quality of Life

A quality of life (QoL) assessment using FACT-G was collected over a one year period with assessments at screening, 3 months, 6 months, and 6 months after the end of treatment. The FACT-G is a questionnaire which assesses physical well-being, social and family well-being, emotional well-being, and functional well-being. The maximum score on FACT-G is 112. In the BO17072 study, the initial scores at screening (median 79.5 and 80.0 in the FC and R-FC arms respectively) were high and these did not change substantially over the study period.

Progression-free Survival in Subgroups of Patients with Relapsed/Refractory Chronic Lymphocytic Leukaemia

In the pivotal study BO17072, results of the PFS subgroup analyses were consistent with the results seen in the overall ITT population. The risk of disease progression or death was reduced in the R-FC arm compared to the FC arm in almost all of the 48 subgroups analysed. Only the subgroup of patients who received treatment 10 years from first diagnosis (unadjusted HR = 1.02; 95% CI: 0.52, 1.99), and the subgroup of patients with negative CD38 at baseline (unadjusted HR = 1.04; 95% CI: 0.67, 1.64), had a hazard ratio >1.0. In all other subgroups, the risk of disease progression or death was reduced with a risk reduction ranging from 1% (for patients > 70 years old) to 80% (for patients who were ZAP70+ and had mutated IgVH). In most of the subgroups analysed, the risk reduction ranged between 40% and 60% and point estimates (not adjusted) were below 1 indicating a clinical benefit for R-FC. Importantly, the risk of progression or death was reduced in patients with and without del17p (del17p being a poor prognostic marker and associated with treatment resistance) and in all Binet stages. Compared with the FC regimen, R-FC reduced the risk of disease progression or death by 25% in 55 patients with Binet stage A disease, by 35% in 326 patients with Binet stage B disease, and by 39% in 171 patients with Binet stage C disease**.**

Supportive Efficacy Data

Phase II study of R-FC in Patients with Relapsed/Refractory Chronic Lymphocytic Leukaemia Treated at the MD Anderson Cancer Centre and a Retrospective Comparison with Other Fludarabine-Treated Patients

In a phase II study by Wierda et al., 177 previously treated patients with CLL were treated with up to 6 cycles of rituximab (375 mg/m^2 day 1 of cycle 1 followed by 500 mg/m^2 on day 1 of cycles 2 to 6) in combination with FC. The median age of patients was 59 years. Most of the patients (97%) had intermediate to high-risk disease using the modified Rai staging criteria.[1] Most of the patients

[1] A staging system is a standardized way to summarize information about how far a cancer has spread. There are 2 different systems for staging CLL:

- Rai system: This is used more often in the United States.
- Binet system: This is used more widely in Europe.

The Rai system divides CLL into 5 stages: **Rai stage 0:** The blood lymphocyte count is too high, usually defined as over 10,000 lymphocytes/mm^3 of blood (this is called lymphocytosis). Some doctors will diagnose CLL if the count is over 5,000/mm^3 and the cells all have the same chemical pattern on special testing). The lymph nodes, spleen, and liver are not enlarged and the red blood cell and platelet counts are near normal. Rai stage I: Lymphocytosis plus enlarged lymph nodes. The spleen and liver are not enlarged and the red blood cell and platelet counts are near normal. **Rai stage II:** Lymphocytosis plus an enlarged spleen (and possibly an enlarged liver), with or without enlarged lymph nodes. The red blood cell and platelet counts are near normal. **Rai stage III:** Lymphocytosis plus anemia (too few red blood cells), with or without enlarged lymph nodes, spleen, or liver. Platelet counts are near normal. **Rai stage IV:** Lymphocytosis plus thrombocytopenia (too few blood platelets), with or without anemia, enlarged lymph nodes, spleen, or liver.

(82%) had received F alone or in combination with other cytotoxic agents as prior treatment; 18% had only received therapies with alkylating agents. Twelve percent had received prior rituximab either alone or in combination with chemotherapy.

Efficacy Results

Complete response was achieved in 25% of patients, and nodular partial remission and partial remission were achieved in 16% and 32% of patients, respectively. The overall response rate (ORR) was 73%. Twelve (32%) of the 37 complete responders tested also achieved a molecular remission in the bone marrow.

Overall, the R-FC regimen was an active and well-tolerated treatment for previously treated patients with CLL. Molecular remissions were achieved in a third of patients achieving CR.

One hundred and forty-three patients were included in a retrospective comparison with two non-overlapping sequential groups of patients enrolled in phase II studies who had received treatment with F alone (n=251 patients) or FC (n=111 patients). The objective of this retrospective sequential group analysis was to determine whether apparent improvements in treatment of patients with relapsed/refractory CLL had an impact on survival. Patients who were treated with R-FC had a higher complete remission rate compared with patients who were treated with FC or with F alone. In this retrospective cohort analysis, a longer estimated median survival was noted for patients who received R-FC, which was considered statistically significant. A Cox proportional hazards, multivariable model for OS that included all patients (n=505) showed that patients who received R-FC had longer survival compared to patients who received F or FC (relative risk = 0.5; $p<0.0001$) after adjusting for other significant pre-treatment characteristics ($p=0.05$), including age, haemoglobin, β2-microglobulin, and number of prior treatments.

The results of this retrospective comparison of patients with recurrent and refractory CLL indicated a higher complete remission rate and the longest estimated survival for patients who were treated with R-FC.

Rituximab in Combination with Fludarabine, Cyclophosphamide and Mitoxantrone

In a randomised phase II study, Hillmen et al. compared the efficacy and safety of FCM (fludarabine [24 mg/m^2 orally for 5 days] and cyclophosphamide [150 mg/m^2 orally for 5 days] plus mitoxantrone [6 mg/m^2 IV] on Day 1 of each cycle) with FCM in combination with rituximab (identical doses of FCM plus rituximab on Day 1 of each cycle [375 mg/m^2 cycle 1; 500 mg/m^2 cycles 2 to 6]) in patients with relapsed CLL.

The primary endpoint was response according to National Cancer Institute (NCI) criteria, 2 months after therapy. Complete remission with incomplete marrow recovery (CR(i)) was defined according to the NCI-Working Group 2007 CLL Guidelines, ie clinical CR with a morphologically normal marrow but persistent cytopenias (that is, platelets $<100x10^9$/L and/or neutrophils $<1.5x10^9$/L). In addition, minimal residual disease (MRD) in the marrow was studied 2 months after therapy by four-colour flow cytometry with MRD negativity defined as <0.01% CLL cells.

Forty-six patients were included in the efficacy and safety analyses, 23 in each arm. The median age was 65 (range 32-79) years. Seventy-nine percent were men. Forty-two percent had a β2-microglobulin >4 mg/L. The median number of prior therapies was 2 (range 1-6), 31 had prior

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For practical purposes, the Rai stages can be separated into low-, intermediate-, and high-risk groups when determining treatment options. Stage 0 is considered low risk; Stages I and II are considered intermediate risk; Stages III and IV are considered high risk.

fludarabine and 6 (12%) were refractory to or relapsed <6 months after fludarabine. A total of 26/44 patients (59%) had unmutated IgVH genes (15/22 R-FCM; 11/22 FCM). Eleven patients had tumour cells with the chromosomal aberration del11q (R-FCM 5, FCM 6) and one patient in the R-FCM arm had >20% tumour cells with del17p. Thirty-six of 52 patients (69%) received 4 or more cycles of therapy, with no difference between FCM and R-FCM (18/26 per arm).

Efficacy Results

In 46 evaluable patients, the overall response rate was 57% in the FCM arm (4% CR, 9% CR(i), 44% partial response [PR]) and 70% in the R-FCM arm (17% CR, 26% CR(i), 27% PR). R-FCM was an effective therapy for patients with relapsed CLL in this trial with over two-thirds of patients responding. The study was not powered to show a statistically significant difference between FCM and R-FCM, but the results suggest that adding rituximab to FCM results in a higher CR rate (CR + CR(i) = 43% for R-FCM and 13% for FCM) with more patients achieving MRD negativity (5 after R-FCM; 2 after FCM).

Study Investigating Rituximab in Combination with Pentostatin and Cyclophosphamide

Lamanna et al. treated 46 patients with either previously treated CLL (32 patients) or other low-grade B-cell neoplasms (14 patients). Patients received (in order of administration): pentostatin 4 mg/m^2, cyclophosphamide 600 mg/m^2 and rituximab 375 mg/m^2 (R-PC). All drugs were administered on the same day (rituximab was omitted in cycle 1), and patients received six cycles at 3-week intervals. Filgrastim, sulfamethoxazole/trimethoprim, and acyclovir were administered prophylactically. The patients' median age was 62 years (range, 30 to 80 years). The median number of prior regimens was two (range, one to seven).

Efficacy Results

For the 32 patients with CLL, there were 24 responses (75%), including eight CRs (25%). In fludarabine-refractory patients, 75% responded. The investigators felt that rituximab did appear to confer a survival advantage.

Study Investigating Rituximab in Combination with Pentostatin, Cyclophosphamide and Mitoxantrone

Another study by Lamanna et al. combined pentostatin 4 mg/m^2, cyclophosphamide 600mg/m^2, rituximab 375 mg/m^2 (omitted from cycle 1), and mitoxantrone (dose starting at 6 mg/m^2, and escalating to 8 mg/m^2, and 10 mg/m^2), all administered on day 1 of 28-day cycles for a total of 6 treatment cycles. Supportive measures included prophylactic administration of pegfilgrastim, sulfamethoxazole/trimethoprim, acyclovir, and antiemetics.

Twenty-one patients (median age 62 years, range 44-74) with CLL (17 patients) or other low grade B cell neoplasms (4 patients) were enrolled. There were 16 men and 5 women. Of the CLL patients, all had either high risk disease (Rai stage 3 or 4, 71%) or "active" intermediate risk disease (Rai stage 1 or 2, 29%). Their median pre-treatment white blood cell (WBC) count was 74,000/μL, haemoglobin 9.9 g/dL, and platelets 144,000/μL. The median β2-microglobulin value was 3.3 mg/L. The median number of prior treatment regimens was two (range 1-6). Most of the CLL patients (65%) had previously been treated with chemo-immunotherapy, using R-PC or R-FC.

Efficacy Results

Response data was available for 16/17 of the CLL patients at the time of reporting. In this group, there were 15 responses (94%), including 4 CRs (25%) and 11 PRs (69%). Prior therapy with R-PC or R-FC did not adversely affect the frequency of response, with 91% of these patients responding

(CR in 19% and PRs in 73%). These preliminary results indicate that R-PCM therapy is very active even in patients who have previously received R-FC or R-PC.

Study Investigating Rituximab in Combination with Cladribine with or without Cyclophosphamide

The aim of the study by Robak et al. was to determine the feasibility, effectiveness and toxicity of combined regimens consisting of rituximab and cladribine (R-Cl), and R-Cl plus cyclophosphamide (R-ClC), in the treatment of patients with recurrent or refractory CLL. The R-Cl regimen consisted of rituximab given on day 1 and cladribine (0.12mg/kg/d IV days 2–6). The R-ClC protocol included rituximab (day 1), cladribine (0.12 mg/kg/d IV days 2–4) and cyclophosphamide (250mg/m^2 IV) given on days 2–4. The courses were readministered at time intervals of 4 weeks or longer if severe myelosuppression occurred. Patients were to be treated until maximum response or prohibitive toxicity was observed.

Forty-six patients with CLL entered the study. Seventy-two percent of patients had relapsed disease and 28% were refractory to prior therapy. The median number of prior regimens was two. Eighteen patients were treated with R-Cl and 28 with R-ClC regimen. The median number of cycles administered was three (range 1–6).

Efficacy Results

Three patients (6.5%; 95% CI 1–14%) achieved a CR and 31 patients (67%; 95% CI 50–83%) a PR, for an ORR of 74%. Twelve of the patients (67%; 95% CI 45–89%) treated with R-Cl responded (ORR 67%; 95% CI 45–89%) and 22 of the patients (78%; 95% CI 62–93%) treated with R-ClC (ORR 78%; 95% CI 62–93%). Overall, after a median observation time of 16 months, the median PFS of responders to the two regimens was 12 months (range 4–46 months).

These data indicate that both R-Cl and R-ClC regimens are feasible in heavily pre-treated patients with CLL. These two regimens show distinct therapeutic activity and relatively low toxicity, even in patients previously treated with cladribine-based regimens.

Study Investigating Rituximab in Combination with Bendamustine

In the phase II study by Fischer et al., the efficacy and toxicity of bendamustine in combination with rituximab (R-B) was investigated in patients with relapsed/refractory B-CLL. 81 patients with relapsed/refractory B-CLL and a median number of 2 prior re-treatments were enrolled into this study. Bendamustine was given at a dose of 70 mg/m^2 on day 1 and 2, combined with 375 mg/m^2 rituximab for the first cycle and 500 mg/m^2 for the second and subsequent cycles. R-B treatment was administered every 28 days for up to 6 cycles. Blood samples were taken for molecular cytogenetics by fluorescence in situ hybridization (FISH), analysis of the IgVH, mutational status, and expression of ZAP70/CD38.

Efficacy Results

Data on all 81 patients (with a median age 66 years) and a total of 328 treatment cycles were available. A mean of 4.5 courses of treatment were administered. There was notable toxicity with 123 reported common toxicity criteria (CTC) grade 3/4 AEs, particularly myelosuppression and infections.

A total of 62 patients were evaluable for response. Nineteen patients were not evaluable for response due to withdrawal of or missing consent, violation of entry criteria or early discontinuation of therapy. The ORR was 77.4% with a CR rate of 14.5% (9 patients) and a PR rate of 62.9% (39 patients). No molecular remission was observed in bone marrow by 4-color flow cytometry. Stable disease (SD) was achieved in 11 patients (17.7%) and 3 patients (4.8%) had progressive disease (PD). Responses were observed in the majority of patients with genomic aberrations del11q (ORR: 12/13, 92.3%) and trisomy 12 (ORR: 8/8, 100%), but only 4/9 patients with del17p had a PR (ORR: ,44.4%). Twenty-nine of 39 patients (74.4%) with unmutated IgVH status were responsive to R-B.

Overall, based on these data, the authors considered R-B to be an effective regimen in patients with relapsed/refractory B-CLL. However, major but tolerable treatment toxicities were seen, notably myelosuppression and infections.

Study Investigating Rituximab in Combination with Cyclophosphamide, Doxorubicin, Vincristine and Prednisone

Eichhorst et al. evaluated the tolerability and efficacy of R-CHOP in patients with CLL who were refractory to fludarabine, or who had auto-immune haemolytic anaemia (AIHA) or Richter's transformation (transformation to a more aggressive haematological malignancy, usually diffuse large B-cell lymphoma [DLBCL]). This was a multicentre, phase II trial from the German CLL Study Group (GCLLSG) (who also conducted the pivotal ML17102 study in patients with previously untreated CLL).

Thirty-four patients with advanced disease (Binet stage B and C) were enrolled in this trial. The patients had a mean age of 66 years (range 40 – 78 years). They started treatment with CHOP therapy, consisting of cyclophosphamide (750 mg/m^2 IV), doxorubicin (50 mg/m^2 IV) and vincristine (1.4 mg/m^2 IV) on day 1, plus prednisolone 100mg/m^2 for five days orally. From the second treatment cycle, 375 mg/m^2 rituximab was given on day 0 if the leukocyte count was less than 50,000/μL. The R-CHOP regimen was then repeated every 21 days for up to 6 courses total in patients with CLL and up to 8 courses in patients with Richter's transformation. Anti-infective prophylaxis with acyclovir and sulfamethoxazole/trimethoprim was recommended for all patients.

Nineteen patients with fludarabine-refractory CLL, 7 patients with AIHA, and 4 patients with Richter's transformation were included. Disease status was unknown in 4 patients. By August 1, 2005 data from 25 patients (17 fludarabine-refractory, 5 patients with AIHA, and 3 with Richter's transformation) and 102 treatment courses were available. 72% of the patients were Binet stage C. The mean number of previously administered treatments was 2.1. Forty-eight percent of the patients had received 3 prior treatments.

Efficacy Results

Seventeen patients were evaluable for response and 12 of these responded. No complete remission was documented. Nine of the 13 fludarabine-refractory patients responded to treatment. Two evaluable patients with AIHA also had a partial remission. The haemoglobin level improved in these patients after 6 courses R-CHOP and the Coombs test became negative in one patient. Overall, 6 patients had died at the time of reporting (4 patients with fludarabine-refractory CLL, and one patient each with AIHA and Richter's transformation), two of them due to infectious complications, and 4 patients because of PD. These preliminary data suggested that R-CHOP is a very effective regimen for poor risk patients with CLL.

Retrospective Cohort Analysis of a Variety of Salvage Therapies Following Failure or Relapse after R-FC Therapy

Keating et al have described the results of salvage therapy in patients treated with first line R-FC at the MD Anderson Cancer Centre (MDACC). Seventy-nine of the original 300 patients who received first line R-FC, received second line therapy after disease relapse/progression. The median age was 59 years and 70% were male. Most patients (56%) had high risk disease according to Rai stage.

Efficacy Results

Median TTF after R-FC in the first line setting was 31 months. Thirty-six patients had CR, 10 patients had nodular partial response (nPR), 14 patients had PR (14 pts), and 7 patients had failed treatment. A range of salvage therapies was used including rituximab monotherapy (3 patients), rituximab plus methylprednisolone (5 patients), rituximab plus granulocyte-macrophage colony

stimulating factor (GMCSF) (10 patients), rituximab plus alemtuzumab (11 patients), R-FC plus alemtuzumab (8 patients), and R-FC +/- lumiliximab (18 patients – the number of patients who received R-FC alone was not specified).

The ORR to first salvage therapy (49%; 15% CR, 10% nPR, 24% PR; n=79 patients) was lower than the ORR to first line R-FC in the overall patient population (94%; 72% CR, 10% nPR, 12% PR; n=300 patients). It was also lower than the initial response to first line R-FC in the group of 79 patients who received salvage treatment (71%; 43% CR, 11% nPR, 17% PR). The response rate to R-FC +/- lumiliximab was 61% including 1 CR (6%), and the response rate to R-FC + alemtuzumab was 88% including 4 CRs (50%). An initial (first line) response to R-FC of CR or nPR, Rai stage, and β2-microglobulin significantly predicted response to first salvage therapy. Median survival after first salvage therapy was 30 months. Duration of initial (first line) R-FC response, β2-microglobulin level and Rai stage predicted survival but the salvage regimens did not.

Response to second salvage therapy was also reported for 44 patients. In this setting, the best results were reported for allogeneic stem cell transplant (7 of 10 patients achieved a CR). However, not all patients are suitable for allogeneic stem cell transplant or have a suitable donor. For patients who did not receive an allogeneic stem cell transplant, the best results reported were for rituximab plus alemtuzumab (2/3 patients responded including one CR), R-FC + alemtuzumab (4/5 patients responded including 3 CRs) and R-FC alone (5/6 patients responded including 1 CR).

Summary

The results of the pivotal study BO17072 demonstrated statistically significant and clinically meaningful benefit when rituximab is used in combination with FC chemotherapy in patients with relapsed/refractory CLL. The primary endpoint of PFS (investigator assessed) was prolonged by a median of 10 months and the risk of disease progression or death was reduced by 35% when rituximab was added to the FC regimen. Significantly more patients in the R-FC arm than in the FC arm responded to therapy, and this was mostly due to a significantly higher CR rate.

These results were supported by published literature from a total of 8 studies involving more than 480 previously treated patients treated with rituximab in combination with a range of chemotherapy regimens. In these supportive studies, high response rates of 65% were achieved. A retrospective cohort analysis comparing R-FC with FC or F alone demonstrated an OS benefit for the cohort treated with rituximab-containing therapy compared to the cohorts treated with chemotherapy alone and this difference was considered by the authors to be medically (and statistically) significant.

Subgroup analyses on the primary endpoint (PFS) in the pivotal study BO17072 demonstrated a consistent treatment effect across almost all the pre-specified subgroups analysed.

Overall, the evaluator considered that the efficacy data presented for evaluation adequately support the indication for treatment of patients with CLL as proposed by the sponsor.

Safety

Safety data for the proposed indication in CLL is mainly based on data from the pivotal phase III study BO17072. The 8 investigator-sponsored studies reported limited safety information.

Study BO17072

A total of 552 patients were enrolled and randomised in the study. The safety population of study BO17072 consisted of 546 patients (272 patients in the FC arm, 274 patients in the R-FC arm) who received at least one dose of at least one component of the study medication.

In the R-FC arm, more patients received six cycles of therapy compared to the FC arm (67.5% [185/274] in R-FC, 61.4% [167/272] in FC). Most patients stopped treatment early for safety reasons; and the number of discontinuations due to safety reasons was balanced between the two

arms. More patients in the FC arm withdrew from study treatment due to PD or patient refusal. More patients in the FC arm had stable disease after 3 cycles (92 patients in FC vs 73 patients in R-FC) and proportionally more of these stopped treatment (19 patients in FC vs 9 patients in R-FC) for this reason compared with the R-FC arm.

At the time of the clinical cut-off (July 23, 2008), the median observation time for the safety analysis population (SAP) was 25.6 months (24.2 months in FC arm and 27.2 months in R-FC). An overview of the safety data reported in this study with a clinical cut-off date of July 23, 2008 is shown in Table 5.

Table 5: Study BO17072 - Overview of Adverse Event (AE) Experience

	FC N = 272 No. of patients (%)	**R-FC N = 274 No. of patients (%)**
Any adverse events	260 (96%)	270 (99%)
Grade 3/4 AEs	200 (74%)	219 (80%)
Serious Adverse Events	130 (48%)	137 (50%)
Fatal AEs	26 (10%)	36 (13%)
AE leading to dose modification/interruption	105 (39%)	141 (51%)
AE leading to treatment discontinuation	69 (25%)	72 (26%)
Total deaths	68 (25%)	62 (23%)
Treatment-related deaths	14 (5%)	19 (7%)

Common Adverse Events

Almost all patients experienced at least one adverse event (AE) (96% in FC, 99% in R-FC). However, the majority of events (70% in FC; 71% in R-FC) were Grade 1/2 in severity. Overall, patients in the R-FC arm experienced more AEs than patients in the FC arm (1468 AEs in FC, 1797 AEs in R-FC), mostly due to AEs in the following system organ classes (SOCs):

- vascular disorders (4% patients in FC vs 17% of patients in R-FC experienced at least one AE)
- general disorders (46% patients in FC vs 54% in R-FC experienced at least one AE),
- respiratory, thoracic and mediastinal disorders (21% patients in FC vs 28% in R-FC experienced at least one AE)
- skin and subcutaneous tissue disorders (25% patients in FC vs 31% in R-FC experienced at least one AE)
- metabolism and nutrition disorders (9% patients in FC vs 15% in R-FC experienced at least one AE).

Adverse events in the following system organ classes (SOCs) also had a slightly higher incidence in the R-FC than in the FC arm:

- musculoskeletal and connective tissue disorders (18% FC vs 22% R-FC)
- gastrointestinal disorders (55% FC vs 58% R-FC)
- blood and lymphatic system disorders (67% FC vs 70% R-FC)
- ear and labyrinth disorders (<1% FC vs 3% R-FC).

Grade 3 or 4 Adverse Events

The severity of AEs was graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. A tabular summary of Grade 3/4 events with an incidence of at least 1% is provided in Table 6.

Table 6: Study BO17072 - Grade 3/4 Adverse Events with an Incidence of at least 1% (SAP)

Body System/ Adverse Event	FC N = 272 No. (%)	R-FC N = 274 No. (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
NEUTROPENIA	108 (40)	116 (42)
FEBRILE NEUTROPENIA	32 (12)	40 (15)
ANAEMIA	35 (13)	33 (12)
THROMBOCYTOPENIA	24 (9)	29 (11)
GRANULOCYTOPENIA	12 (4)	18 (7)
PANCYTOPENIA	13 (5)	9 (3)
LEUKOPENIA	7 (3)	10 (4)
AGRANULOCYTOSIS	6 (2)	7 (3)
ANAEMIA HAEMOLYTIC AUTOIMMUNE	5 (2)	2 (<1)
FEBRILE BONE MARROW APLASIA	2 (<1)	3 (1)
HAEMOLYTIC ANAEMIA	4 (1)	1 (<1)
APLASIA PURE RED CELL	1 (<1)	3 (1)
INFECTIONS AND INFESTATIONS		
PNEUMONIA	17 (6)	15 (5)
BRONCHITIS	3 (1)	5 (2)
SEPSIS	3 (1)	5 (2)
RESPIRATORY TRACT INFECTION	4 (1)	3 (1)
SEPTIC SHOCK	2 (<1)	5 (2)
HEPATITIS B	-	6 (2)
HERPES ZOSTER	3 (1)	3 (1)
INFECTION	3 (1)	3 (1)
NEUTROPENIC SEPSIS	4 (1)	1 (<1)
PNEUMOCYSTIS JIROVECI PNEUMONIA	3 (1)	1 (<1)
UPPER RESPIRATORY TRACT INFECTION	3 (1)	1 (<1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
PYREXIA	5 (2)	9 (3)
ASTHENIA	4 (1)	5 (2)
FATIGUE	3 (1)	2 (<1)
CHILLS	-	4 (1)
GASTROINTESTINAL DISORDERS		
VOMITING	4 (1)	4 (1)
DIARRHOEA	1 (<1)	5 (2)
NAUSEA	2 (<1)	4 (1)
VASCULAR DISORDERS		
HYPOTENSION	-	5 (2)
METABOLISM AND NUTRITION DISORDERS		
ANOREXIA	-	3 (1)

Investigator text for Adverse Events encoded using MedDRA version 11.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.

Overall, the proportion of patients reporting at least one Grade 3/4 AE was higher in the R-FC arm than in the FC arm (80% versus 74%), mostly due to an imbalance (2% difference) in the following SOCs:

- blood and lymphatic system disorders (60% patients in FC versus 65% in R-FC with at least one Grade 3/4 event)
- general disorders (6% patients in FC versus 8% patients in R-FC with at least one Grade 3/4 event) benign and malignant neoplasms (3% patients in FC versus 7% R-FC with at least one Grade 3/4 event)

- vascular disorders (1% patients in FC versus 4% patients in R-FC with at least one Grade 3/4 event)
- investigations (1% patients in FC versus 4% patients in R-FC with at least one Grade 3/4 event)
- metabolism and nutrition disorders (<1% patients in FC versus 3% patients in R-FC with at least one Grade 3/4 event).

The incidence of Grade 3/4 AEs in other SOCs (including infections and infestations) was balanced between the treatment arms. Grade 3/4 AEs which occurred with a 2% or higher incidence in the R-FC arm compared with the FC arm included (febrile) neutropenia, granulocytopenia and hepatitis B infections. It was proposed that this updated information be included in the Product Information (PI). Granulocytopenia has not previously been reported in the PI and it was proposed to report it in the "common" frequency grouping (1% <10%).

The incidence of thrombocytopenia in the R-FC arm of study BO17072 was slightly higher (1.8%) than in the FC arm. This event is already reported in the PI in the frequency grouping "common" and, based on the frequency observed in study BO17072, it was proposed that this be changed to "very common".

In study BO17072 hepatitis B infection was reported in 7 patients, and 5 experienced Grade 3/4 hepatitis B. It was proposed to report this event in the "common" frequency grouping in the PI.

Deaths

At the time of clinical cut-off (July 23, 2008), a total of 130 patients had died. There was a slightly higher number of deaths in the FC arm than in the R-FC arm (68 patients (25%) and 62 patients (23%), respectively). General disorders and administration site conditions, including progressive disease (PD), were the major cause of death in both treatment arms (18 patients (7%) in FC vs 17 patients (6%) in R-FC). Infections and infestations (including pneumonia, septic shock and sepsis) were responsible for the deaths of 19 patients (7%) in the FC arm and 14 patients (5%) in the R-FC arm. Fourteen patients died due to cardiac disorders (6 patients (2%) in FC, 8 patients (3%) in R-FC).

The investigator considered 14 deaths (5%) in the FC arm and 19 deaths (7%; including one death due to Stevens-Johnson syndrome [probably related to cefotaxime] and one death from Hodgkin's disease/CLL transformation) in the R-FC arm related to treatment. Of the 33 patients who died from infections and infestations, 16 deaths were considered to be related to study treatment (3% [7/272] in FC vs 3% [9/274] in R-FC).

Serious Adverse Events (SAEs)

Overall, a slightly higher incidence of SAEs was observed in the R-FC arm (130 patients [48%] in FC; 137 patients [50%] in R-FC with at least one serious adverse event [SAE]). A slight increase in incidence of febrile neutropenia was observed in the R-FC arm (11%) compared to the FC arm (8%), while there was a higher incidence of anaemia (reported as an SAE) in the FC arm (4% in FC vs 1% in R-FC). An equal number of patients in each arm (54 patients [20%]) experienced an SAE categorised under infections and infestations; however SAEs of hepatitis B infection occurred uniquely in the R-FC arm (5 patients).

Thirty-six percent (36%) of the patients in the FC arm experienced at least one treatment-related SAE compared to 39% of patients in the R-FC arm. This difference was driven by a higher incidence of general disorders in the R-FC arm: 14 events versus 6 events in the FC arm (mainly pyrexia). An increase in incidence of serious febrile neutropenia was observed in the R-FC arm (8% FC vs 11% R-FC). Most of these cases (8% FC vs 9% R-FC) were considered related to treatment.

A higher incidence of serious anaemia was noted in the FC arm (4% FC vs 1% R-FC). All of these cases were considered related to treatment.

Twenty-six patients in the FC arm experienced a fatal SAE, 14 of which were considered related to treatment, compared to 36 patients in the R-FC arm, 19 of which were considered related to treatment.

Adverse Events Leading to Treatment Discontinuation, Dose Modifications or Interruptions

Overall, findings were consistent with known manifestations of rituximab-related infusion-related reactions and the haematological effects of rituximab when used in combination with chemotherapy.

The proportion of patients who discontinued treatment due to AEs was similar between the treatment arms (69 pts [25%] in FC, 72 pts [26%] in R-FC). The most common AEs that led to treatment discontinuation were blood and lymphatic system disorders (19% in FC, 17% in R-FC), such as neutropenia (7% in FC, 5% in R-FC) and thrombocytopenia (4% in each arm), and infections and infestations (5% in each arm).

Adverse events leading to dose modifications or interruptions were reported more often in the R-FC arm than the FC arm (39% patients in FC, 51% patients in R-FC). The most common reasons for dose modifications or interruptions in the two arms were blood and lymphatic system disorders (26% in FC, 23% in R-FC), and infections and infestations (10% in each arm).

More patients in the R-FC arm had the dose modified or interrupted because of general disorders and administration site conditions (4% in FC, 14% in R-FC), gastrointestinal disorders (1% in FC, 7% in R-FC), vascular disorders (none in FC, 6% in R-FC), skin and subcutaneous tissue disorders (< 1% in FC, 5% in R-FC), cardiac disorders (none in FC, 3% in R-FC) and immune system disorders (none in FC, 3% in R-FC).

Adverse Events by Organ System or Syndrome

Infusion-related Reactions

Sixty-one percent of the patients in the R-FC arm reported at least one AE that started during or within 24 hours of finishing a rituximab infusion, most frequently events of the SOCs “general disorders and administration sites” and “GI disorders”. Eleven percent of the patients reported at least one Grade 3/4 and 4% experienced an SAE during or within 24 hours of finishing a rituximab infusion. No AE that started during or within 24 h of a rituximab infusion had a fatal outcome.

The incidence of AEs occurring on the first day or the next day of a treatment cycle was higher in the R-FC arm than in the FC arm (48% of patients in FC vs 64% of patients in R-FC with at least one event). There was an increased incidence of typical rituximab infusion-related reactions (pyrexia, chills, pruritus, urticaria, etc) in the R-FC arm. The highest rate of Grade 3/4 AEs reported on the day of, or the day after the start of therapy occurred in the first treatment cycle in both arms. In both arms, the number of patients with Grade 3/4 AEs gradually decreased over subsequent cycles with only 1% of patients experiencing a Grade 3/4 AE on the day of or the day after the start of therapy in Cycle 6.

Tumour Lysis Syndrome

Nine patients (3%) in the FC arm versus 6 patients (2%) in the R-FC arm had probable or definite tumour lysis syndrome (TLS). In 7 of these patients (5 in FC, 2 in R-FC), the events were serious and in 4 patients, the SAE resulted in or substantially contributed to the patient’s death (2 in FC, 2 in R-FC). These data are similar to results reported in patients with previously untreated CLL.

Blood and Lymphatic System Disorders

As expected in a leukaemia study, there was a high incidence of (all Grade) blood and lymphatic system disorders in both arms (67% in FC, 70% in R-FC). This high incidence of AEs was mainly driven by events of anaemia, thrombocytopenia and white blood cell disorders. A higher proportion of patients in the R-FC arm experienced Grade 3/4 AEs (179 patients (65%) in R-FC vs 164 patients (60%) in FC), mainly due to more events (2%-3% difference) of Grade 3/4 neutropenia, thrombocytopenia, febrile neutropenia and granulocytopenia in the R-FC arm compared to the FC arm. No patient in the R-FC arm experienced an event leading to death. These data are similar to those obtained in previously untreated patients in study ML17102.

Neutropenia

The incidence of Grade 3/4 neutropenia and granulocytopenia was higher in the R-FC arm (91% and 87%, respectively) compared to the FC arm (85% and 71%, respectively). This was consistent with the higher incidence of Grade 3/4 neutropenia, febrile neutropenia and granulocytopenia, reported as AEs in the R-FC arm (42%, 15% and 7%, respectively) compared to the FC arm (40%, 12% and 4%, respectively).

Thrombocytopenia

The incidence of thrombocytopenia in the R-FC arm of study BO17072 was slightly higher than in the FC arm (11% versus 9% for Grade 3/4 AEs; 28% vs 24% for Grade 3/4). One patient experienced acute reversible thrombocytopenia which appeared to be an unusual form of rituximab infusion-related reaction.

Infections

The incidence of infections and infestations was similar in both treatment groups (51% [139/272] patients in FC versus 49% [135/274] in R-FC). Apart from a slightly higher incidence of bacterial infections in the FC arm (4%) compared to the R-FC arm (2%), the number of incidents reported and the type of infections and infestations were comparable in the two treatment groups. Similarly, the incidence of Grade 3/4 infections (including opportunistic infections) was comparable in the two treatment arms (19% FC vs 17% RFC); however, the incidence of Grade 3/4 hepatitis B was higher in the R-FC arm than in the FC arm (0 patients in FC vs 5 patients in R-FC).

Second Malignancies

Overall, 40 patients experienced 44 AEs classified as neoplasms (17/272 [6%] in FC; 23/274 [8%] in R-FC). When second malignancies were analysed further, results suggested that rituximab is unlikely to play a contributory role to the secondary malignancies reported in CLL patients.

Safety Analysis by Patient Age

The proportion of patients experiencing at least one event of any Grade, and Grade3/4 AEs increased with age in both arms of study BO17072. In the age category < 65 years, the higher proportion of SAEs in the FC arm was driven by an increased incidence of serious blood and lymphatic system disorders (22% in FC, 16% in R-FC) as well as infections (16% in FC, 11% in R-FC). In the category 65 - 70 years, more serious infections (18% in FC, 31% in R-FC), blood and lymphatic system disorders (7% in FC, 26% in R-FC), and neoplasms (7% in FC, 11% in R-FC) were observed in the R-FC arm compared to the FC arm.

Summary

Data from study BO17072 showed that there were no unexpected safety concerns when previously treated CLL patients were treated with R-FC. Rituximab in combination with FC was generally well tolerated and the majority of patients in both arms received the scheduled six cycles of therapy. The

proportion of patients who discontinued therapy due to an AE was similar in the two treatment arms.

The incidence of all Grade AEs, Grade 3/4 AEs and SAEs was slightly higher in the R-FC arm. The frequency and severity of AEs tended to be higher in older patients. The number of patients experiencing an AE with an outcome of death was higher in the R-FC than in the FC arm (13 % in R-FC versus 10% in FC). Most fatal AEs were due to infections and infestations.

As could be expected in a leukaemia trial, there was a relatively high but balanced occurrence of blood and lymphatic system disorders in the two arms of the study. However, there was a slightly higher rate of Grade 3/4 neutropenia, thrombocytopenia, febrile neutropenia and granulocytopenia in the R-FC arm.

The incidence of Grade 3/4 infections or infestations was comparable between the treatment arms.

In general, there were no unexpected safety signals observed during this study; however the incidence and severity of hepatitis B infections (primary infections and reactivation) was somewhat higher than expected. Also of note one patient did experience an acute reversible thrombocytopenia which appeared to be an unusual form of rituximab infusion-related reaction. In the Clinical Overview it was stated that there have been other similar cases reported in the literature.

Clinical Summary and Conclusions

In this application the sponsor is seeking to register an additional indication for MabThera (rituximab) for the treatment of patients with relapsed/refractory chronic lymphocytic leukaemia (CLL), and

Data to support the application to register MabThera for the treatment of relapsed/refractory CLL were based primarily on the full analysis of a randomised phase III study BO17072 (REACH), a trial investigating MabThera in combination with fludarabine and cyclophosphamide in patients with relapsed/refractory CLL.

Supportive efficacy and safety data from published phase II studies of rituximab in combination with a range of other cytotoxic therapies in patients with relapsed/refractory CLL were also included. Some of these studies were already included in the first line CLL dossier, previously submitted to the TGA.

The results of the pivotal study BO17072 demonstrated statistically significant and clinically meaningful benefit when rituximab is used in combination with FC chemotherapy in patients with relapsed/refractory CLL. The primary endpoint of PFS (investigator assessed) was prolonged by a median of 10 months and the risk of disease progression or death was reduced by 35% when rituximab was added to the FC regimen. Significantly more patients in the R-FC arm than in the FC arm responded to therapy, and this was mostly due to a significantly higher CR rate.

These results were supported by published literature from a total of 8 studies involving more than 480 previously treated patients treated with rituximab in combination with a range of chemotherapy regimens. In these supportive studies, high response rates of 65% were achieved. A retrospective cohort analysis comparing R-FC with FC or F alone demonstrated an OS benefit for the cohort treated with rituximab-containing therapy compared to the cohorts treated with chemotherapy alone and this difference was considered by the authors to be medically (and statistically) significant.

Subgroup analyses on the primary endpoint (PFS) in the pivotal study BO17072 demonstrated a consistent treatment effect across almost all the pre-specified subgroups analysed.

Overall, the evaluator considered that the efficacy data presented for evaluation adequately support the indication for treatment of patients with CLL as proposed by the sponsor and it was recommended that the application be approved with the indication proposed by the sponsor.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the Delegate's overview and recommendation.

Quality

There was no requirement for a quality evaluation in an application of this type.

Non-Clinical

There was no requirement for a non-clinical evaluation in an application of this type.

Clinical

There were no new pharmacodynamic or pharmacokinetic data.

In the pivotal efficacy trial (BO17072), a multicentre trial in 17 countries (Europe, Australia, New Zealand, USA), patients with relapsed or refractory CD20-positive CLL were randomised to receive either fludarabine and cyclophosphamide alone (FC) or with rituximab (R-FC). FC is one of several standard treatments[2]. Treatment cycles were 28 days and up to six cycles of treatment were given. Fludarabine 25 mg/m^2 IV and cyclophosphamide 250 mg/m^2 IV were given on days 1-3 of each cycle (days 2-4 in cycle 1 in the R-FC group). Rituximab IV was given before fludarabine and cyclophosphamide, at a dose of 375 mg/m^2 on day 1 in cycle 1 and 500 mg/m^2 on day 1 in cycles 2-6. The median age of subjects was 63 years (range 35-83), with most being male (67%).

Randomisation was stratified by response or resistance to previous therapy. Most subjects (56%) were alkylator-sensitive, 26% were alkylator-refractory, 16% had received fludarabine and 1% had received sequential alkylating agents and fludarabine. The trial was open-label. The primary endpoint was progression-free survival (PFS) assessed by the investigator.

The addition of rituximab significantly increased PFS by a median 10 months to 30.6 months in the intent-to-treat analysis (Table 7). There was a trend to increased overall survival with rituximab that was not statistically significant. There were similar results for PFS and overall survival in the per protocol analysis. Tumour response was significantly increased. Results for other endpoints except disease-free survival were supportive as were results for subgroups.

Table 7. Trial BO17072 – Results (Intent-to-Treat)

	FC n=276	**R-FC** n=276
Best Overall Response Rate	58.0%	69.9%
- Complete Response	13.0%	24.3%
- Partial Response	44.9%	45.7%
Difference from FC		12.0%
[95% CI]		[3.8%, 20.1%]
Chi-Square p value		

[2] Cancer Institute NSW: https://www.treatment.cancerinstitute.org.au/cancerinstitute/cancerinstituteDADAServlet?sid=883602CIS&page=0BENPC&gen=0

		0.0034
Progression-Free Survival median *mths* Hazard Ratio[1] vs FC [95% CI] Log-Rank p value	20.6	30.6 0.65 [0.51, 0.82] 0.0002
Overall Survival median *mths* Hazard Ratio[1] vs FC [95% CI] Wald p value	51.9	NR 0.83 [0.59, 1.17] 0.29

[1] unadjusted. NR – not reached.

A retrospective comparison of patients treated at the MD Anderson Cancer Centre in the USA supported the superior efficacy of R-FC over FC.

The use of rituximab in combination with other chemotherapy regimens for relapsed or refractory CLL was examined in seven literature reports (Table 8). In six reports, response rates were similar or greater than the 70% achieved for R-FC in the pivotal trial. Only one of the trials was controlled.

Table 8: Other Trials – Results

Trial	Regimen	No. Subj	PFS *median mths*	ORR (CR)
Hillmen	FCM[1] R-FCM[2]	23 23	ND ND	57% (43%) 70% (13%)
Lamanna 8627	R-PC[3]	32	ND	75% (25%)
Lamanna 8628	R-PCM[4]	16	ND	94% (25%)
Robak	R-Cl[5] R-ClC[6]	18 28	12 (4-46) for R-Cl + R-ClC	67% 78%
Fischer	R-B[7]	62	ND	77% (15%)
Eichhorst	R-CHOP[8]	17	ND	71% (0%)
Keating	Various[9]	79	30	49% (15%)

PFS: Progression-Free Survival, ORR: Overall Response Rate. CR: Complete Response Rate (including with incomplete marrow recovery – NCI-WG 2007 CLL Guidelines). ND – Not Done. F – Fludarabine. R – Rituximab. C – Cyclophosphamide. M – Mitoxantrone. P – Pentostatin. Cl – Cladribine. B – Bendamustine. CHOP – Cyclophosphamide, Doxorubicin (H), Vincristine (O) and Prednisolone.

[1] 4-week cycle for 6 cycles: F 24 mg/m^2 po days 1-5, C 150 mg/m^2 po days 1-5; M 6 mg/m^2 iv day 1.

[2] FCM as above plus R 375 mg/m^2 iv day 1, cycle 1 & 500 mg/m^2 iv day 1, cycle 2-6.

[3] 3-week cycle for 6 cycles: P 4 mg/m^2, C 600 mg/m^2 and R 375 mg/m^2 day 1 (R omitted from cycle 1).

[4] 4-week cycle for 6 cycles: R-PC doses as above plus M 6-10 mg/m^2 iv day 1.

[5] 4-week cycle for up to 6 cycles: R day 1 dose not stated, Cl 0.12 mg/kg/d iv days 2-6.

[6] 4-week cycle for up to 6 cycles: R day 1 dose not stated, Cl 0.12 mg/kg/d iv days 2-4, C 250 mg/m^2 iv days 2-4.

[7] 4-week cycle for up to 6 cycles: B 70 mg/m^2 days 1-2, R 375 mg/m^2 iv day 1, cycle 1 & 500 mg/m^2 iv day 1, cycle 2-6.

[8] 3-week cycle for up to 8 cycles: C 750 mg/m^2 iv, H 50 mg/m^2 iv and O 1.4 mg/m^2 iv day 1, Prednisolone 100 mg/m^2 po days 1-5, R 375 mg/m^2 iv day 1 from cycle 2.
[9] R monotherapy (3), R+methyprednisolone (5), R+GM-CSF (10), R+alemtuzumab (11), R-FC+alemtuzumab (8), R-FC±lumiliximab (18), unspecified (24).

The safety population of trial BO17072 consisted of 272 subjects in the FC arm and 274 in the R-FC arm who received at least one dose of at least one of the study drugs. The incidence of serious events was 48% in the FC group and 50% in the R-FC group and the incidence of grade 3/4 events 74% and 80% respectively. Adverse events leading to dose modification or interruption occurred in 39% of FC subjects and 51% of R-FC subjects.

Common grade 3/4 events were neutropenia, febrile neutropenia, anaemia, thrombocytopenia, granulocytopenia and pneumonia. The incidence of grade 3/4 neutropenia, febrile neutropenia, granulocytopenia and hepatitis B were higher by at least two percentage points with R-FC compared to FC. By systems, grade 3/4 blood and lymphatic, neoplastic, vascular, metabolism and nutrition, general and investigation abnormalities were higher by at least two percentage points with R-FC compared to FC.

Treatment-related death occurred in 5% of FC subjects and 7% of R-FC subjects. The most common cause of death was infection. The incidence of infection-related death was 3% in each group.

There were no safety data for the other trials.

The evaluator recommended approval.

Risk-Benefit Analysis

Rituximab in combination with fludarabine and cyclophosphamide (R-FC) significantly increased PFS in patients with relapsed or refractory CD20-positive CLL in a randomised controlled trial. There was a trend to increased overall survival. The data were limited and from literature for rituximab with other types of chemotherapy. Based on tumour response rates, rituximab is likely to improve efficacy when added to other chemotherapy.

The addition of rituximab to fludarabine and cyclophosphamide was associated with an increased incidence of severe and serious adverse events. However, the diminished safety is outweighed by the additional benefit of rituximab. There was a lack of safety data of rituximab with other chemotherapy combinations.

Similar data were presented for first line treatment of CLL, which the Australian Drug Evaluation Committee (ADEC) considered at its August 2009 meeting. In spite of the limited data for combinations other than R-FC, the ADEC did not think it necessary to restrict the indication to the R-FC combination. Several chemotherapy regimens are used in CLL and all appear equally effective. Therefore, it is appropriate to allow flexibility in the choice of chemotherapy for use with rituximab since it is likely that the addition of rituximab will enhance efficacy whatever the chemotherapy. In view of the minimal safety data for combinations other than R-FC, prescribers are advised in the product information to exercise caution and to review the toxicity of both rituximab and the chemotherapy drugs.

The Delegate recommended restricting the indication to CD20-positive CLL, the population in the pivotal trial. Rituximab was considered unlikely to be effective in CD20-negative disease.

The Delegate recommended approval for the following CLL indication, subject to finalisation of product information:

MabThera is indicated for the treatment of patients with <u>CD20 positive</u> chronic lymphocytic leukaemia in combination with chemotherapy.

The Australian Drug Evaluation Committee (ADEC), having considered the evaluations and the Delegate's overview, agreed with the Delegate's proposal.

In making this recommendation, the Committee noted that rituximab in combination with fludarabine and cyclophosphamide (R-FC) significantly increased PFS in patients with relapsed or refractory CD20-positive CLL in a randomised controlled trial. Furthermore, a trend to increased overall survival was also observed. The addition of rituximab to fludarabine and cyclophosphamide was associated with an increased incidence of severe and serious adverse events. However, the Committee determined that the diminished safety is outweighed by the additional benefit of rituximab.

Similar data were presented for first line treatment of CLL, which the ADEC considered at its August 2009 meeting. At that meeting, in spite of the limited data for combinations other than R-FC, the ADEC did not think it necessary to restrict the indication to the R-FC combination and considered that it was appropriate to allow flexibility in the choice of chemotherapy. Likewise, the ADEC did not think it necessary to restrict the indication to the R-FC combination in relapsed or refractory disease.

The Committee discussed the issue of patients who are carriers of hepatitis B and C and concluded that given the availability of sensitive laboratory diagnostics and emerging effective treatments with antivirals, chronic viral hepatitis does not warrant a contraindication for receiving MabThera. Additionally, the Committee noted that there are adequate precautionary statements concerning hepatitis B and C virus reactivation in the current product information.

Outcome

Based on review of quality, safety and efficacy data, TGA approved the registration of MabThera for injection vial containing rituximab 100mg/10mL and 500mg/50mL for the new indication

for the treatment of patients with CD20 positive chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.

Attachment 1. Product Information

MABTHERA®

Rituximab, recombinant for intravenous infusion (CAS registry number: 174722-31-7).

DESCRIPTION

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

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

MABTHERA is a sterile, clear, colourless, preservative-free, concentrated solution for intravenous infusion.

MABTHERA is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated in 7.35 mg/mL sodium citrate buffer containing 0.7 mg/mL polysorbate 80, 9.0 mg/mL sodium chloride and sterile water for injection. The pH is adjusted to 6.5 with sodium hydroxide or hydrochloric acid.

PHARMACOLOGY

Pharmacodynamics

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

In rheumatoid arthritis the putative mechanism of action of rituximab involves the depletion of surface antigen-positive B lymphocytes from synovial tissue, with downstream effects potentially including reduced activation of T-cells and the associated release of pro-inflammatory cytokines.

In Vitro Mechanisms of Action: The Fab domain of rituximab binds to the CD20 antigen on B-lymphocytes and the Fc domain recruits immune effector functions to mediate B-cell lysis.

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

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

In Vivo: In cynomolgus monkeys, four or eight weekly doses of 269 mg/m^2 of rituximab resulted in plasma concentrations of 161 to 386 µg/mL, approximately 24 hours after the first dose. Two weeks after the last dose, rituximab was still detected in the plasma of 3/6 monkeys treated for four weeks and in 4/6 monkeys treated for eight weeks.

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

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

In patients treated for haematological malignancies, B-cell recovery began at approximately six months following the completion of treatment. B-cell levels returned to normal between nine and twelve months following completion of treatment.

In patients with rheumatoid arthritis, the duration of peripheral B cell depletion was variable. The majority of patients who received further treatment did so prior to full B cell recovery.

Pharmacokinetics

Non-Hodgkin's Lymphoma

Pharmacokinetic studies performed in a Phase I study in which patients (N=15) with relapsed B-cell lymphoma were given single doses of rituximab at 10, 50, 100 or 500 mg/m² indicated that serum levels and half-life of rituximab were proportional to dose.

In a cohort of 14 patients among the 166 patients with relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma enrolled in the Phase III pivotal trial and given rituximab 375mg/m² as an IV infusion for 4 weekly doses, the mean serum half-life was 76.3 hours (range 31.5 to 152.6 hours) after the first infusion and 205.8 hours (range 83.9 to 407.0 hours) after the fourth infusion. The mean C_{max} after the first and fourth infusion were 205.6 ±59.9 µg/mL and 464.7 ±119.0 µg/mL, respectively. The mean plasma clearance after the first and fourth infusion was 0.0382 ±0.0182 L/h and 0.0092 ±0.0033 L/h, respectively. However variability in serum levels was large. Rituximab serum concentrations were statistically significantly higher in responding patients than in non-responding patients just prior to and

after the fourth infusion and post-treatment. Serum concentrations were negatively correlated with tumour burden and the number of circulating B-cells at baseline. Typically, rituximab was detectable for three to six months following completion of treatment.

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

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

Rheumatoid Arthritis
Following two intravenous infusions of rituximab at a dose of 1000 mg, two weeks apart, the mean terminal half-life was 20.8 days (range 8.58 to 35.9 days), mean systemic clearance was 0.23 L/day (range 0.091 to 0.67 L/day), and mean steady-state distribution volume was 4.6 L (range 1.7 to 7.51 L). Population pharmacokinetic analysis of the same data gave similar mean values for systemic clearance and half-life, 0.26 L/day and 20.4 days, respectively. Population pharmacokinetic analysis revealed that BSA and gender were the most significant covariates to explain inter-individual variability in pharmacokinetic parameters. After adjusting for BSA, male subjects had a larger volume of distribution and a faster clearance than female subjects. The gender- related pharmacokinetic differences are not considered to be clinically relevant and dose adjustment is not required. Following the intravenous administration of 500 and 1000 mg doses of rituximab on two occasions, two weeks apart, mean Cmax values were 183 μg/mL (range 81.8 to 279 μg/mL) and 370 μg/mL (212 to 637 μg/mL), and mean half-lives were 17.9 days (range 12.3 to 31.3 days) and 19.7 days (range 12.3 to 34.6 days), respectively. No pharmacokinetic data are available for patients receiving multiple courses of therapy. The pharmacokinetic parameters in the anti-TNF inadequate responder population, following the same dosage regimen (2 x 1000 mg IV, 2 weeks apart), were similar with a mean maximum serum concentration of 369 μg/mL and a mean terminal half-life of 19.2 days.

CLINICAL TRIALS

Non-Hodgkin's Lymphoma

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

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

In a subgroup analysis, the ORR was significantly higher in patients with IWF B, C, and D histological subtypes as compared to IWF A subtype (58% vs 12%) and in patients with prior

autologous bone marrow transplantation (ABMT) compared to those with no prior ABMT (78% vs 43%). Age, sex, lymphoma grade, years since initial diagnosis, presence or absence of bulky disease, normal or high LDH, or presence of extranodal disease did not have a significant effect (Fisher's exact test) on response to MABTHERA.

ORR was also significantly higher in patients with no bone marrow involvement compared to those with bone marrow involvement (59% vs 40%). This finding was not supported by a stepwise logistic regression analysis in which the following factors were identified as prognostic factors: histologic type, bcl-2 positivity at baseline, resistance to last chemotherapy and bulky disease.

Re-treatment

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

Bulky Disease

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

Clinical Laboratory Findings

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

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

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

Previously Untreated Follicular non-Hodgkin's Lymphoma

Combination with chemotherapy

In an open-label randomised study (M39021), a total of 322 previously untreated Stage III or IV follicular B cell NHL patients were randomised to receive either CVP chemotherapy

(cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1 –5) every 3 weeks for 8 cycles or MABTHERA 375 mg/m^2 in combination with CVP (R-CVP). MABTHERA was administered on the first day of each treatment cycle. A total of 321 patients (162 R-CVP, 159 CVP) received therapy and were analysed for efficacy.

The median follow-up of patients was 53 months. Addition of MABTHERA to CVP significantly increased time to treatment failure (the primary endpoint), tumour response, progression-free survival (PFS) and overall survival (OS) (Table 1).

Table 1 Summary of key results from study M39021

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

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

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

Table 2 Summary of key results from three phase III randomised studies evaluating the benefit of MabThera with different chemotherapy regimens in follicular lymphoma

Study	Treatment, n	Median follow up, months	ORR, %	CR, %	Outcome[1] (months)	OS rates, %
GLSG'00	CHOP, 205 R-CHOP, 223	18	90 96	17 20	Median TTF: 31.2 Not reached p<0.001	90 95 p=0.016
OSHO-39	MCP, 96 R-MCP, 105	47	75 92	25 50	Median PFS: 28.8 Not reached p<0.0001	74 87 p=0.0096
FL2000	CHVP-IFN, 183 R-CHVP-IFN, 175	42	85 94	49 76	Median EFS: 36 Not reached p<0.0001	84 91 p=0.029

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

Maintenance Therapy

In a prospective, open label, international, multicentre, Phase III trial, 465 patients with relapsed/refractory follicular NHL were randomised in a first step to induction therapy with either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone; n=231) or MABTHERA plus CHOP (R-CHOP, n=234), one dose of rituximab combined with each cycle of chemotherapy. The two treatment groups were well balanced with regard to baseline characteristics and disease status. A total of 334 patients achieving a complete or partial remission following induction therapy were randomised in a second step to MABTHERA maintenance therapy (n=167) or observation (n=167). MABTHERA maintenance treatment consisted of a single infusion of MABTHERA at 375 mg/m^2 body surface area given every 3 months until disease progression or for a maximum period of two years. Patients with hypogammaglobulinaemia (IgG <3g/L) or known HIV infection were excluded from the trial.

The final efficacy analysis included all patients randomised to both parts of the study. After a median observation time of 31 months for patients randomised to the induction phase, R-CHOP significantly improved the outcome of patients with relapsed/refractory follicular NHL when compared to CHOP (see Table 3).

Table 3 Induction phase: overview of efficacy results for CHOP vs R-CHOP (31 months median observation time)

	CHOP	R-CHOP	p-value	Risk Reduction[1)]
Primary Efficacy				
ORR[2)]	74%	87%	0.0003	NA
CR[2)]	16%	29%	0.0005	NA
PR[2)]	58%	58%	0.9449	NA
Secondary Efficacy				
OS (median)	NR	NR	0.0508	32%
PFS(median)	19.4 mo.	33.2 mo.	0.0001	38%

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

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

The median time to new anti-lymphoma treatment was significantly longer with MABTHERA maintenance treatment than with observation (38.8 months vs. 20.1 months, $p< 0.0001$ log-rank test). The risk of starting a new treatment was reduced by 50% (95% CI; 30%-64%). In patients achieving a CR/CRu (complete response unconfirmed) as best

response during induction treatment, MABTHERA maintenance treatment significantly prolonged the median disease free survival (DFS) compared to the observation group (53.7 vs 16.5 months, p=0.0003) log-rank test (Table 4). The risk of relapse in complete responders was reduced by 67% (95% CI; 39%-82%).

Table 4 Maintenance phase: overview of efficacy results MABTHERA vs. observation (28 months median observation time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Risk Reduction
	Observation (N=167)	MabThera (N=167)	Log-Rank p value	(95% CI)
Progression-free survival (PFS)	14.3	42.2	<0.0001	61% (45-72%)
Overall Survival	NR	NR	0.0039	56% (22-75%)
Time to new lymphoma treatment	20.1	38.8	<0.0001	50% (30-64%)
Disease-free survival[a]	16.5	53.7	0.0003	67% (39-82%)
Subgroup Analysis				
PFS				
CHOP	11.6	37.5	<0.0001	71% (54-82%)
R-CHOP	22.1	51.9	0.0071	46% (15-65%)
CR	14.3	52.8	0.0008	64% (33-81%)
PR	14.3	37.8	<0.0001	54% (33-69%)
OS				
CHOP	NR	NR	0.0348	55% (4-79%)
R-CHOP	NR	NR	0.0482	56% (-2-81%)

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

The benefit of MABTHERA maintenance treatment was confirmed in all subgroups analysed, regardless of induction regimen (CHOP or R-CHOP) or quality of response to induction treatment (CR or PR) (Table 3). MABTHERA maintenance treatment significantly prolonged median PFS in patients responding to CHOP induction therapy (median PFS 37.5 months vs 11.6 months, p< 0.0001) as well as in those responding to R-CHOP induction (median PFS 51.9 months vs 22.1 months, p=0.0071). Although analysed subgroups were small, and the median survival had not been reached after an overall median observation period of 47.2 months, a clinically meaningful benefit in terms of overall survival was observed for patients receiving MABTHERA maintenance treatment when compared to observation, in the overall population.

MABTHERA maintenance treatment provided consistent benefit in all subgroups tested [gender (male, female), age (≤ 60 years, > 60 years), stage (III, IV), WHO performance status (0 versus > 0), B symptoms (absent, present), bone marrow involvement (no versus yes), IPI (0-2 versus 3-5), FLIPI score (0-1, versus 2 versus 3-5), number of extra-nodal sites (0-1 versus > 1), number of nodal sites (< 5 versus ≥ 5), number of previous regimens (1 versus 2), best response to prior therapy (CR/PR versus NC/PD), haemoglobin (< 12 g/dL versus ≥ 12 g/dL), β_2-microglobulin (< 3mg/L versus ≥ 3 mg/L), LDH (elevated, not elevated) except for the small subgroup of patients with bulky disease.

Diffuse Large B-cell non-Hodgkin's Lymphoma

In a randomised, Phase III, open-label trial, a total of 399 previously untreated elderly ambulatory patients (age 60 to 80 years, ECOG performance status 0-2) with moderate to advanced (Ann Arbor stage II-IV) diffuse large B-cell lymphoma received standard CHOP chemotherapy (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisone 40 mg/m^2/day on days 1-5) every 3 weeks for eight cycles, or MABTHERA 375 mg/m^2 administered as an intravenous infusion plus CHOP (R-CHOP). MABTHERA was administered on the first day of the treatment cycle.

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

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

In all patient subgroups (gender, age, age-adjusted IPI, Ann Arbor stage, ECOG, Beta 2 Microglobulin, LDH, Albumin, B-symptoms, Bulky disease, extranodal sites, bone marrow involvement), the risk ratios for event-free survival and overall survival (R-CHOP compared with CHOP) were less than 0.83 and 0.95 respectively, although the benefit with R-CHOP was not always statistically significant.

A subsequent analysis of the duration of overall survival, carried out with a median follow-up duration of 60 months, confirmed the benefit of R-CHOP over CHOP treatment (p=0.0071), representing a risk reduction of 32%.

Chronic Lymphocytic Leukaemia (CLL)

In two open-label randomised studies, a total of 817 previously untreated patients and 552 patients with relapsed/refractory CLL were randomised to receive either fludarabine and cyclophosphamide (FC) chemotherapy (fludarabine 25 mg/m^2, cyclophosphamide 250 mg/m^2, days 1-3) every 4 weeks for 6 cycles or MABTHERA in combination with FC (R-FC). MABTHERA was administered at a dosage of 375 mg/m^2 during the first cycle one day prior to chemotherapy and at a dosage of 500 mg/m^2 on day 1 of cycles 2-6. A total of 810 patients (403 R-FC, 407 FC) from the first-line study (Table 5) and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study (Table 6) were analysed for efficacy.

In the first-line study, the primary endpoint of progression-free survival (PFS) was a median of 40 months in the R-FC group and a median of 32 months in the FC group (p<0.0001, log-rank test). The analysis of overall survival demonstrated improved survival in favour of the R-FC arm (p=0.0427), however longer follow-up is needed to confirm this observation. The benefit in terms of PFS was consistently observed in most patient subgroups analysed according to disease risk at baseline.

Table 5 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	R-FC vs FC [95% CI]
Progression-free survival	32.2	39.8	<0.0001	0.56 [0.43, 0.72]
Overall Survival	NR	NR	0.0427	0.64 [0.41, 1.00]
Response rate (CR, nPR, or PR)	72.7%	86.1%	<0.0001	NA
CR rates	17.2%	36.0%	<0.0001	NA

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

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

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

Table 6 Treatment of relapsed/refractory Chronic Lymphocytic Leukaemia – overview of efficacy results for MABTHERA plus FC vs. FC alone (25.3 months median observation time)

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

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

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

Rheumatoid Arthritis

The efficacy and safety of MABTHERA in alleviating the symptoms and signs of rheumatoid arthritis was demonstrated in three randomised, controlled, double-blind, multicentre studies.

Study 1 (REFLEX) was a double blind comparative study which included 517 patients that had experienced an inadequate response or intolerance to one or more TNF inhibitor therapies. Eligible patients had severe active rheumatoid arthritis, diagnosed according to the criteria of the American College of Rheumatology (ACR). The study population was comprised of adult patients aged ≥ 18 years with rheumatoid arthritis for at least 6 months who had experienced an inadequate response to previous treatment with an anti-TNF therapy. The primary endpoint was the percent of patients who achieved an ACR20 response at week 24. Patients received two 1000 mg IV infusions of MABTHERA, each following an IV infusion of 100 mg methylprednisone and separated by an interval of 15 days. All patients received concomitant oral methotrexate (10-25 mg/week) and 60 mg oral prednisone on days 2-7 and 30 mg on days 8-14 following the first infusion. Patients were followed beyond week 24 for long term endpoints, including radiographic assessment at 56 weeks. During this time patients may have received further courses of MABTHERA under an open label extension study protocol (see Radiographic Response).

Study 2 (DANCER) was a randomised, double-blind, double-dummy, controlled, 3 x 3 multifactorial study which compared two different dose levels of MABTHERA (2 x 1000 mg or 2 x 500 mg) given with or without one of two corticosteroid infusion regimens in combination with weekly methotrexate. All patients received concomitant oral methotrexate. The primary endpoint was the proportion of RF (Rheumatoid Factor) positive patients with an

ACR20 response at week 24. The study population was comprised of adult patients aged ≥ 18 years with rheumatoid arthritis who had previously failed 1-5 DMARDs and who currently had an inadequate response to methotrexate.

Study 3 was a double-blind, double-dummy, controlled study evaluating MABTHERA monotherapy, and MABTHERA in combination with either cyclophosphamide or methotrexate in patients with active rheumatoid arthritis who had not responded to one or more prior DMARDs. The primary endpoint was the proportion of patients with an ACR50 response at week 24. The study population was comprised of adult patients aged ≥ 21 years with rheumatoid arthritis who had failed 1-5 DMARDs, were rheumatoid factor seropositive at screening, and who currently had a partial clinical response to methotrexate monotherapy.

An ACR20 response was defined as at least a 20% improvement, compared to baseline, in both swollen and tender joint counts (SJC and TJC), as well as in 3 out of 5 additional parameters: physician's global assessment of disease activity, patient's global assessment of disease activity, patient's assessment of pain, Health Assessment Questionnaire Disability Index (HAQ-DI) and C-reactive protein (CRP).

The comparator drug in all three studies was weekly methotrexate (10-25 mg weekly).

Disease Activity Outcomes

In all three studies, MABTHERA 2 x 1000 mg + methotrexate (MTX) significantly increased the proportion of patients achieving at least a 20% improvement in ACR score compared with patients treated with MTX alone (Table 7). The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, body surface area, race, number of prior treatments or disease status.

Clinically and statistically significant improvement was also noted on all individual components of the ACR response (tender and swollen joint counts, patient and physician global assessment, disability index scores (HAQ), pain assessment and CRP (mg/dL).

Table 7 Cross-Study Comparison of ACR Responses at Week 24 (ITT Population)

	ACR Response	**Placebo+MTX**	**MABTHERA +MTX**
Study 1 REFLEX		(N=201)	(N=298)
	ACR20 ACR50 ACR70	36 (18%) 11 (5%) 3 (1%)	153 (51%)[1] 80 (27%)[1] 37 (12%)[1]
Study 2 DANCER		(N=143)	(N=185)
	ACR20 ACR50 ACR70	45 (31%) 19 (13%) 6 (4%)	96 (52%)[2] 61 (33%)[2] 28 (15%)[2]
Study 3		(N= 40)	(N= 40)
	ACR20 ACR50 ACR70	15 (38%) 5 (13%) 2 (5%)	28 (70%)[3] 17 (43%)[3] 9 (23%)[3]

[1] $p \leq 0.0001$; [2] $p \leq 0.001$; [3] $p < 0.05$

MABTHERA + MTX treated patients had a significantly greater reduction in disease activity score (DAS28) than patients treated with MTX alone. A good to moderate EULAR response

was achieved by significantly more MABTHERA + MTX treated patients compared to patients treated with MTX alone (Table 8).

Table 8 Cross-Study Comparison of DAS and EULAR Responses at Week 24 (ITT Population)

	Placebo+MTX	**MABTHERA +MTX 2 × 1g**
Study 1	(N=201)	(N=298)
Change in DAS28 [Mean (SD)]	-0.4 (1.2)	-1.9 (1.6)*
EULAR Response (%)		
None	78%	35%
Moderate	20%	50%*
Good	2%	15%
Study 2	(N= 143)	(N=185)
Mean change in DAS28 (SD)	–0.8 (1.4)	–2.0 (1.6)
EULAR response		
None	61%	37%
Moderate	35%	40%
Good	4%	23%
Study 3	(N=40)	(N=40)
Change in DAS [Mean (SD)]	-1.3 (1.2)	-2.6 (1.3)
EULAR response		
None	50%	18%
Moderate	45%	63%
Good	5%	20%

*p value <0.0001. p values not calculated for studies 2 and 3.

Radiographic Response

After week 24 of Study 1 (REFLEX) eligible patients could receive further courses of 2 x 1000 mg MABTHERA + MTX under an open-label extension protocol. In addition, from weeks 16 to 24 of Study 1 a rescue arm permitted patients receiving placebo and failing to respond to treatment to receive open-label therapy with 2 x 1000 mg MABTHERA + MTX. At any time from 16 weeks following rescue therapy eligible patients were then permitted to transfer to the open-label extension protocol and receive further courses of MABTHERA + MTX.

Radiographic assessments of patients receiving one or more treatment courses of MABTHERA + MTX were performed at week 56. Table 9 summarises the total number of patients providing radiographic data and their exposure to MABTHERA + MTX or placebo + MTX.

Table 9 MABTHERA exposure for Patients providing 56 week radiographic data*

No. of Treatment Courses of MABTHERA	**Placebo + MTX N=186 n (%)**	**MABTHERA + MTX N=277 n (%)**
Placebo only	36 (19.4)	NA
1	118 (63.4)	149 (53.8)
2	31 (16.7)	110 (39.7)
3	1 (<1)	18 (6.5)

* Of 517 patients treated in REFLEX, 18 were excluded from the ITT population due to: unblinding of treatment allocation (7 patients), QC check irregularities (5 patients) and treatment prior to allocation of a randomisation number (6 patients). A

further 36 patients were excluded either because no baseline scan was performed or the scan occurred outside the screening window, leaving 463 patients in the radiographic ITT population (186 placebo; 277 MABTHERA).

In Study 1, conducted in patients with inadequate response or intolerance to one or more TNF inhibitor therapies, structural joint damage was assessed radiographically and expressed as change in modified total Sharp score and its components, the erosion score and joint space narrowing score. Patients originally receiving MABTHERA + MTX demonstrated significantly less radiographic progression than patients originally receiving MTX alone at 56 weeks. Of the patients originally receiving MTX alone, 81% received MABTHERA either as a rescue between weeks 16-24 or in the extension trial, before week 56. A higher proportion of patients receiving MABTHERA also had no erosive progression over 56 weeks (Table 10).

Table 10 Radiographic mean changes over 56 weeks in Study 1

	Placebo + MTX	**MABTHERA + MTX 2 x 1 g**
Study 1	(N=184)	(N=273)
Total Sharp score	2.31	1.00 p=0.0046
Erosion Score	1.32	0.59 p=0.0114
Joint Space narrowing score	0.99	0.41 p=0.0006
Proportion of patients with no erosive progression over 56 weeks	52%	61% p=0.0494

Quality of Life Outcomes

MABTHERA + MTX treated patients reported an improvement in all patient-reported outcomes such as Health Assessment Questionnaire Disability Index (HAQ-DI), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and Short Form-36 (SF-36) questionnaires. Significant reductions in disability index (HAQ-DI), fatigue (FACIT-F) (Table 11), and improvement in both the physical and mental health domains of the SF-36 were observed in patients treated with MABTHERA + MTX compared to patients treated with MTX alone.

Table 11 HAQ and FACIT –F responses at Week 24 in Study 1

Week 24 response: Change from baseline	**Placebo+MTX[1]** **N=201** **mean (SD)**	**MABTHERA+MTX[1]** **N=298** **mean (SD)**	**p-value**
HAQ[2]	**-0.1 (0.5)**	**-0.4 (0.6)**	**<0.0001**
FACIT-F[3]	**-0.5 (9.8)**	**-9.1 (11.3)**	**<0.0001**

[1] MTX. [2] Health assessment questionnaire (HAQ), [3] Functional assessment of chronic illness therapy (FACIT-F)

At week 24, in all three studies, the proportion of MABTHERA + MTX treated patients showing a clinically relevant improvement in HAQ-DI (defined as an individual total score decrease of > 0.25) was higher than among patients receiving MTX alone.

Laboratory Evaluations

At the data lock date of 14 October 2005 a total of 1039 patients with active rheumatoid arthritis had received at least one or part of an infusion of MABTHERA, either as part of the pivotal trials or during an open-label extension protocol. Of 1039, 96 (9.2%) of patients tested positive for HACA (Human Anti-Chimeric Antibody). 5 patients developed HACA without

exposure to MABTHERA. The mechanism of development of HACA in these 5 patients is unknown. The emergence of HACA was not associated with clinical deterioration or with an increased risk of reactions to subsequent infusions in the majority of patients. The presence of HACA may be associated with worsening of infusion or allergic reactions after the second infusion of subsequent courses, and failure to deplete B cells after receipt of further treatment courses has been observed rarely.

In study 1 (REFLEX), 15/308 (4.8%) MABTHERA + MTX treated patients and 8/209 (3.8%) patients treated with methotrexate alone were anti-nuclear antibody (ANA) negative at day 1 and became ANA positive at week 16 and/or week 24. The adverse event profile in these patients did not provide any evidence of new onset autoimmune disease.

In rheumatoid factor (RF) positive patients, marked decreases were observed in rheumatoid factor concentrations following treatment with MABTHERA in all three studies (range 45-64%).

Hyperuricaemia (Grade 3/4) occurred in 143/950 (15%) patients, with the majority post-infusion on days 1 and/or 15. It was not associated with any clinical symptoms, and none of these patients developed evidence of renal disease. Increases in serum uric acid are often associated with the catabolism of DNA. This finding is consistent with the destruction of B cells resulting from MABTHERA therapy.

Hypophosphataemia (Grade 3) occurred in 193/950 (21%) patients. There was also one case of Grade 4 hypophosphataemia. Most cases occurred post-infusion, where patients received oral and/or IV corticosteroids. Low phosphate levels are associated with corticosteroid treatment and osteoporosis.

Plasma total immunoglobulin concentrations, total lymphocytes counts, and white cells generally remained within normal limits following MABTHERA treatment, with the exception of a transient drop in white cell counts over the first four weeks following therapy. Lymphopenia (Grade 3/4) was experienced by 679/1003 (68%) of patients compared to 52%-54% of patients who experienced Grade 3 lymphopenia and 1%-3% of patients who experienced Grade 4 lymphopenia in the 24-week double-blind populations. Most cases occurred immediately after the first infusion, consistent with peripheral B-cell depletion, and lymphocyte numbers recovered thereafter. The majority of the Grade 4 cases were transient though 6 patients had more persistent Grade 4 lymphopenia, one of whom had a serious infection (2 occurrences of pneumonia in a diabetic patient; both cases resolved). All 6 patients had low lymphocyte counts before exposure to MABTHERA, including 2 patients who experienced up to Grade 4 lymphopenia whilst on placebo. A total of 17 non serious infections were reported all of which resolved without sequelae.

Titres of IgG antigen specific antibody to mumps, rubella, varicella, tetanus toxoid, influenza and streptococcus pneumococci remained stable over 24 weeks following exposure to MABTHERA in rheumatoid arthritis patients.

The effect of MABTHERA on a variety of biomarkers was evaluated in patients enrolled into Study 3. This substudy evaluated the impact of a single treatment course of MABTHERA on levels of biochemical markers, including markers of inflammation [Interleukin 6, C Reactive protein, Serum amyloid type A protein, Protein S100 isotypes A8 and A9], autoantibody (RF and anti-cyclic citrullinated peptide immunoglobulin) production and bone turnover

[osteocalcin and procollagen 1 N terminal peptide (P1NP). MABTHERA treatment, whether as monotherapy or in combination with MTX or cyclophosphamide reduced the levels of inflammatory markers significantly, relative to MTX alone, over the first 24 weeks of follow-up. Levels of markers of bone turnover, osteocalcin and P1NP, increased significantly in the MABTHERA + MTX groups compared to MTX alone.

Multiple Course Therapy
Following completion of the 24-week double blind comparative study period, patients were permitted to enrol into an open-label long term follow up study. Patients received subsequent courses of MABTHERA as needed according to the treating clinician's assessment of disease activity and irrespective of the peripheral B lymphocyte count.

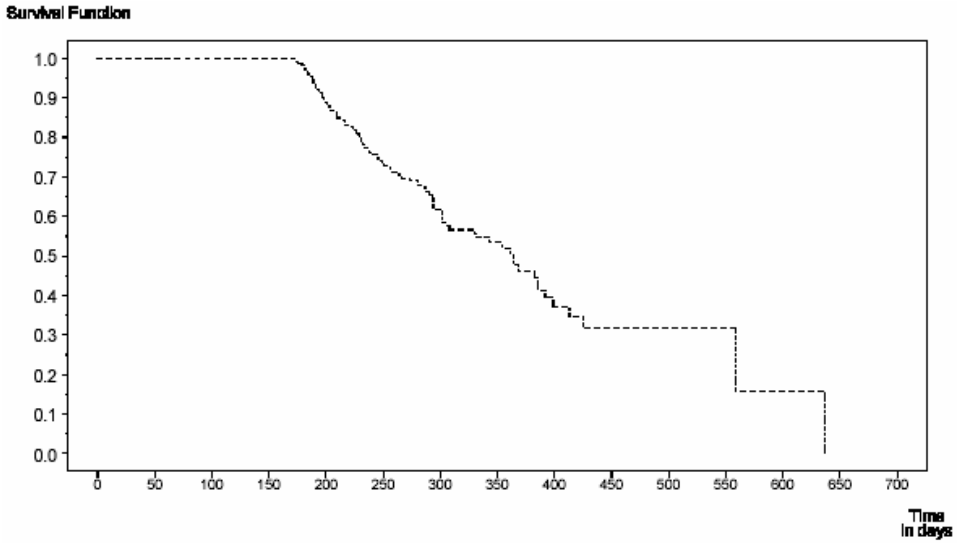
The all exposure population in the three double blind controlled trials (one Phase III and two Phase II trials) was 990 patients. Of these, 301 patients received a second course of MABTHERA 2 x 1000 mg + MTX, and 46 patients received a third course of MABTHERA 2 x 1000 mg + MTX.

At the point of data cut-off, 24.7% (193/781) of patients who had enrolled in the MABTHERA 2 x 1000 mg + MTX arms of the Phase II and Phase III studies had been retreated (point of data cut-off was defined as the time when all patients had been followed up for at least 24 weeks). Also at the data cut-off point, the majority of patients from the double blind comparative study period had received one course of treatment in the year. Kaplan-Meier analysis of time to second treatment course (censoring patients who did not receive a second treatment course or who withdrew from the study) shows an estimated median time for retreatment in the prior anti-TNF population of 364 days (interquartile range: 245-559 days), Figure 1, and 547 days (interquartile range: 302-889 days) in the no prior anti-TNF population, Figure 2.

The time interval between courses was variable. The majority of patients, who had two treatment courses at the time of cut-off, received their second course of treatment 6 to 12 months after the first treatment course. Some patients required even less frequent retreatment. The response to further therapy was at least the same magnitude as that following the initial treatment course, as evidenced by the change from baseline DAS28 (Figure 3).

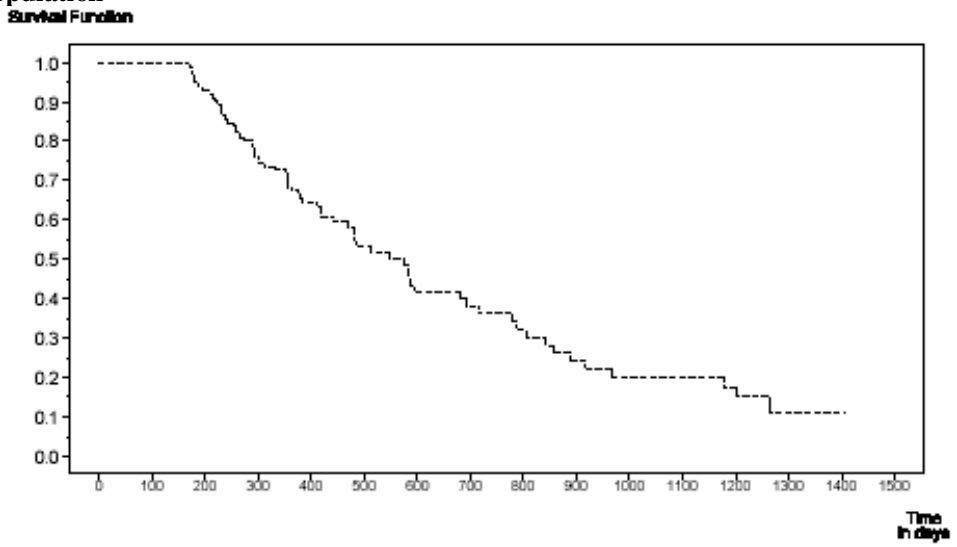
Since many patients in the prior anti-TNF population remain in the studies after a single course of treatment with MABTHERA + MTX, these results are subject to change as the observation period increases.

Figure 1 Kaplan-Meier Analysis of Time to Second Treatment Course, Prior Anti-TNF Population



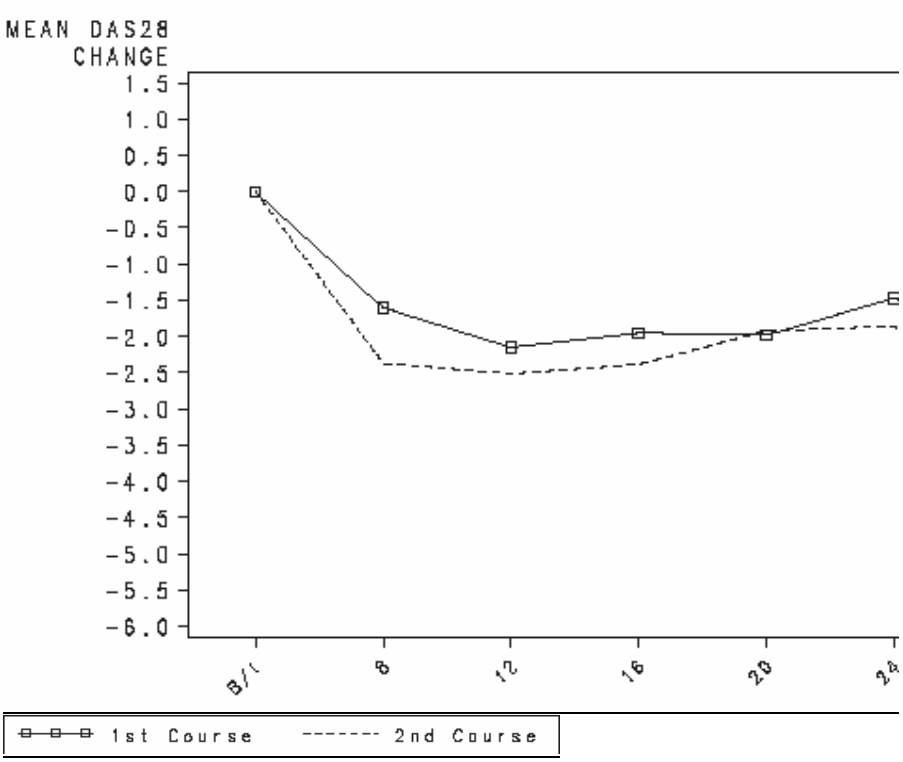
Survival function = Probability of not switching to re-treatment
n = 525

Figure 2 Kaplan-Meier Analysis of Time to Second Treatment Course, No Prior Anti-TNF Population



Survival function = Probability of not switching to re-treatment
n = 256

Figure 3 Mean Change in DAS28 Over Time Following First and Second Course Therapy (Prior anti-TNF population)



INDICATIONS

Non-Hodgkin's Lymphoma

MABTHERA is indicated for treatment of patients with:

- CD20 positive, previously untreated, Stage III/IV follicular, B-cell non-Hodgkin's lymphoma,
- CD20 positive, relapsed or refractory low grade or follicular, B-cell non-Hodgkin's lymphoma,
- CD20 positive, diffuse large B-cell non-Hodgkin's lymphoma, in combination with chemotherapy.

Chronic Lymphocytic Leukaemia

*MABTHERA is indicated for the treatment of patients with CD20 positive chronic lymphocytic leukaemia (CLL) in combination with chemotherapy.

Rheumatoid Arthritis

MABTHERA (rituximab) in combination with methotrexate is indicated to reduce signs and symptoms in adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to at least one tumour necrosis factor (TNF) antagonist therapy.

CONTRAINDICATIONS

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

PRECAUTIONS

***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.

Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukaemia

Infusion-related reactions

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

Adrenaline, antihistamines and corticosteroids should be available for immediate use in the event of a hypersensitivity reaction to MABTHERA.

Patients with a high number (>25 x 10^9/L) of circulating malignant cells or high tumour burden such as patients with CLL and mantle cell lymphoma, who may be at higher risk of especially severe infusion-related reactions, should only be treated with extreme caution and when other therapeutic alternatives have been exhausted. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients, or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still >25 x 10^9/L.

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

Rapid tumour lysis
MABTHERA mediates the rapid lysis of benign and malignant CD20-positive cells. Signs and symptoms (e.g. hyperuricaemia, hyperkalaemia, hypocalcaemia, acute renal failure, elevated LDH) consistent with tumour lysis syndrome (TLS) have been reported to occur after the first MABTHERA 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 and 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.

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

Cardiovascular
Since hypotension may occur during MABTHERA infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to and throughout MABTHERA infusion. Angina pectoris or cardiac arrhythmia, such as atrial flutter and fibrillation have occurred in patients treated with MABTHERA. Therefore patients with a history of cardiac

disease should be monitored closely. Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias.

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

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

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

Cases of Hepatitis B virus (HBV) reactivation, occasionally with fulminant hepatitis, hepatic failure, and death have been reported in some patients with haematologic malignancies treated with MABTHERA. The majority of patients received MABTHERA in combination with chemotherapy. Isolated cases have been reported in patients who either had evidence of antibodies against Hepatitis B surface antigen before treatment or did not have any such antibodies. The median time to diagnosis of hepatitis was approximately 4 months after the initiation of MABTHERA and approximately one month after the last dose.

Persons at high risk of HBV infection should be screened before initiation of MABTHERA. Reactivation of HBV infection is a well-known complication in patients with chronic hepatitis B, especially in those receiving cytotoxic or immunosuppressive therapy. In addition, non-Hodgkin's lymphoma of itself may be an independent risk factor for HBV reactivation. Carriers of hepatitis B, and patients with evidence of having recovered from hepatitis B, should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and up to one year following therapy with MABTHERA.

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

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

Progressive Multifocal Leukoencephalopathy (PML)
Very rare cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported during post-marketing use of MABTHERA in NHL. The majority of patients had received

MABTHERA in combination with chemotherapy or as part of a haematopoietic stem cell transplant.

For further information see PML warning at the beginning of the PRECAUTIONS section.

Rheumatoid Arthritis

Infusion Reactions
MABTHERA is associated with infusion reactions, which may be related to release of cytokines and/or other chemical mediators. Premedication with IV glucocorticoid significantly reduced the incidence and severity of these events.

Most infusion events reported were mild to moderate in severity. The proportion of affected patients decreases with subsequent infusions. The reactions reported were usually reversible with a reduction in rate, or interruption, of MABTHERA infusion and administration of an anti-pyretic, an antihistamine, and, occasionally, oxygen, IV saline or bronchodilators, and glucocorticoids if required. 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.

Anaphylactic and other hypersensitivity reactions have been reported following the IV administration of proteins to patients. Medicinal products for the treatment of hypersensitivity reactions, e.g., adrenaline, antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of MABTHERA. The presence of HACA may be associated with worsening infusion or allergic reactions after the second infusion of subsequent courses.

In clinical studies 10/990 (1%) patients with rheumatoid arthritis who received a first infusion of MABTHERA at any dose experienced a serious reaction during the infusion.

Infections
Based on the mechanism of action of MABTHERA and the knowledge that B cells play an important role in maintaining normal immune response, patients may have an increased risk of infection following MABTHERA therapy. MABTHERA should not be administered to patients with an active infection or severely immunocompromised patients (eg. In hypogammaglobulinaemia or where levels of CD4 or CD8 are very low). Physicians should exercise caution when considering the use of MABTHERA in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection. Patients who develop infection following MABTHERA therapy should be promptly evaluated and treated appropriately (see Precautions for Infections under *Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukaemia* section).

Progressive Multifocal Leukoencephalopathy (PML)
Cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported following use of MABTHERA for the treatment of autoimmune diseases including rheumatoid arthritis. Several but not all of the reported cases involved patients with multiple risk factors for PML, including the underlying disease and long term immunosuppressive therapy or chemotherapy.

The efficacy and safety of MABTHERA for the treatment of autoimmune diseases other than rheumatoid arthritis has not been established.

For further information see PML warning at the beginning of the PRECAUTIONS section.

Cardiovascular Events
Patients with a history of cardiac disease should be monitored closely during infusions (see Precautions for Cardiovascular Events under *Non-Hodgkin's Lymphoma* section). There are no data on the safety of MABTHERA in patients with moderate heart failure (NYHA class III) or severe, uncontrolled cardiovascular disease. In patients treated with MABTHERA, the occurrence of pre-existing ischaemic cardiac conditions becoming symptomatic, such as angina pectoris, has been observed, as well as atrial fibrillation and flutter. Therefore, in patients with a known cardiac history, the risk of cardiovascular complications resulting from infusion reactions should be considered before treatment with MABTHERA and patients closely monitored during administration. Since hypotension may occur during MABTHERA infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the MABTHERA infusion.

Concomitant/Sequential Use of Other DMARDs
The concomitant use of MABTHERA and antirheumatic therapies other than those specified under the rheumatoid arthritis indication and dosing is not recommended.

Limited data are available on the safety of the use of biologic agents or DMARDs other than methotrexate in patients exhibiting peripheral B cell depletion following treatment with MABTHERA. If biologic agents and/or DMARDs are used following MABTHERA therapy, patients should be observed for signs of infection.

***Methotrexate (MTX) naïve populations**
The use of MABTHERA is not recommended in MTX-naïve patients since a favourable benefit-risk relationship has not been established.

Malignancy
Immunomodulatory drugs may increase the risk of malignancy. On the basis of limited experience with MABTHERA in rheumatoid arthritis patients (see 'Adverse Effects - Experience from Rheumatoid Arthritis Clinical Trials') a possible risk for the development of solid tumours cannot be excluded at this time, although present data do not seem to suggest any increased risk.

General Precautions

Immunisation
There are no data concerning the use of vaccines while patients are B cell depleted following MABTHERA therapy. Physicians should review the vaccination status of patients being considered for treatment with MABTHERA and follow local/national guidance for adult vaccination against infectious disease. Vaccination should be completed at least four weeks prior to first administration of MABTHERA. Live vaccines are not recommended in patients while B cell depleted.

Carcinogenicity, Mutagenicity and Impairment of Fertility
No animal studies have been performed to establish the carcinogenic or mutagenic potential of MABTHERA, or to determine its effects on fertility in males or females.

Use in Pregnancy (Category C)
It is not known whether MABTHERA can cause foetal harm when administered to a pregnant woman. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to rituximab. In clinical studies in patients with rheumatoid arthritis, three pregnancies occurred following exposure to MABTHERA + MTX with two resulting in spontaneous abortions and the third ongoing at the time. Rituximab has been shown to cause B-cell depletion in the monkey foetus. MABTHERA should not be given to a pregnant woman, unless the potential benefit outweighs the potential risk.

Individuals of child-bearing potential should use effective contraceptive methods during treatment and for up to 12 months following MABTHERA therapy.

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

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

Use in Children
The safety and effectiveness of MABTHERA in children have not been established.

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

Drug /Laboratory Interactions
Currently, there are limited data on possible drug 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 was no apparent effect of fludarabine and cyclophosphamide on the pharmacokinetics of MABTHERA.

Co-administration with MTX had no effect on the pharmacokinetics of MABTHERA in RA patients.

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

The tolerability of simultaneously or sequential combination of MABTHERA with chemotherapy other than CHOP or CVP, or agents which are liable to cause depletion of normal B cells is not well defined.

In a small cohort of patients with rheumatoid arthritis, 110 patients received subsequent therapy with other DMARDs (including biologicals). Patients received subsequent DMARDs 4-6 months following therapy with MABTHERA and generally while peripherally B cell depleted. The rate of clinically relevant infections was 7.8 per 100 patient years.

ADVERSE EFFECTS

Experience from Clinical Trials in Haemato-Oncology

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

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

MABTHERA monotherapy/maintenance therapy

The ADRs in the table below are based on data from single-arm studies including 356 patients with low-grade or follicular lymphoma, treated with MABTHERA weekly as a single agent for the treatment or re-treatment of non-Hodgkin's lymphoma up to 4 weeks in most patients and from 25 patients who received doses other than 375 mg/m^2 for four doses and up to 500 mg/m^2 single dose in the Phase I setting (see CLINICAL TRIALS). The table also contains ADRs based on data from 166 patients with follicular lymphoma who received MABTHERA as maintenance therapy for up to 2 years following response to initial induction with CHOP or R-CHOP (see CLINICAL TRIALS). The ADRs were reported up to 12 months after treatment with monotherapy and up to 1 month after treatment with MABTHERA maintenance.

Table 12 Summary of ADRs reported in patients with low-grade or follicular lymphoma receiving MABTHERA monotherapy (N = 356) or MABTHERA maintenance treatment (N = 166) in clinical trials

System Organ Class	Very Common (≥ 10%)	Common (≥1% - < 10%)	Uncommon (≥0.1% - < 1%)
Infections and infestations	bacterial infections, viral infections	sepsis, [+]pneumonia, [+]febrile infection, [+]herpes zoster, [+]respiratory tract infection, fungal infections, infections of	

		unknown aetiology	
Blood and the lymphatic system disorders	neutropenia, leucopenia	anaemia, thrombocytopenia	coagulation disorders, transient aplastic anaemia, haemolytic anaemia, lymphadenopathy
Immune system disorders	angioedema	hypersensitivity	
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral oedema, face oedema, increased LDH, hypocalcaemia	
Psychiatric disorders			depression, nervousness
Nervous system disorders		paresthesia, hypoesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	dysgeusia
Eye disorders		lacrimation disorder, conjunctivitis	
Ear and labyrinth disorders		tinnitus, ear pain	
Cardiac disorders		+myocardial infarction, arrhythmia, +atrial fibrillation, tachycardia, +cardiac disorder	+left ventricular failure, +supraventricular tachycardia, +ventricular tachycardia, +angina, +myocardial ischaemia, bradycardia
Vascular disorders		hypertension, orthostatic hypotension, hypotension	
Respiratory, thoracic and 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	pruritis, 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	pain at the infusion site
Investigations	decreased IgG levels		

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

MABTHERA in combination with chemotherapy in NHL and CLL

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

relapsed/refractory CLL patients treated with rituximab in combination with fludarabine and cyclophosphamide (R-FC) (see CLINICAL TRIALS).

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

Table 13 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	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.

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

Further information on selected, serious adverse drug reactions

Infusion-related reactions

Monotherapy – 4 weeks treatment

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. Such infusion-related symptoms occurred in the majority of patients during the first MABTHERA infusion (see PRECAUTIONS). The incidence of infusion-related symptoms decreased from 77% (7% Grade 3/4) with the first infusion to approximately 30% (2% Grade 3/4) with the fourth infusion and to 14% (no Grade 3/4 events) with the eighth infusion.

Maintenance Treatment (NHL) up to 2 years

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

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL; R-FC in CLL)
Severe infusion-related reactions occurred in up to 12% of all patients at the time of the first treatment cycle with rituximab in combination with chemotherapy. The incidence of Grade 3 or 4 infusion-related reactions decreased to less than 1% by the eighth cycle of therapy. The signs and symptoms were consistent with those observed during monotherapy (see PRECAUTIONS), but also included dyspepsia, rash, hypertension, tachycardia, features of tumour lysis syndrome. Additional reactions reported in isolated cases at the time of R-chemotherapy were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia.

Infections
Monotherapy – 4 weeks treatment
MABTHERA induced B-cell depletion in 70% to 80% of patients and was associated with decreased serum immunoglobulins in only a minority of patients. Infectious events, irrespective of causal assessment, occurred in 30.3% of 356 patients: 18.8% of patients had bacterial infections, 10.4% had viral infections, 1.4% had fungal infections, and 5.9% had infections of unknown aetiology. Severe infectious events (Grade 3 or 4), including sepsis occurred in 3.9% of patients; in 1.4% during the treatment period and in 2.5% during the follow-up period.

Maintenance Treatment (NHL) up to 2 years
The proportion of patients with Grade 1 to 4 infections was 25% in the observation group and 45% in the MABTHERA group with Grade 3 or 4 infections in 3% of patients on observation and 11% receiving MABTHERA maintenance treatment. Grade 3 to 4 infections reported in ≥ 1% of patients in the MABTHERA arm were pneumonia (2%), respiratory tract infection (2%), febrile infection (1%) and herpes zoster (1%). In a large proportion of infections (all grades), the infectious agent was not specified or isolated, however, where an infectious agent was specified, the most frequently reported underlying agents were bacterial (observation 2%, MABTHERA 10%), viruses (observation 7%, MABTHERA 11 %) and fungi (observation 2%, MABTHERA 4%). There was no cumulative toxicity in terms of infections reported over the 2-year maintenance period.

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL; R-FC in CLL)
In the R-CVP study the overall proportion of patients with infections or infestations during treatment and for 28 days after trial treatment end was comparable between the treatment groups (33% R-CVP, 32% CVP). The most common infections were upper respiratory tract infections which were reported for 12.3% patients on R-CVP and 16.4% patients receiving CVP; most of these infections were nasopharyngitis. Serious infections were reported in 4.3% of the patients receiving R-CVP and 4.4% of the patients receiving CVP. No life threatening infections were reported during this study.

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, including ophthalmic herpes zoster, was higher in the R-CHOP group (4.5%) than in the CHOP group (1.5%), with 7 of a total of 9 cases in the R-CHOP group occurring during the treatment phase. The proportion of patients with Grade 2 to 4 infections and/or febrile neutropenia was 55.4% in the R-CHOP group and 51.5% in the CHOP group. Febrile neutropenia (i.e. no report of concomitant documented infection) was

reported only during the treatment period, in 20.8% in the R-CHOP group and 15.3% in the CHOP group.

In patients with CLL, the overall incidence of Grade 3 or 4 infections during treatment and for 28 days after the end of trial treatment was comparable between the treatment groups both in the first-line (18% R-FC vs 17% FC) and in the relapsed/refractory setting (19% R-FC vs 18% FC). The incidence of Grade 3 or 4 hepatitis B infection (reactivation and primary infection) was 2% R-FC vs 0% FC.

Haematologic Events

Monotherapy – 4 weeks treatment

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

Maintenance Treatment (NHL) up to 2 years

Leucopenia (all grades) occurred in 26% of patients on observation vs 31% of patients in the MABTHERA arm, and neutropenia was reported in 13% of patients on observation and in 25% of patients on MABTHERA. There was a higher incidence of Grade 3-4 neutropenia (observation 5%, MABTHERA 11%) and leucopenia (observation 2%, MABTHERA 5%) in the MABTHERA arm compared to the observation arm. The incidence of Grade 3 to 4 thrombocytopenia (observation 1%, MABTHERA < 1%) was low.

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

Severe (Grade 3 or 4) Neutropenia: There was a higher incidence of Grade 3 or 4 neutropenia in the MABTHERA containing study arms compared to the chemotherapy arms. In the R-CVP study, the incidence of neutropenia was 24% in the R-CVP arm versus 14% of patients in the CVP arm. These laboratory findings were reported as adverse events and resulted in medical intervention in 3.1% of patients on R-CVP and 0.6% of patients on CVP. The higher incidence of neutropenia in the R-CVP group was not associated with a higher incidence of infections and infestations. In patients with previously untreated CLL, Grade 3 or 4 neutropenia was reported as an adverse event in 30% of patients in the R-FC arm and in 19% of patients in the FC arm. In patients with relapsed/refractory CLL, the incidence of Grade 3 or 4 neutropenia adverse events was slightly higher in the R-FC arm (42% R-FC) compared to FC arm (40%).

Severe (Grade 3 or 4) Leucopenia: In the R-CHOP study, the incidence of severe leucopenia was 88% in the R-CHOP arm versus 79% in the CHOP arm. In CLL first-line, more patients receiving R-FC experienced Grade 3 or 4 leucopenia (23%) compared with patients receiving FC (12%). In patients with relapsed/refractory CLL, the overall incidence of Grade 3 or 4 leucopenia adverse events was comparable between the treatment arms (4% R-FC vs 3% FC).

Severe (Grade 3 or 4) Anaemia and Thrombocytopenia: No relevant difference between the treatment arms was observed with respect to Grade 3 and 4 anaemia or thrombocytopenia for the R-CHOP and R-CVP studies. In the R-CVP study, the incidence of anaemia was 0.6% in the R-CVP arm versus 1.9% in the CVP arm. The incidence of thrombocytopenia was 1.2% in the R-CVP arm versus 0% in the CVP arm. In the R-CHOP study, the incidence of anaemia was 14% in the R-CHOP arm versus 19% in the CHOP arm. The incidence of thrombocytopenia was 15% in the R-CHOP arm versus 16% in the CHOP arm. The time to

recovery from all haematological abnormalities was comparable in the two treatment groups. In the CLL first-line study, Grade 3 or 4 anaemia was reported by 4% of patients treated with R-FC compared to 7% of patients receiving FC, and Grade 3 or 4 thrombocytopenia was reported by 7% of patients in the R-FC group compared to 10% of patients in the FC group. In the relapsed/refractory CLL study, adverse events of Grade 3 or 4 anaemia were reported in 12% of patients treated with R-FC compared to 13% of patients receiving FC and Grade 3 or 4 thrombocytopenia was reported by 11% of patients in the R-FC group compared to 9% of patients in the FC group.

Cardiovascular 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. Two patients (0.6%) experienced Grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) during a MABTHERA infusion and one patient with a history of myocardial infarction experienced angina pectoris, evolving into myocardial infarction 4 days later.

Maintenance Treatment (NHL) up to 2 years

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

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

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

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

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

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). Monitoring of IgG levels should be considered for patients treated with MABTHERA. IV Ig substitution may be indicated for patients with decreased IgG levels.

Neurologic Events

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

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

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

Subpopulations

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

Elderly patients (≥65 years)

Monotherapy – 4 weeks treatment: The incidence of any ADR and of Grade 3 and 4 ADRs was similar in elderly (N=94) and younger (N=237) patients (88.3% versus 92.0% for any ADR and 16.0% versus 18.1% for Grade 3 and 4 ADR).

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

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

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

Experience from Clinical Trials in Rheumatoid Arthritis

The clinical efficacy of MABTHERA, given together with methotrexate, was studied in three double blind controlled clinical trials (one Phase III and two Phase II trials) in patients with rheumatoid arthritis. 1039 patients received at least one treatment course, 570 patients received two or more courses of treatment during the follow up period, 191 patients three or more courses, 40 patients four or more courses and 3 patients received 5 or more courses during the follow up period. So far 839 patients have been followed for more than a year, 139 for more than 2 years and 89 for more than 3 years post MABTHERA treatment.

Patients received 2 x 1000 mg of MABTHERA separated by an interval of two weeks; in addition to methotrexate (10-25 mg/week). MABTHERA infusions were administered after an IV infusion of 100 mg methylprednisolone; the majority of patients also received treatment with oral prednisone for 15 days. ADRs, which occurred with at least a 2% difference

compared to the control arm and more frequently by patients who had received at least one infusion of MABTHERA than among patients that had received placebo in the Phase III trial and the combined population included in Phase II studies, are listed in the table below. Frequencies are defined as very common (≥ 10%) and common (≥ 1% to < 10%).

The most frequent ADRs considered due to receipt of 2 x 1000 mg MABTHERA in Phase II and III studies were acute infusion reactions. Infusion reactions occurred in 15% patients following the first infusion of MABTHERA and 5% in placebo patients. Infusion reactions decreased to 2% following the second infusion in both MABTHERA and placebo groups.

Table 14 Summary of Adverse Reactions Occurring in Patients with Rheumatoid Arthritis receiving MABTHERA during Phase II and III Clinical Studies †

	Pooled Phase II Study Population		Phase III Study Population	
	Very Common (≥ 10%)	**Common** (≥ 1 % - < 10%)	**Very Common** (≥ 10%)	**Common** (≥ 1% - < 10%)
Acute Infusion reactions*		hypertension, rash, pruritus, chills, pyrexia, rhinitis, throat irritation		hypertension, nausea, rash, pyrexia, pruritus, urticaria, throat irritation, hot flush, hypotension
Gastrointestinal disorders		dyspepsia		dyspepsia
Infections and Infestations	any infection	urinary tract infections	any infection, upper respiratory tract infection	
Metabolism and Nutritional disorders				hypercholesterolemia
Musculo skeletal disorders		arthralgia/ musculoskeletal pain		arthralgia/ musculoskeletal pain, osteoarthritis
Nervous System disorders		migraine		paraesthesia

† This table include all events with an incidence difference of ≥ 2 % for rituximab compared to placebo
* Reactions occurring during or within 24 hours of infusion

The following adverse events were reported at a frequency between 1% and 2% greater in the MABTHERA-arms compared to control arms: lower respiratory tract infections/pneumonia, abdominal pain upper, muscle spasms, asthenia.

In addition to the events tabulated above, medically significant events reported rarely in the MABTHERA treated population and considered potential reactions to treatment include the following:

General Disorders:	Generalised oedema
Respiratory Disorders:	Bronchospasm, wheezing, laryngeal oedema
Skin and Subcutaneous Disorders:	Angioneurotic oedema, generalised pruritis
Immune system Disorders:	Anaphylaxis, anaphylactoid reaction.

Multiple Courses

Multiple courses of treatment are associated with a similar ADR profile to that observed following first exposure. However, worsening of infusion or allergic reactions and failure to B cell deplete following rituximab cannot be excluded in HACA positive patients after repeated exposure to rituximab on the basis of the available data. The incidence of acute

infusion reactions following subsequent treatment courses was generally lower than the incidence following the first infusion of MABTHERA.

Acute Infusion reactions
Symptoms suggesting an acute infusion reaction (pruritis, fever, urticaria/rash, chills, pyrexia, rigors, sneezing, angioneurotic oedema, throat irritation, cough and bronchospasm, with or without associated hypotension or hypertension) were observed in 79/540 (15%) patients following their first exposure to MABTHERA. In a study comparing the effect of glucocorticoid regimen, these events were observed in 5/149 (3%) of patients following their first placebo infusion and 42/192 (22%) of patients receiving their first infusion of 1000 mg MABTHERA. Premedication with IV glucocorticoid significantly reduced the incidence and severity of these events. Of the patients who received 1000 mg MABTHERA without premedication with glucocorticoids, 18/65 (28%) experienced an acute infusion reaction, compared with 24/127 (19%) in patients given IV glucocorticoid premedication, respectively.

In Study 1 (REFLEX) 5/308 (1.6%) patients from the MABTHERA + methotrexate group and no patients from the placebo + methotrexate group withdrew from the study due to acute infusion reactions. A reduced number of acute infusion reactions occurred during the second infusion, and none resulted in withdrawal of a patient.

In Study 2 (DANCER) 5/192 (3%) patients in the 2 x 1000 mg MABTHERA + methotrexate group were withdrawn due to acute infusion reactions. No patients in the placebo or 2 x 500 mg MABTHERA groups withdrew from treatment.

In Study 3 one patient in the 2 x 1000 mg MABTHERA group withdrew due to an acute infusion reaction.

Infections
The rate of infection was approximately 0.9 per patient year in MABTHERA treated patients. The infections consisted mostly of upper respiratory tract infections and urinary tract infections. Clinically significant infections (defined as those which were reported as serious and/or were treated with IV antibiotics) were observed in 68/1039 (7%) of patients treated with MABTHERA compared to 3/107 (3%) of patients treated with only placebo. The rate of clinically significant infection was 0.05 per patient year in MABTHERA treated patients. Clinically significant infections predominantly included those of the lower respiratory, urinary and gastrointestinal tracts. Three clinically significant infections resulted in fatal outcomes, one was considered related to MABTHERA (septic shock) and two unrelated (neutropenic sepsis and bronchopneumonia).

Malignancies
The observed incidence of malignancies following exposure to rituximab (1.6 per 100 person years) lies within the range expected for a population with similar age and gender profile. A total of 26 malignancies have been reported in 22/1039 (2%) patients treated with MABTHERA. The most common types were skin cancer (basal cell carcinoma squamous cell cancer, or melanoma) and breast cancer. Four malignancies (thyroid gland cancer, oligodendroglioma, basal cell carcinoma and malignant melanoma) were assessed by the investigator as being related to trial treatment.

Latency of onset was variable, ranging from 35 to 1324 days. There was no evidence that the incidence of malignancies altered over time, with fourteen malignancies occurring following

the first course of MABTHERA, ten following the second course, and two following the third course. Malignancies were reported mainly in patients aged ≥60 years (mean 60 years; range 37-80 years).

Post-Marketing Experience

Non-Hodgkin's Lymphoma

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

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

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

- *Cardiovascular system*: Severe including fatal cardiac events, such as heart failure and myocardial infarction have been observed, mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and mostly associated with infusion-related reactions. Vasculitis, predominantly cutaneous, such as leucocytoclastic vasculitis, has been reported very rarely.
- **Blood and lymphatic system*: Rarely the onset of neutropenia has occurred more than four weeks after the last infusion of MABTHERA. Cases of infusion-related acute reversible thrombocytopenia have been reported.
- *In post-marketing*: Studies of rituximab in patients with Waldenstrom's macroglobulinaemia, transient increases in serum IgM levels have been observed following treatment initiation, which may be associated with hyperviscosity and related symptoms. The transient IgM increase usually returned to at least baseline level within 4 months.
- **Respiratory system*: Fatal bronchiolitis obliterans and pneumonitis (including interstitial pneumonitis) have been reported. Respiratory failure/insufficiency and pulmonary infiltrates in the context of infusion-related reactions. 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 fatal cases of toxic epidermal necrolysis have been reported rarely.
- *Nervous system*: Cases of cranial neuropathy with or without peripheral neuropathy have been reported rarely. Signs and symptoms of cranial neuropathy, such as severe vision loss, hearing loss, loss of other senses and facial nerve palsy, occurred at various times up to several months after completion of MABTHERA therapy.
- *Body as a whole*: Serum sickness-like reactions have been reported rarely.
- *Infections and infestations:* Cases of hepatitis B reactivation have been reported in subjects receiving MABTHERA in combination with cytotoxic chemotherapy (see PRECAUTIONS). 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)) and Hepatitis C virus. Progression of Kaposi's sarcoma has been observed in rituximab-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV (Human Immunodeficiency Virus)-positive.

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

– *Renal and urinary system:* Renal failure has been reported.

Rheumatoid Arthritis

*In addition to ADRs seen in RA clinical trials for MABTHERA (see ADVERSE EFFECTS - *Experience from Clinical Trials in Rheumatoid Arthritis*), progressive multifocal leukoencephalopathy (PML) and serum sickness-like reaction have been reported during post-marketing experience.

DOSAGE AND ADMINISTRATION

MABTHERA may be administered in an outpatient setting.

Dosage

Non-Hodgkin's Lymphoma

Relapsed or refractory Low Grade or Follicular non-Hodgkin's lymphoma

The recommended dosage of MABTHERA when used in monotherapy is 375 mg/m^2 administered as an intravenous infusion once weekly for four weeks.

The recommended dosage of MABTHERA when used in combination with CHOP chemotherapy is 375 mg/m^2 administered on day 1 of each chemotherapy cycle (6 cycles).

Previously untreated stage III/IV Follicular non-Hodgkin's lymphoma

The recommended dosage of MABTHERA in combination with chemotherapy is 375 mg/m^2 administered on day 1 of each chemotherapy cycle for up to 8 cycles as induction therapy.

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

Maintenance treatment

Patients who have responded to induction treatment may receive maintenance therapy with MABTHERA given at 375 mg/m^2 body surface area once every 3 months until disease progression or for a maximum period of two years.

Diffuse large B-cell non-Hodgkin's lymphoma

The recommended dosage for MABTHERA in combination with CHOP chemotherapy is 375 mg/m^2, administered as an intravenous infusion on day 1 of each chemotherapy cycle, for up to 8 cycles.

Chronic Lymphocytic Leukaemia

The recommended dosage of MABTHERA in combination with chemotherapy is 375 mg/m^2 administered on day 1 of the first treatment cycle followed by 500 mg/m^2 administered on day 1 of each subsequent cycle, for a total of 6 cycles (see CLINICAL TRIALS). The chemotherapy should be given after the infusion of MABTHERA.

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

Dosage adjustments during treatment

No dose reductions of MABTHERA are recommended. When MABTHERA is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic drugs should be applied.

First Infusion: The recommended initial rate of infusion is 50 mg/h. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h. If hypersensitivity or an infusion-related event develops, the infusion should be temporarily slowed or interrupted (see PRECAUTIONS). The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

Subsequent Infusions: Subsequent MABTHERA infusions can be administered at an initial rate of 100 mg/h and increased by 100 mg/h increments at 30-minute intervals, to a maximum of 400 mg/h.

Rheumatoid Arthritis

A course of MABTHERA consists of two 1000 mg IV infusions. The recommended dosage of MABTHERA is 1000 mg by intravenous infusion followed by a second 1000 mg intravenous infusion two weeks later. The course of MABTHERA is given concomitantly with the dose of methotrexate tolerated by the patient. The minimal effective dose is not yet known. There has only been limited study of the 2 x 500 mg regimen.

Rheumatoid arthritis patients should receive treatment with 100 mg IV methylprednisolone 30 minutes prior to MABTHERA to decrease the rate and severity of acute infusion reactions.

Background therapy with glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, or analgesics can be continued during treatment with MABTHERA.

Disease activity should be regularly monitored. Patients may receive further courses of treatment, based on signs and symptoms of disease. In clinical studies, no patient received a second course of MABTHERA treatment within 16 weeks of the first infusion of the first course. The time interval between courses was variable, with the majority of patients who received additional courses doing so 6 -12 months after the previous course. Some patients

required even less frequent retreatment. The efficacy and safety of further courses is comparable to the first course.

Human anti chimeric antibodies (HACA) develop in some patients after the first course of MABTHERA. The presence of HACA may be associated with the worsening of infusion or allergic reactions after the second infusion of subsequent course. Furthermore, in one case with HACA, failure to deplete B-cells after receipt of further treatment courses has been observed. Thus, the benefit/risk balance of therapy with MABTHERA should be carefully considered before administering subsequent courses of MABTHERA. If a repeat course of treatment is considered it should not be given at an interval less than 16 weeks.

First infusion of each course: The recommended initial rate for infusion is 50 mg/h; after the first 30 minutes, it can be escalated in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h.

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

Preparation
MABTHERA vials do not contain an antimicrobial agent or preservative; therefore, care must be
taken to ensure the sterility of the vials and prepared solution. Each vial should be used once only and any residue discarded.

Aseptically withdraw the necessary amount of MABTHERA and dilute to a calculated concentration between 1 mg/mL to 4 mg/mL of rituximab into an infusion bag containing either 0.9% sodium chloride or 5% dextrose in water. To mix the solution, gently invert the bag to avoid foaming. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration.

To reduce microbiological hazard, prepared infusion solutions of MABTHERA should be used as soon as practicable after dilution. If necessary, the prepared solutions may be stored in the refrigerator (2^{O}C to 8^{O}C) for up to 24 hours. This timeframe allows for the temporary interruption of the infusion and subsequent recommencement if the patient has an infusion reaction (see *Administration* below).

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

Administration
The MABTHERA solution for infusion should be administered intravenously through a dedicated line.

As with all parenteral products, appropriate aseptic technique should be used during the administration of MABTHERA. Do not administer as an intravenous push or bolus. Hypersensitivity reactions may occur whenever protein solutions such as MABTHERA are administered (see PRECAUTIONS). Premedication, consisting of an analgesic/antipyretic such as paracetamol and an antihistamine such as diphenhydramine should always be administered 30 to 60 minutes before each infusion of MABTHERA. Premedication with

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

OVERDOSAGE

There has been no experience of overdosage in human clinical trials. Single doses higher than 1000 mg have not been tested in controlled clinical trials. The highest dose tested to date is 5 g in patients with CLL. No additional safety signals were identified. Patients who experience overdose should have immediate interruption or reduction of their infusion and be closely supervised. Consideration should be given to the need for regular monitoring of blood cell count and for increased risk of infections while patients are B cell-depleted.
Treatment of overdose should also consist of general supportive measures.

Contact the Poisons Information Centre for advice on management of overdosage.

PRESENTATION AND STORAGE

Packs of 2:

- Single-use vials containing concentrated solution for dilution and intravenous infusion 100 mg/10 mL

Pack of 1:

- Single-use vial containing concentrated solution for dilution and intravenous infusion 500 mg/50 mL

Rituximab 100 mg (10 mL) or 500 mg (50 mL) is formulated in a 7.35 mg/mL sodium citrate buffer containing 0.7 mg/mL polysorbate 80, 9.0 mg/mL sodium chloride and sterile water for injection. The pH is adjusted to 6.5 with sodium hydroxide and/or hydrochloric acid.

Storage
MABTHERA vials must be refrigerated between 2°C to 8°C. Do not freeze MABTHERA vials. MABTHERA vials must be protected from direct sunlight. Do not use beyond the expiry date stamped on the carton/vial. MABTHERA vials should be used once only and any unused portion left in the vials should be discarded.

Disposal of Medicines
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.

POISON SCHEDULE

Prescription only medicine- Schedule 4

SPONSOR

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ABN 70 000 132 865
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Customer Enquires: 1800 233 950

Date of TGA approval: 8 January 2010

* Please note changes in Product Information