PRODUCT MONOGRAPH

Pr RITUXAN® SC

rituximab
120 mg/mL Solution for Subcutaneous Injection

Professed Standard

Antineoplastic

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PrRITUXAN® SC
rituximab

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Subcutaneous	Solution for Injection / 120 mg/mL	rHuPH20: an enzyme used to increase the dispersion and absorption when co-administered with rituximab *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION
RITUXAN (rituximab) is a chimeric mouse/human monoclonal antibody that binds specifically to the transmembrane antigen CD20.

INDICATIONS AND CLINICAL USE

Non-Hodgkin's Lymphoma (NHL)
RITUXAN (rituximab) is indicated for:
- the treatment of patients with CD20 positive, diffuse large B-cell non-Hodgkin's lymphoma (DLBCL) in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy.
- the treatment of patients with previously untreated Stage III/IV follicular, CD20 positive, B-cell non-Hodgkin's lymphoma in combination with CVP (cyclophosphamide, vincristine and prednisolone) chemotherapy.
- the maintenance treatment of patients with follicular non-Hodgkin's lymphoma who have responded to induction therapy with either CHOP or CHOP plus RITUXAN.
- single-agent maintenance treatment of previously untreated patients with advanced follicular non-Hodgkin's lymphoma with high tumour burden and who have responded to induction therapy with either CHOP plus RITUXAN or CVP plus RITUXAN.

Chronic Lymphocytic Leukemia (CLL)
RITUXAN (rituximab) is indicated for the treatment of patients with previously untreated or previously treated B-cell chronic lymphocytic leukemia (B-CLL), Binet Stage B or C, in combination with fludarabine and cyclophosphamide.

The use of RITUXAN in CLL is based on an improvement in progression-free survival. Overall survival benefit has not been demonstrated in patients with previous treatment for CLL. The

efficacy of treatment with R-FC (RITUXAN-fludarabine and cyclophosphamide) in CLL patients who were previously treated with RITUXAN in combination with fludarabine and cyclophosphamide has not been studied (see CLINICAL TRIALS for details).

Geriatrics (≥ 65 years of age): *In the CLL setting, exploratory subgroup analysis indicates that use in the geriatric population is associated with differences in efficacy and safety. See CLINICAL TRIALS and ADVERSE REACTIONS for details.*

CONTRAINDICATIONS

RITUXAN (rituximab) is contraindicated in patients with known Type I hypersensitivity or anaphylactic reactions to murine proteins, Chinese Hamster Ovary (CHO) cell proteins, or to its excipients (see WARNINGS AND PRECAUTIONS).

RITUXAN is also contraindicated in patients who have or have had progressive multifocal leukoencephalopathy (PML).

RITUXAN is not recommended for use in patients with severe, active infections.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

General

RITUXAN (rituximab) is a potent drug. Several adverse reactions are associated with RITUXAN, some of which are severe and life-threatening (see WARNINGS AND PRECAUTIONS). This drug should only be used by health professionals experienced in treating Non-Hodgkin's Lymphoma (NHL) and Chronic Lymphocytic Leukemia (CLL). Patients should be treated in a setting where full resuscitation facilities are immediately available, and where medications and supportive care measures for the treatment of hypersensitivity reactions (e.g., epinephrine, antihistamines, glucocorticoids) are immediately available in the event of an allergic reaction during administration (see DOSAGE AND ADMINISTRATION).

Infusion Reactions

Deaths within 24 hours of RITUXAN infusion have occurred. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. Carefully monitor patients during infusions. Discontinue RITUXAN infusion and provide medical treatment for Grade 3 or 4 infusion reactions (see WARNINGS AND PRECAUTIONS, Infusion/Administration Related Events).

Progressive Multifocal Leukoencephalopathy (PML)

Patients with NHL and CLL who received treatment with RITUXAN may have an increased risk of PML. PML can cause disability or death. Healthcare professionals should monitor patients on RITUXAN for any new sign or symptom that may be suggestive of PML. Further treatment with RITUXAN should be withheld immediately at the first sign or symptom suggestive of PML (see WARNINGS AND PRECAUTIONS, Progressive Multifocal Leukoencephalopathy).

Tumor Lysis Syndrome (TLS)
Acute renal failure requiring dialysis has been reported in the setting of TLS following treatment of NHL and CLL patients with RITUXAN. Fatal instances of TLS have been observed in NHL patients. (see WARNINGS AND PRECAUTIONS, Infusion/Administration Related Events).

Hepatitis B Virus (HBV) Reactivation
HBV reactivation has occurred in patients treated with RITUXAN, in some cases resulting in fulminant hepatitis, hepatic failure, and death. All patients should be screened for HBV infection before treatment initiation, and should be monitored during and after treatment with RITUXAN. In the event of HBV reactivation, RITUXAN and concomitant medications should be discontinued.

Mucocutaneous Reactions
Severe, including fatal, mucocutaneous reactions including Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have occurred in patients treated with RITUXAN. Patients experiencing a severe mucocutaneous reaction should discontinue treatment with RITUXAN and seek prompt medical evaluation (see WARNINGS AND PRECAUTIONS, Skin).

Infections
Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during or following the completion of RITUXAN-based therapy. RITUXAN treatment should not be initiated in patients with severe active infections. Patients should be screened for infectious disease history (see WARNINGS AND PRECAUTIONS, Infections).

Cardiovascular
Serious and potentially fatal cardiovascular events have been reported rarely following administration of RITUXAN (see WARNINGS AND PRECAUTIONS).

General
In order to improve the traceability of biological medicinal products, the trade name and batch number of the administered product should be clearly recorded (or stated) in the patient file.

Infusion/Administration Related Events

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

Infusion-related reactions to intravenous RITUXAN:

Severe infusion-related reactions with fatal outcome have been reported during post-marketing use. Severe infusion-related reactions usually manifested within 30 minutes to 2 hours after starting the first infusion with RITUXAN. These reactions were characterized 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, bronchospasm, acute respiratory distress syndrome, angioedema and other symptoms (see ADVERSE REACTIONS: Experience From Clinical Trials).

Infusion related deaths (death within 24 hours of infusion) have been reported at a rate of approximately 0.04-0.07% (4-7 per 10,000 patients treated). Nearly all fatal events occurred in association with the first infusion.

Patients with a high number (> 25 X 10^9/L) of circulating malignant cells or high tumour burden, such as patients with CLL, who may be at higher risk of especially severe cytokine release syndrome, should only be treated with extreme caution and when other therapeutic alternatives have been exhausted. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients 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; in the CLL ML17102 trial, 47% of patients required a delayed and/or slowed infusion, and 17% of patients required split dosing.

Premedication consisting of an anti-pyretic and an antihistaminic (e.g. acetaminophen and diphenhydramine) should always be administered before each infusion of RITUXAN. Premedication with glucocorticoids should also be considered, particularly if RITUXAN is not given in combination with steroid-containing chemotherapy (see DOSAGE AND ADMINISTRATION).

Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines and glucocorticoids should be available for immediate use in the event of a reaction during administration. In the CLL clinical trials, most patients received high-dose boluses of intravenous corticosteroids [100 mg Prednisone IV or equivalent] before each RITUXAN infusion / injection.

Patients should be monitored closely throughout the infusion. 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, may be at higher risk of developing severe infusion-related reactions. If mild, the symptoms are usually reversible with interruption of RITUXAN infusion. Treatment of infusion-related symptoms with diphenhydramine and acetaminophen is recommended. Additional treatment with bronchodilators or IV saline or IV corticosteroids may be indicated and should be immediately available. In patients with severe reaction, the infusion should be interrupted immediately (see DOSAGE AND ADMINISTRATION) and they should receive aggressive symptomatic treatment. Since initial improvement may be followed by deterioration, these patients should be closely monitored until Tumour Lysis Syndrome (TLS) and pulmonary infiltration have been ruled out. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Most patients who have experienced non-life-threatening reactions have been able to complete the full course of therapy (see DOSAGE AND ADMINISTRATION). Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe infusion-related reactions. In the patients with a severe reaction, the decision to administer further infusions should be made by the treating physician on a case-by-case basis after assessing the risk versus

benefit to the patient.

Administration-related reactions to subcutaneous RITUXAN

Local cutaneous reactions, including injection site reactions, have been reported in patients receiving RITUXAN SC. Symptoms included pain, swelling, induration, haemorrhage, erythema, pruritus and rash (see ADVERSE REACTIONS). Some local cutaneous reactions occurred more than 24 hours after the SC drug administration. The majority of local cutaneous reactions seen following administration of the SC formulation were mild or moderate and resolved without any specific treatment.

All patients must always receive their first dose of RITUXAN by intravenous administration, using the intravenous formulation in order to avoid an irreversible administration of the full RITUXAN SC dose during Cycle 1. During this cycle the patient would have the highest risk of experiencing an infusion-related reaction that can be treated effectively by slowing or stopping the infusion. The subcutaneous formulation must only be given at the second or subsequent cycles. Patients unable to receive the full RITUXAN IV infusion dose should continue to receive subsequent cycles with RITUXAN IV until a full IV dose is successfully administered. For patients who are able to receive the full RITUXAN IV infusion dose the second or subsequent RITUXAN dose can be given subcutaneously using the RITUXAN SC formulation (*see* DOSAGE AND ADMINISTRATION*)*. As with the intravenous formulation, RITUXAN SC should be administered in an environment where full resuscitation facilities are immediately available and under the close supervision of a health care professional. Premedication consisting of an analgesic/antipyretic and an antihistamine should always be administered before each dose of RITUXAN SC. Premedication with glucocorticoids should also be considered.

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

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

Pulmonary Events

Pulmonary events have included hypoxia, lung infiltration and acute respiratory failure. Some of these events have been preceded by severe bronchospasm and dyspnea. 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 edema, 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 RITUXAN administration interrupted immediately (see DOSAGE AND ADMINISTRATION) and should receive aggressive symptomatic treatment. 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.

Tumour Lysis Syndrome

RITUXAN mediates the rapid lysis of benign and malignant CD20 positive cells. Signs and symptoms (e.g., hyperuricemia, hyperkalemia, hypocalcemia, hyperphosphatemia, acute renal failure, elevated LDH, high fevers) consistent with Tumour Lysis Syndrome (TLS) have been reported to occur within 1 to 2 hours though initial reports of TLS were not diagnosed until 12-24 hours after the first IV infusion in NHL patients with high numbers of circulating malignant lymphocytes. Acute renal failure requiring dialysis with instances of fatal outcome has been reported in the setting of TLS in NHL patients. 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 [$>25 \times 10^9$/L] of circulating malignant cells, such as patients with CLL). 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 RITUXAN IV therapy has been administered in conjunction with prophylactic therapy for TLS in a limited number of cases.[1]

Anaphylaxis

Anaphylactic reactions, including fatalities, have been reported in patients treated with RITUXAN. These reactions may be clinically indistinguishable from severe infusion-related reactions, other hypersensitivity reactions or cytokine release syndrome. True hypersensitivity reactions typically occur after starting the second or subsequent infusion of RITUXAN. Epinephrine, antihistamines and glucocorticoids should be available for immediate use in the event of a hypersensitivity reaction to RITUXAN.

Carcinogenesis and Mutagenesis

No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of RITUXAN.

Fertility

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

RITUXAN SC contains recombinant human hyaluronidase (rHuPH20). Animal studies, designed to investigate the impact of rHuPH20 on male and female fertility, did not indicate any deleterious effects.

Cardiovascular

Since transient hypotension may occur during administration of RITUXAN, consideration should be given to withholding anti-hypertensive medications 12 hours prior to and throughout administration of RITUXAN. Serious and potentially fatal cardiovascular events have been reported rarely following administration of RITUXAN. These events included: angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation, heart failure, myocardial infarction and cardiogenic shock. Administration of RITUXAN should be discontinued in the event of serious

or life-threatening cardio-pulmonary events. Patients who develop clinically significant cardiovascular events should undergo cardiac monitoring during and after subsequent administration of RITUXAN. Patients with pre-existing cardiac conditions including arrhythmias and angina have had recurrences of these events during therapy of RITUXAN and should be monitored throughout the administration and immediate post-administration period.

Effects on Ability to Drive and Use Machines

It is not known whether RITUXAN 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.

Gastrointestinal

Abdominal pain, bowel obstruction and perforation, in some cases leading to death, were observed in patients receiving RITUXAN in combination with chemotherapy for DLBCL. A causal association with RITUXAN has not been established.

In post-marketing reports, which include both patients with low-grade or follicular NHL and DLBCL, the mean time to onset of symptoms was 6 days (range 1-77) in patients with documented gastro-intestinal perforation. Complaints of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.

Hematologic

Myelosuppression

Although RITUXAN is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophil counts < 1.5 x 10^9/L and/or platelet counts of <75 x 10^9/L, as clinical experience with such patients is limited. RITUXAN IV 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.

Grade 3-4 neutropenia and decreased white blood cell counts were very common in ML17102 with combination therapy of RITUXAN with fludarabine and cyclophosphamide. Grade 4 lymphopenia was not captured. Neutropenia and febrile neutropenia occurred in higher frequencies in the R-FC arm. This increase did not result in a statistically significant increase in hospitalization rates.

Immune

HAMA/HACA Formation

Human anti-murine antibody (HAMA) was not detected in 67 patients evaluated. Of 356 patients receiving RITUXAN IV evaluated for human anti-chimeric antibody (HACA), 1.1% (4 patients) were positive. Patients who develop HAMA/HACA titers may have allergic or hypersensitivity reactions when treated with RITUXAN or other murine or chimeric monoclonal antibodies.

In SABRINA study (BO22334) the incidence of treatment-induced/enhanced anti-rituximab antibodies in the RITUXAN SC group was 2% compared to 1.5% in the RITUXAN IV group. The incidence of treatment-induced/enhanced anti-rHuPH20 antibodies was 7.6% in the IV

group compared with 13.2% in the SC group, and none of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies.

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

Immunization
The safety of immunization with live viral vaccines, following therapy with RITUXAN has not been studied. Therefore, vaccination with live virus vaccines is not recommended while on RITUXAN or during peripheral B-cell depletion.

Patients treated with RITUXAN may receive non-live vaccinations. However, with non-live vaccines response rates to the vaccination could be reduced. In a non-randomized study, patients with relapsed or refractory low-grade NHL who received RITUXAN IV monotherapy when compared to healthy untreated controls had a lower rate of response to vaccination with tetanus recall antigen (16% vs 81%) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4% vs 76%) when assessed for >2-fold increase in antibody titer.

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

Infections
Infections have been reported in some patients with prolonged hypogammaglobulinemia (defined as hypogammaglobulinemia >11 months after RITUXAN exposure).

Hepatitis B Reactivation with Related Fulminant Hepatitis
Cases of Hepatitis B virus (HBV) reactivation, occasionally with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with RITUXAN IV. The majority of patients received RITUXAN 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 RITUXAN and approximately one month after the last dose (see ADVERSE REACTIONS).

Hepatitis B reactivation can occur in oncology patients even if Hepatitis B surface antigen status is normal. HBV screening should be performed in all patients before initiation of treatment with RITUXAN. At minimum, this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Reactivation of HBV infection is a well-known complication in patients with chronic hepatitis B, especially in those receiving cytotoxic or immunosuppressive therapy. In addition, non-Hodgkin's lymphoma of itself may be an independent risk factor for HBV reactivation. Patients with active hepatitis B disease should not be treated with RITUXAN. Patients with positive hepatitis B serology should

consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

In patients who develop reactivation of viral hepatitis B, RITUXAN 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 RITUXAN in patients who develop hepatitis subsequent to HBV reactivation.

Additional Serious Viral Infections
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)(see WARNINGS AND PRECAUTIONS)], 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 RITUXAN and have resulted in death. RITUXAN treatment should not be initiated in patients with an active and/or severe infection or severely immunocompromised patients.

Tuberculosis Reactivation
In the CLL clinical trial ML17102, one patient treated with RITUXAN plus fludarabine and cyclophosphamide experienced reactivation of tuberculosis. Patients who develop reactivation of tuberculosis should be treated as per current medical practice and RITUXAN should be discontinued. There are no data regarding the safety of resuming therapy with RITUXAN in patients who develop tuberculosis reactivation.

Pneumocystis Jiroveci Pneumonia
Cases of Pneumocystis Jiroveci Pneumonia (PJP) have been reported in patients receiving RITUXAN in combination with chemotherapy. These cases included patients with multiple risk factors for PJP, including the underlying disease state and other immunosuppressive therapies. The use of PJP prophylaxis should be considered according to local guidelines.

Monitoring and Laboratory Tests
Complete blood counts (CBC) and platelet counts should be obtained at regular intervals in patients with hematologic malignancies during therapy with RITUXAN and more frequently in patients who develop cytopenias (see ADVERSE REACTIONS).

Neurologic
Four cases of stroke or cerebral ischemia originated from a clinical study (GELA, LNH98-5) and concerned patients from 72 to 79 years of age, who had received RITUXAN in combination with CHOP chemotherapy, all with a history of cardiovascular disease or cardiovascular risk factors. In particular, lacunar lesions were seen in two patients, both of whom had a medical history of hypertension, the major risk factor of such small vessel disease. In 2 of these reports, the events were fatal and in the other two, the events were reported to have resolved. Furthermore, if the accepted definition of transient ischemic attack (TIA) (duration of signs/symptoms <24 hours) is applied, then one of the four patients with reported stroke experienced a TIA.

Progressive Multifocal Leukoencephalopathy

Cases of Progressive Multifocal Leukoencephalopathy have been reported during the use of RITUXAN IV in hematologic malignancies (NHL, CLL) (see ADVERSE REACTIONS). The majority of patients had received RITUXAN IV in combination with chemotherapy or as part of a hematopoietic stem cell transplant.

Patients being treated with RITUXAN should be instructed to report any new neurological signs or symptoms to their physician. Physicians treating patients with non-Hodgkin's lymphoma and chronic lymphocytic leukemia should be alert to any new signs or symptoms that may be suggestive of PML and consider PML in the differential diagnosis of patients reporting new-onset neurological symptoms. Consultation with a neurologist should be considered as clinically indicated. Symptoms of PML are diverse, progress over days to weeks, and can include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory and orientation leading to confusion and personality changes. Further treatment with RITUXAN should be withheld immediately at the first sign or symptom suggestive of PML and an evaluation that includes a magnetic resonance imaging (MRI) scan without and, where clinically indicated, with gadolinium-enhancement of the brain should be performed. Cerebrospinal fluid analysis for JC viral DNA is recommended to confirm a diagnosis of PML. Discontinue RITUXAN and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients with confirmed PML.

The absolute risk for PML in patients treated with RITUXAN cannot be precisely estimated and factors that might increase an individual patient's risk for PML have not been identified. There are no known interventions that can reliably prevent or adequately treat PML if it occurs. It is not known whether early detection of PML and discontinuation of RITUXAN will mitigate the disease. The relationship between the risk of PML and the duration of treatment is unknown.

Skin

Severe mucocutaneous reactions including Stevens-Johnson syndrome (SJS), lichenoid dermatitis, vesiculobullous dermatitis, Toxic Epidermal Necrolysis (TEN) and paraneoplastic pemphigus have been reported rarely. Some of these cases were fatal. The onset varied from days to several months following exposure to RITUXAN. Patients experiencing a severe mucocutaneous reaction should discontinue treatment with RITUXAN and seek prompt medical evaluation. In case of such an event, with a suspected relationship to RITUXAN, treatment should be permanently discontinued. Skin biopsy may help to establish a diagnosis and guide subsequent treatment.

Pharmacokinetic Differences between RITUXAN SC and IV Formulations

Fixed doses of RITUXAN SC result in a higher systemic exposure to rituximab than is seen with intravenous RITUXAN at recommended doses in CLL and NHL (see ACTION and CLINICAL PHARMACOLOGY - Pharmacokinetics). This increase in systemic exposure is observed in low, medium and high BSA levels.

Special Populations

Pregnant Women

IgG immunoglobulins are known to pass the placental barrier. Developmental toxicity studies performed in cynomolgus monkeys revealed no evidence of embryotoxicity in utero. Newborn offspring of maternal animals exposed to RITUXAN were noted to have depleted B-cell populations during the postnatal phase. B-cell levels in human neonates following maternal exposure to RITUXAN have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women, however, transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to RITUXAN during pregnancy. For these reasons, RITUXAN should not be administered to pregnant women unless the possible benefit outweighs the potential risk. Women of childbearing age must employ effective contraceptive methods during and for 12 months after treatment with RITUXAN.

The potential risk of transmissible maternal infections either recently acquired or reactivated through the use of RITUXAN should also be considered when prescribing RITUXAN to pregnant women.

The subcutaneous formulation contains recombinant human hyaluronidase (rHuPH20) (see DOSAGE FORMS, COMPOSITION AND PACKAGING). Animal studies demonstrated reductions in fetal weight, and increases in the rates of resorptions, after exposure to rHuPH20 at levels comparable to those that could occur if a bolus dose of RITUXAN SC were to be accidentally administered via the IV route.

To reduce the potential risk of embryofetal toxicity resulting from exposure to rHuPH20, patients who conceive whilst treated with RITUXAN SC should discontinue treatment with the SC formulation.

Nursing Women

It is not known whether RITUXAN is excreted in human milk. Because human IgG is excreted in human milk and the potential for absorption and immunosuppression in the infant is unknown, women should be advised to discontinue nursing until circulating drug levels are no longer detectable (see ACTION AND CLINICAL PHARMACOLOGY).

Pediatrics

The safety and effectiveness of RITUXAN in pediatric patients have not been established. Hypogammaglobulinemia has been observed in pediatric patients treated with RITUXAN, in some cases severe and requiring long-term immunoglobulin substitution therapy.

Geriatrics

No dose adjustment is required in geriatric patients (aged >65 years). In diffuse large B-cell lymphoma clinical studies, no overall differences in effectiveness were observed between elderly and younger subjects. However, geriatric patients were more likely to experience cardiac adverse events, mostly supraventricular arrhythmias. Serious pulmonary adverse events were also more common among the elderly, including pneumonia and pneumonitis.

In low-grade or follicular lymphoma clinical studies, no overall differences in safety or effectiveness were observed between geriatric and younger subjects.

In the trial of previously untreated CLL patients, patients over the age of 65 had, in general, more Grade 3/4 AEs with increasing age, and more AEs were recorded in the R-FC arm compared with FC alone. Similar patterns were observed for SAEs (See ADVERSE REACTIONS). The effect of RITUXAN when added to FC seems to be most pronounced with younger age. Due to the small size of the subgroup of patients over the age of 70 (FC n=25, R-FC n=33), no meaningful conclusion can be drawn for the effect RITUXAN might have in this age category (see CLINICAL TRIALS).

Safety findings were similar in the BO17072 trial in previously treated CLL patients. Grade 3/4 AEs and SAEs generally increased with age in both arms of the study and were more frequently reported in the R-FC arm than the FC arm. However, the incidence of Grade 3/4 AEs was the same in R-FC and FC-treated patients over the age of 70 years (see CLINICAL TRIALS).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

RITUXAN has been tested in clinical trials conducted in patients with various malignancies and/or benign hematological disorders, predominantly in combination with chemotherapy. Across all hematologic indications, the most frequently observed serious adverse drug reactions were:

- bacterial infections, viral infections, bronchitis
- neutropenia, leucopenia, febrile neutropenia, thrombocytopenia
- infusion/ administration related reactions, angioedema

The majority of serious infusion-related reactions occurred during the first infusion of RITUXAN.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

EXPERIENCE FROM CLINICAL TRIALS

SUBCUTANEOUS FORMULATION

Non-Hodgkin's Lymphoma

In the phase III study, SABRINA, patients that received RITUXAN SC (n=197) experienced more adverse events (any grade) than patients that received only RITUXAN IV (n=210) (Total Adverse Events: RITUXAN IV - 1757; RITUXAN SC - 1995). The proportion of patients experiencing any grade adverse events was similar between the two treatment arms (RITUXAN IV: 95%; RITUXAN SC: 96%). The most common adverse events, occurring in > 20% of patients in either treatment arm, were neutropenia (RITUXAN IV: 27%; RITUXAN SC: 32%), nausea (RITUXAN IV: 22%; RITUXAN SC: 31%) and constipation (RITUXAN IV: 26%; RITUXAN SC: 25%). The proportion of patients experiencing pneumonia was 11% in the RITUXAN SC arm and 4% in the RITUXAN IV arm.

Local cutaneous reactions, including injection site reactions, were very common (≥ 1/10) in patients receiving RITUXAN SC. In the phase 3 SABRINA (BO22334) study, local cutaneous reactions were reported in 23% (45/197) of patients that received RITUXAN SC. The most common local cutaneous reactions in the RITUXAN SC arm were: injection site erythema (13%), injection site pain (8%), and injection site edema (4%). Events seen following subcutaneous administration were mild or moderate, apart from one patient in the SABRINA study who reported a local cutaneous reaction of Grade 3 intensity (injection site rash) following the first RITUXAN SC administration at Cycle 2. Local cutaneous reactions of any Grade in the RITUXAN SC arm were most common during the first subcutaneous cycle (Cycle 2), followed by the second and the incidence decreased with subsequent injections.

Neutropenia was observed more frequently among patients randomized to RITUXAN SC in the phase 3 study, SABRINA (BO22334). Overall, 32% of patients that received RITUXAN SC experienced neutropenia compared to 27% that received RITUXAN IV. Severe neutropenia (Grade ≥3) occurred in 26% of RITUXAN SC patients compared to 21% of RITUXAN IV patients. The incidence of serious adverse events corresponding to the preferred term neutropenia was comparable between the treatment arms (4 patients [2%] for RITUXAN IV vs. 6 patients [3%] for the RITUXAN SC arm). The proportion of patients experiencing febrile neutropenia in each treatment arm was: RITUXAN IV: 6%; RITUXAN SC: 8%.

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

The risk of acute administration-related reactions (ARRs) associated with the subcutaneous formulation of RITUXAN was assessed in two open-label studies involving patients with follicular lymphoma during induction and maintenance (SABRINA BO22334) and during maintenance only (SparkThera BP22333). In the SABRINA study, patients that received RITUXAN SC experienced ARRs more often than patients that received RITUXAN IV (48% vs. 35%); the most frequently reported ARRs (RITUXAN IV vs. RITUXAN SC) were chills (7% vs. 5%), injection site erythema (0% vs. 11%), injection site pain (0% vs. 5%), pruritis (6% in each arm), and rash (2% vs. 5%).

In the SABRINA study, severe administration-related reactions (Grade ≥3) were reported in six patients (3%) following RITUXAN SC administration; these events were Grade 3 injection site rash,dry mouth urine output decreased, tumour lysis syndrome, chest pain, dyspnea, throat irritation, and hypoxia. In SparkThera, no severe administration-related reactions were reported.

Table 1 Adverse Events Occurring in at Least 5% of Subjects in Either Treatment Arm - Study BO22334 (SABRINA) Stage 1 and Stage 2 Pooled Analysis (Safety Analysis Population)

Body System/ Adverse Event	Rituximab IV + Chemo N=210 No. (%)	Rituximab SC + Chemo N=197 No. (%)
Gastrointestinal Disorders		
Nausea	46 (22)	62 (31)
Constipation	55 (26)	49 (25)
Diarrhea	33 (16)	35 (18)
Abdominal pain	26 (12)	28 (14)
Vomiting	26 (12)	27 (14)
Dyspepsia	14 (7)	16 (8)
Stomatitis	11 (5)	11 (6)
Abdominal pain upper	11 (5)	10 (5)
General Disorders and Administration Site Conditions		
Fatigue	37 (18)	39 (20)
Pyrexia	33 (16)	30 (15)
Asthenia	27 (13)	34 (17)
Chills	18 (9)	15 (8)
Injection site erythema	-	26 (13)
Oedema peripheral	13 (6)	10 (5)
Mucosal inflammation	12 (6)	9 (5)
Chest pain	7 (3)	12 (6)
Influenza like illness	12 (6)	5 (3)
Injection site pain	-	16 (8)
Blood and Lymphatic System Disorders		
Neutropenia	57 (27)	63 (32)
Anaemia	27 (13)	30 (15)
Leukopenia	23 (11)	12 (6)
Febrile neutropenia	13 (6)	15 (8)
Nervous System Disorders		
Paraesthesia	26 (12)	31 (16)
Neuropathy peripheral	30 (14)	23 (12)
Headache	18 (9)	26 (13)
Dizziness	14 (7)	13 (7)
Musculoskeletal and Connective Tissue Disorders		

Body System/ Adverse Event	Rituximab IV + Chemo N=210 No. (%)	Rituximab SC + Chemo N=197 No. (%)
Arthralgia	20 (10)	25 (13)
Back pain	25 (12)	18 (9)
Bone pain	16 (8)	19 (10)
Pain in extremity	11 (5)	19 (10)
Myalgia	10 (5)	15 (8)
Muscle spasms	6 (3)	16 (8)
Infections and Infestations		
Upper respiratory tract infection	21 (10)	29 (15)
Urinary tract infection	29 (14)	15 (8)
Nasopharyngitis	21 (10)	19 (10)
Bronchitis	16 (8)	16 (8)
Pneumonia	9 (4)	21 (11)
Sinusitis	9 (4)	14 (7)
Influenza	13 (6)	8 (4)
Conjunctivitis	11 (5)	9 (5)
Skin and Subcutaneous Tissue Disorders		
Alopecia	22 (10)	28 (14)
Pruritus	25 (12)	19 (10)
Rash	14 (7)	19 (10)
Erythema	11 (5)	17 (9)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	28 (13)	45 (23)
Dyspnoea	16 (8)	22 (11)
Oropharyngeal pain	17 (8)	17 (9)
Psychiatric Disorders		
Insomnia	18 (9)	18 (9)
Vascular Disorders		
Hypertension	12 (6)	11 (6)

Chronic Lymphocytic Leukemia

In Part 2 of the Phase Ib study, BO25341 (SAWYER), the proportion of patients reporting an AE of any grade during the study was 91% in the RITUXAN IV arm (81/89 patients) compared with 96% in the RITUXAN SC arm (82/85 patients). The most common adverse events, occurring in > 20% of patients in either treatment arm, were neutropenia (RITUXAN IV: 58%; RITUXAN SC: 65%), thrombocytopenia (RITUXAN IV: 26%; RITUXAN SC: 24%), pyrexia (RITUXAN IV: 25%; RITUXAN SC: 32%), nausea (RITUXAN IV: 35%; RITUXAN SC: 38%) and vomiting (RITUXAN IV: 22%; RITUXAN SC: 21%). The most common SAE overall was febrile neutropenia (RITUXAN IV: 4%; RITUXAN SC: 11%).

Local cutaneous reactions, including injection site reactions, were very common (≥ 1/10) in patients receiving RITUXAN SC. In study BO25341 (SAWYER), local cutaneous reactions were reported in up to 42% of patients in the RITUXAN SC arm. The most common local cutaneous reactions were: injection site erythema (26%), injection site pain (16%), and injection

site swelling (5%). Events seen following subcutaneous administration were mild or moderate, apart from two patients who experienced Grade 3 local cutaneous reactions (injection site erythema, injection site pain, and injection site swelling). Local cutaneous reactions of any Grade in the RITUXAN SC arm were most common during the first subcutaneous cycle (Cycle 2), followed by the second and the incidence decreased with subsequent injections.

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

Table 2 Adverse Events Occurring in at Least 5% of Subjects in Either Treatment Arm – Study BO25341 (SAWYER) Part 2 (Safety Analysis Population)

Body System / Adverse Event	Rituximab IV + Chemo N = 89 No. (%)	Rituximab SC +Chemo N = 85 No. (%)
Blood And Lymphatic System Disorders		
Neutropenia	52 (58)	55 (65)
Thrombocytopenia	23 (26)	20 (24)
Anaemia	21 (24)	11 (13)
Leukopenia	14 (16)	16 (19)
Febrile Neutropenia	7 (8)	9 (11)
Gastrointestinal Disorders		
Nausea	31 (35)	32 (38)
Vomiting	20 (22)	18 (21)
Diarrhoea	10 (11)	10 (12)
Constipation	7 (8)	7 (8)
Abdominal Pain	5 (6)	8 (9)
General Disorders and Administration Site		
Pyrexia	22 (25)	27 (32)
Asthenia	15 (17)	7 (8)
Injection Site Erythema	-	22 (26)
Chills	9 (10)	11 (13)
Fatigue	9 (10)	9 (11)
Injection Site Pain	-	14 (16)
Infections and Infestations		
Upper Respiratory Tract Infection	11 (12)	11 (13)
Bronchitis	5 (6)	6 (7)
Respiratory Tract Infection	4 (4)	7 (8)
Urinary Tract Infection	7 (8)	2 (2)
Pneumonia	5 (6)	2 (2)
Skin and Subcutaneous Tissue Disorders		
Erythema	6 (7)	13 (15)
Rash	9 (10)	10 (12)
Pruritus	4 (4)	7 (8)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	10 (11)	11 (13)
Dyspnoea	7 (8)	3 (4)
Oropharyngeal Pain	3 (3)	5 (6)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	1 (1)	8 (9)
Pain in Extremity	2 (2)	6 (7)
Bone Pain	2 (2)	5 (6)

Body System / Adverse Event	Rituximab IV + Chemo N = 89 No. (%)	Rituximab SC +Chemo N = 85 No. (%)
Nervous System Disorders		
Headache	8 (9)	6 (7)
Vascular Disorders		
Hypotension	6 (7)	1 (1)
Hypertension	5 (6)	-
Psychiatric Disorders		
Insomnia	6 (7)	1 (1)

INTRAVENOUS FORMULATION

Information in this section reports data from a separate Product Monograph for RITUXAN IV.

The frequencies of adverse drug reactions (ADRs) reported with RITUXAN 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 randomized 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, common ≥ 1/100 to < 1/10 and uncommon ≥ 1/1,000 to < 1/100.

RITUXAN Monotherapy/Maintenance Therapy

The ADRs in Table 3 are based on data from single-arm studies including 356 patients with low-grade or follicular lymphoma treated with RITUXAN weekly as 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. The table also contains ADRs based on data from 671 patients with follicular lymphoma who received RITUXAN as maintenance therapy for up to 2 years following response to initial induction with CHOP or R-CHOP, R-CVP or R-FCM (see CLINICAL TRIALS section for further details). The ADRs were reported up to 12 months after treatment with monotherapy and up to 1 month after treatment with RITUXAN maintenance.

Table 3 Summary of ADRs Reported in Patients with Low-Grade or Follicular Lymphoma Receiving RITUXAN Monotherapy (N=356) or RITUXAN maintenance Treatment (N=166) in Clinical Trials

System Organ Class	Very Common (≥ 10%)	Common (≥1% to < 10%)	Uncommon (≥0.1% to < 1%)
Infections and infestations	bacterial infections, viral infections	sepsis , [+]pneumonia, [+]febrile infection, [+]herpes zoster, [+]respiratory tract infection, fungal infections, infections of unknown etiology	
Blood and the	neutropenia , leucopenia	anemia, thrombocytopenia	coagulation disorders,

System Organ Class	Very Common (≥ 10%)	Common (≥1% to < 10%)	Uncommon (≥0.1% to < 1%)
lymphatic system disorders			transient aplastic anemia, hemolytic anemia, lymphadenopathy
Immune system disorders	angioedema	hypersensitivity	
Metabolism and nutrition disorders		hyperglycemia, weight decrease, peripheral edema, face edema, increased LDH, hypocalcemia	
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 ischemia, bradycardia
Vascular disorders		hypertension, orthostatic hypotension, hypotension	
Respiratory, thoracic and mediastinal disorders		bronchospasm, respiratory disease, chest pain, dyspnea, cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia
Gastrointestinal disorders	nausea	vomiting, diarrhea, abdominal pain, dysphagia, stomatitis, constipation dyspepsia, anorexia, throat irritation	abdominal enlargement
Skin and subcutaneous tissue disorders	pruritus, rash	urticaria, +alopecia, sweating, night sweats	
Musculoskeletal, connective tissue and bone disorders		hypertonia, myalgia, arthralgia, back pain, neck pain, pain	
General disorders and administration site conditions	fever, chills, asthenia, headache	tumour pain, flushing, malaise, cold syndrome	infusion site pain
Investigations	decreased IgG levels		
For each term, the frequency count was based on reactions of all grades (from mild to severe), except for terms marked with "+" where the frequency count was based only on severe (≥ Grade 3 NCI common toxicity criteria) reactions. Only the highest frequency observed in either trial is reported.			

RITUXAN Maintenance Treatment

Previously Untreated Follicular Non-Hodgkin's Lymphoma
In a study (MO18264) of patients with previously untreated Follicular non-Hodgkin's Lymphoma (see CLINICAL TRIALS), detailed safety data collection was limited to Grade ≥ 2 infections, Grade ≥ 3 adverse events, and serious adverse events (see Table 4).

Table 4 Summary of Adverse Events Reported in ≥ 1% of Patients Receiving RITUXAN Maintenance Therapy in MO18264

Body System Adverse Event	**Observation** **N = 508** **n (%)**	**RITUXAN** **N = 501** **n (%)**
All Body Systems	179 (35.2)	263 (52.5)
Infections and Infestations	114 (22.4)	184 (36.7)
Bronchitis	24 (4.7)	47 (9.4)
Upper respiratory tract infection	11 (2.2)	26 (5.2)
Sinusitis	8 (1.6)	19 (3.8)
Infection	10 (2.0)	12 (2.4)
Nasopharyngitis	14 (2.8)	8 (1.6)
Urinary tract infection	8 (1.6)	13 (2.6)
Oral herpes	2 (0.4)	10 (2.0)
Rhinitis	2 (0.4)	10 (2.0)
Lung infection	4 (0.8)	7 (1.4)
Pharyngitis	4 (0.8)	7 (1.4)
Pneumonia	4 (0.8)	7 (1.4)
Respiratory tract infection	3 (0.8)	8(1.6)
Viral infection	3 (0.6)	5 (1.0)
Ear infection	1 (0.2)	5(1.0)
Gastroenteritis	1 (0.2)	5 (1.0)
Blood and Lymphatic System Disorders	7 (1.4)	26 (5.2)
Neutropenia	5 (1.0)	19 (3.8)
Leukopenia	1 (0.2)	8 (1.6)
Neoplasms Benign, Malignant and Unspecified (incl. cysts and polyps)	19 (3.7)	22 (4.4)
Basal cell carcinoma	4 (0.8)	5 (1.0)

Uncommon (<1%) Adverse Events Reported in Clinical Trial MO18264 (not already listed in the Oncology Adverse Events Section)

Infections and infestations: escherichia urinary tract infection, herpes virus infection, cystitis, folliculitis, haemophilus infection, viral upper respiratory tract infection, skin infection, acute tonsillitis, catheter related infection, cellulitis, central line infection, paronychia, pyelonephritis, skin candida, staphylococcal infection, viral pharyngitis, abscess limb, appendicitis, ascariasis, broncopneumonia, campylobacter infection, campylobacter intestinal infection, cystitis escherichia, device related infection, endocarditis, fungal skin infection, gastric infection,

gastrointestinal infection, helicobacter infection, herpes ophthalmic, impetigo, infective exacerbation of chronic obstructive airways disease, klebsiella infection, laryngitis, lower respiratory tract infection, lyme disease, meningitis, moraxella infection, mycobacterial infection, oral fungal infection, pertussis, postoperative abscess, postoperative wound infection, pulmonary tuberculosis, roseola, salmonellosis, serratia infection, skin bacterial infection, staphylococcal bacteraemia, staphylococcal skin infection, streptococcal bacteraemia, tinea cruris, tinea pedis, tracheitis, upper aerodigestive tract infection, vaginitis bacterial, vulvovaginal candidiasis, vulvovaginal mycotic infection

Neoplasms benign, malignant and unspecified (including cysts and polyps): colon cancer, bowen's disease, breast cancer, dysplastic naevus syndrome, prostate cancer, acute myeloid leukaemia, adenocarcinoma, hypergammaglobulinaemia benign monoclonal, lipoma, lung adenocarcinoma, stage unspecified meningioma, neoplasm prostate, neuroendocrine carcinoma of the skin, skin cancer, skin papilloma, squamous cell carcinoma of skin

Nervous system disorders: carpal tunnel syndrome, convulsion, transient ischaemic attack, aphasia, facial palsy, Parkinson's disease, subarachnoid hemorrhage

Cardiac disorders: aortic valve disease, cardiac arrest, congestive cardiomyopathy, ventricular extrasystoles

Respiratory, thoracic and mediastinal disorders: oropharyngeal pain, dyspnea, sleep apnea syndrome, pulmonary hemorrhage, rhinorrhea

Gastrointestinal disorders: intestinal obstruction, abdominal hernia, inguinal hernia, umbilical hernia, colonic polyp, gastrooesophagitis, jejunal perforation, parotid gland enlargement, sigmoiditis

Musculoskeletal and connective tissue disorders: artharalgia, intervertebral disc protrusion, crest syndrome

General Disorders and Administration Site Conditions: hyperthermia

Psychiatric disorders: depression, suicide attempt, anxiety disorder, panic attack

Eye disorders: conjunctivitis, glaucoma, maculopathy

Investigations: neutrophil count decreased, aspartate aminotransferase increased, gamma-glutamyltransferase increased

Vascular disorders: thrombophlebitis, vena cava thrombosis

Renal and urinary disorders: hydronephrosis

Table 5 Summary of Grade 3–5 AEs by Age Group (MSAP) in MO18264

Age Group (years)	Observation N=508 n (%)	RITUXAN N=501 n (%)
< 65	n = 387	n = 379
Total patients with at least one Grade 3/4 AE	54 (13.9)	84 (22.2)
Total patients with at least one Grade 3/4 Infection & Infestations AE	2 (0.5)	16 (4.2)
Total patients with a Grade 5 AE	1 (0.2)	2 (0.5)
Total patients with a Grade 5 Infection & Infestations AE	—	—*
65–74 inclusive	n = 97	n = 99
Total patients with at least one Grade 3/4 AE	18 (18.6)	24 (24.2)
Total patients with at least one Grade 3/4 Infection & Infestations AE	2 (2.1)	4 (4.0)
Total patients with a Grade 5 AE	1 (1.0)	—
Total patients with a Grade 5 Infection & Infestations AE	—	—
≥ **75**	n = 24	n = 23
Total patients with at least one Grade 3/4 AE	9 (37.5)	6 (26.1)
Total patients with at least one Grade 3/4 Infection & Infestations AE	1 (4.2)	2 (8.7)
Total patients with a Grade 5 AE	—	1 (4.3)
Total patients with a Grade 5 Infection & Infestations AE	—	—

MSAP: Maintenance Safety Analysis Population
Percentages are based on the corresponding number (n).
* One patient died of fulminant hepatitis B (categorized as a hepatobiliary AE rather than an Infection & Infestation AE).

The results of RITUXAN maintenance treatment in patients older than 75 years of age should be interpreted with caution due to the small number of patients in this subgroup.

Relapsed/Refractory Follicular Non-Hodgkin's Lymphoma
The following data are from a phase III clinical trial where patients with relapsed or refractory follicular non-Hodgkin's lymphoma were randomized in a first phase to induction treatment with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or RITUXAN plus CHOP (R-CHOP). Patients who responded to induction treatment with CHOP or R-CHOP were randomized in a second phase to receive no further treatment (observation) or maintenance treatment with RITUXAN.

In the induction phase of the trial, a total of 462 patients (228 on CHOP, 234 on R-CHOP) contributed to the safety evaluation of the two induction regimens.

Table 6 Induction Phase: Summary of NCIC-CTC Grade 3 and 4 Adverse Events Reported in ≥ 1% of 462 Patients in Either Treatment Group (CHOP or R-CHOP)

System Organ Class	Incidence N (%)	
	CHOP	R-CHOP
Adverse Event	**152 (67)**	**185 (79)**
Blood and Lymphatic System Disorders		
Neutropenia*	108 (47)	129 (55)
Leucopenia	106 (46)	111 (47)
Thrombocytopenia	18 (8)	17 (7)

System Organ Class	Incidence N (%)	
	CHOP	R-CHOP
Adverse Event	**152 (67)**	**185 (79)**
Febrile neutropenia*	8 (4)	14 (6)
Hematotoxicity	12 (5)	9 (4)
Anemia	5 (2)	6 (3)
Lymphopenia	3 (1)	2 (<1)
Cardiac Disorders		
Cardiac disorder	6 (3)	2 (<1)
Gastrointestinal Disorders		
Nausea*	9 (4)	13 (6)
Vomiting	8 (4)	7 (3)
Diarrhea	5 (2)	6 (3)
Abdominal pain	6 (3)	4 (2)
Constipation*	1 (<1)	7 (3)
Stomatitis*	1 (<1)	4 (2)
General Disorders and Administration Site Conditions		
Asthenia	10 (4)	5 (2)
Pyrexia	6 (3)	7 (3)
Pain	1 (<1)	3 (1)
Immune System Disorders		
Hypersensitivity*	-	10 (4)
Infections and Infestations		
Neutropenic infection	18 (8)	15 (6)
Sepsis	5 (2)	3 (1)
Urinary tract infection	4 (2)	3 (1)
Pneumonia	-	3 (1)
Metabolism and Nutrition Disorders		
Hyperglycemia	5 (2)	4 (2)
Musculoskeletal and Connective Tissue Disorders		
Back pain*	1 (<1)	4 (2)
Pain in extremity	3 (1)	-
Nervous System Disorders		
Sensory disturbance	4 (2)	7 (3)
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	6 (3)	3 (1)
Skin and Subcutaneous Tissue Disorders		
Alopecia*	15 (7)	30 (13)
Skin disorder*	2 (<1)	4 (2)
Vascular Disorders		
Deep vein thrombosis	3 (1)	2 (<1)

* Adverse events that were reported at a higher incidence (≥ 2% difference) in the R-CHOP group compared to the CHOP group and, therefore, may be attributable to RITUXAN.

A total of 333 patients (167 observations, 166 RITUXAN) were included in the safety evaluation of the maintenance phase of the study. Maintenance treatment with RITUXAN consisted of a single infusion of RITUXAN at 375 mg/m^2 body surface area administered every 3 months for a maximum period of 2 years or until disease progression.

Table 7 Maintenance Phase: Summary of NCIC-CTC Adverse Events (Grades 1–4 and Grades 3-4) Reported in ≥ 1% of 333 Patients in Either Treatment Group (Observation or RITUXAN Maintenance)

System Organ Class	Incidence			
	Observation N=167		RITUXAN N=166	
	Grades 1-4 N (%)	Grades 3-4 N (%)	Grades 1-4 N (%)	Grades 3-4 N (%)
Adverse Event **Total patients with at least one adverse event**	**138 (83)**	**41 (25)**	**151 (91)**	**64 (39)**
Blood and Lymphatic System Disorders				
Leukopenia* [#]	37 (22)	4 (2)	50 (30)	9 (5)
Neutropenia* [#]	22 (13)	8 (5)	40 (24)	18 (11)
Thrombocytopenia	23 (14)	2 (1)	20 (12)	1 (<1)
Hematotoxicity	4 (2)	4 (2)	2 (1)	2 (1)
Lymphopenia	2 (1)	-	2 (1)	-
Cardiac Disorders				
Cardiac disorder [#]	9 (5)	4 (2)	10 (6)	6 (4)
Palpitations*	-	-	3 (2)	-
Angina pectoris	2 (1)	2 (1)	-	-
Arrhythmia	-	-	2 (1)	-
Ear and Labyrinth Disorders				
Hearing impaired	1 (<1)	-	2 (1)	-
Eye Disorders				
Conjunctivitis*	-	-	3 (2)	-
Gastrointestinal Disorders				
Diarrhea*	14 (8)	2 (1)	17 (10)	2 (1)
Abdominal pain*	11 (7)	-	17 (10)	-
Nausea	14 (8)	-	14 (8)	-
Stomatitis*	2 (1)	-	14 (8)	-
Dyspepsia	6 (4)	-	8 (5)	-
Vomiting*	4 (2)	-	9 (5)	-
Constipation*	2 (1)	-	8 (5)	-
Abdominal pain upper	3 (2)	-	4 (2)	-
Abdominal distension	3 (2)	-	2 (1)	-
Dry mouth	3 (2)	-	2 (1)	-
Reflux esophagitis	3 (2)	-	-	-
Gastric ulcer	2 (1)	-	-	-
Gastrointestinal ulcer	-	-	2 (1)	-
Intestinal obstruction	-	-	2 (1)	2 (1)
General Disorders and Administration Site Conditions				
Asthenia*	43 (26)	4 (2)	50 (30)	1 (<1)
Pyrexia*	6 (4)	1 (<1)	12 (7)	2 (1)
Influenza like illness*	6 (4)	-	10 (6)	-
Pain*	2 (1)	-	7 (4)	-
Chest Pain	5 (3)	-	3 (2)	-
Edema due to cardiac disease	3 (2)	-	4 (2)	-
Edema peripheral	3 (2)	-	3 (2)	-
Chills*	-	-	5 (3)	-
Chest discomfort	1 (<1)	-	2 (1)	-
Immune System Disorders				
Hypersensitivity*	1 (<1)	-	12 (7)	-
Infections and Infestations				

System Organ Class	Incidence			
	Observation N=167		RITUXAN N=166	
	Grades 1-4 N (%)	Grades 3-4 N (%)	Grades 1-4 N (%)	Grades 3-4 N (%)
Nasopharyngitis*	5 (3)	-	14 (8)	-
Upper respiratory tract infection*	4 (2)	-	13 (8)	-
Sinusitis*	2 (1)	-	10 (6)	-
Herpes zoster*	4 (2)	-	7 (4)	2 (1)
Bronchitis	6 (4)	-	4 (2)	-
Lower Respiratory tract infection*	2 (1)	-	7 (4)	-
Urinary tract infection	4 (2)	-	5 (3)	-
Herpes simplex*	2 (1)	-	6 (4)	-
Influenza	3 (2)	-	5 (3)	-
Pharyngitis*	1 (<1)	-	6 (4)	-
Pneumonia*	2 (1)	1 (<1)	5 (3)	4 (2)
Respiratory tract infection*	-	-	7 (4)	3 (2)
Candidiasis	1 (<1)		3 (2)	
Gastroenteritis	2 (1)	-	2 (1)	-
Lung infection	1 (<1)	-	3 (2)	-
Rhinitis	1 (<1)	-	3 (2)	-
Cystitis	1 (<1)	-	2 (1)	-
Diverticulitis	1 (<1)	-	2 (1)	-
Ear infection	1 (<1)	-	2 (1)	-
Eye infection*	-	-	3 (2)	-
Localized infection	1 (<1)	-	2 (1)	-
Onychomycosis	1 (<1)	-	2 (1)	-
Oral infection	1 (<1)		2 (1)	
Vaginal candidiasis	1 (<1)	-	2 (1)	-
Viral infection*	-	-	3 (2)	-
Cellulitis	2 (1)		-	
Febrile infection	-	-	2 (1)	2 (1)
Infection	2 (1)	-	-	-
Otitis externa	-	-	2 (1)	-
Investigations				
Weight decreased	6 (4)	-	8 (5)	-
Weight increased*	3 (2)	-	7 (4)	-
Blood lactate dehydrogenase increased	1 (<1)	-	3 (2)	-
Blood alkaline phosphatase increased	-	-	2 (1)	-
Metabolism and Nutrition Disorders				
Anorexia	8 (5)	-	5 (3)	-
Hyperglycemia	3 (2)	-	2 (1)	-
Hypokalemia	2 (1)	-	1 (<1)	-
Diabetes mellitus	2 (1)	-	-	-
Gout	-	-	2 (1)	-

System Organ Class	Incidence			
	Observation N=167		RITUXAN N=166	
	Grades 1-4 N (%)	Grades 3-4 N (%)	Grades 1-4 N (%)	Grades 3-4 N (%)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia*	13 (8)	-	20 (12)	-
Myalgia*	12 (7)	-	17 (10)	-
Back pain	8 (5)	-	12 (7)	-
Pain in extremity*	2 (1)	-	11 (7)	-
Bone pain	5 (3)	-	7 (4)	-
Shoulder pain	2 (1)	-	5 (3)	-
Groin pain	2 (1)	-	4 (2)	-
Musculoskeletal pain	3 (2)	-	1 (<1)	-
Neck pain	1 (<1)	-	2 (1)	-
Flank pain	-	-	2 (1)	-
Muscle spasms	-	-	2 (1)	-
Muscular weakness	-	-	2 (1)	-
Neoplasms Benign, Malignant and Unspecified (including Cysts and Polyps)				
Cancer pain	1 (<1)	-	2 (1)	-
Nervous System Disorders				
Sensory disturbance	40 (24)	2 (1)	38 (23)	3 (2)
Headache	8 (5)	-	9 (5)	-
Dizziness	6 (4)	-	3 (2)	-
Insomnia	5 (3)	-	4 (2)	-
Dysgeusia	2 (1)	-	1 (<1)	-
Vertigo	1 (<1)		2 (1)	
Syncope	2 (1)	-	-	-
Psychiatric Disorders				
Anxiety	6 (4)	-	6 (4)	-
Depression	4 (2)	-	4 (2)	-
Mood altered	1 (<1)	-	2 (1)	-
Renal and Urinary Disorders				
Dysuria	3 (2)	-	4 (2)	-
Pollakisuria	1 (<1)	-	4 (2)	-
Nephrolithiasis	2 (1)	-	1 (<1)	-
Nocturia	1 (<1)	-	2 (1)	-
Hematuria	-	-	2 (1)	-
Renal colic	-	-	2 (1)	-
Urinary incontinence	2 (1)	-	-	-
Reproductive System and Breast Disorders				
Amenorrhea	-	-	2 (1)	-
Testicular pain	2 (1)	-	-	-
Respiratory, Thoracic and Mediastinal Disorders				
Cough*	15 (9)	-	22 (13)	2 (1)
Dyspnea	7 (4)	-	5 (3)	-
Dyspnea exertional	2 (1)	-	4 (2)	-
Rhinitis allergic	2 (1)	-	2 (1)	-
Nasal congestion	-	-	3 (2)	-

System Organ Class	Incidence			
	Observation N=167		RITUXAN N=166	
	Grades 1-4 N (%)	Grades 3-4 N (%)	Grades 1-4 N (%)	Grades 3-4 N (%)
Pharyngolaryngeal pain	-	-	3 (2)	-
Lung disorder	-	-	2 (1)	-
Pleural effusion	2 (1)	-	-	-
Pleuritic pain	-	-	2 (1)	-
Skin and Subcutaneous Tissue Disorders				
Alopecia	12 (7)	-	12 (7)	3 (2)
Rash	11 (7)	-	10 (6)	-
Hyperhidrosis	10 (6)	2 (1)	7 (4)	-
Night sweats	10 (6)	-	6 (4)	-
Pruritus	6 (4)	-	6 (4)	-
Skin disorder	4 (2)	-	3 (2)	-
Rash pruritic	3 (2)	-	3 (2)	-
Nail disorder	2 (1)	-	2 (1)	-
Dermatitis	1 (<1)		2 (1)	
Psoriasis	3 (2)	-	-	-
Rash erythematous	1 (<1)	-	2 (1)	-
Periorbital edema	2 (1)	-	-	-
Vascular Disorders				
Hot Flush*	3 (2)	-	7 (4)	-
Hemorrhage	3 (2)	-	3 (2)	-
Hypertension	3 (2)	2 (1)	3 (2)	3 (2)
Lymphedema	-	-	2 (1)	-

* Adverse events (Grades 1-4) that were reported at a higher incidence (≥ 2% difference) in the RITUXAN maintenance group compared to observation and, therefore, may be attributable to RITUXAN.

Adverse events (Grades 3-4) that were reported at a higher incidence (≥ 2% difference) in the RITUXAN maintenance group compared to observation and, therefore, may be attributable to RITUXAN.

RITUXAN in Combination with Chemotherapy in NHL and CLL

The ADRs listed in the table below are based on RITUXAN-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, and 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 previously treated CLL patients, treated with RITUXAN in combination with fludarabine and cyclophosphamide (R-FC) (see CLINICAL TRIALS for further details).

Table 8 Summary of Severe ADRs Reported in Patients Receiving R-CHOP in DLBCL (N=202), R-CHOP in Follicular Lymphoma (N=234) and R-CVP in Follicular Lymphoma (N=162) and R-FC in Previously Untreated CLL (N=397) or Previously Treated CLL (N=274)

System Organ Class	Very Common (≥ 10%)	Common (≥ 1% to <10%)
Infections and infestations	bronchitis	acute bronchitis, sinusitis, hepatitis B*

Blood and the lymphatic system disorders	neutropenia[#] febrile neutropenia thrombocytopenia	Pancytopenia granulocytopenia
Skin and subcutaneous tissue disorders	alopecia	skin disorder
General disorders and administration site conditions		fatigue, shivering

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

RITUXAN in Combination with CVP Chemotherapy

The following data are based on 321 patients from a randomized phase III clinical trial comparing RITUXAN plus CVP (R-CVP) to CVP alone (162 R-CVP, 159 CVP). Differences between the treatment groups with respect to the type and incidence of adverse event were mainly accounted for by typical adverse events associated with RITUXAN monotherapy.

Table 9 Summary of Adverse Events (all Intensities) Reported in ≥ 1% of 321 Patients in Either Treatment Group (CVP or R-CVP)

	Incidence	
	CVP N=159	**R-CVP N=162**
Body System	**N (%)**	**N (%)**
Blood and Lymphatic System Disorders		
Neutropenia	3 (1.9)	13 (8.0)
Anemia NOS	4 (2.5)	4 (2.5)
Leukopenia NOS	-	2 (1.2)
Lymphadenopathy	2 (1.3)	-
Cardiac Disorders		
Palpitations	2 (1.3)	2 (1.2)
Tachycardia NOS	1 (0.6)	2 (1.2)
Ear and Labyrinth Disorders		
Ear Pain	3 (1.9)	4 (2.5)
Tinnitus	1 (0.6)	2 (1.2)
Vertigo	2 (1.3)	-
Eye Disorders		
Vision Blurred	4 (2.5)	5 (3.1)
Eye Pain	1 (0.6)	4 (2.5)
Dry Eye NOS	1 (0.6)	2 (1.2)
Eye Irritation	2 (1.3)	1 (0.6)
Gastrointestinal Disorders		
Nausea	56 (35.2)	55 (24.0)
Constipation	43 (27.0)	42 (25.9)
Abdominal Pain NOS	21 (13.2)	23 (14.2)
Vomiting NOS	25 (15.7)	19 (11.7)
Dyspepsia	16 (10.1)	23 (14.2)
Diarrhea NOS	19 (11.9)	19 (11.7)
Abdominal Pain Upper	10 (6.3)	11 (6.8)
Stomatitis	11 (6.9)	7 (4.3)

	Incidence	
	CVP N=159	R-CVP N=162
Body System	**N (%)**	**N (%)**
Oral Pain	3 (1.9)	9 (5.6)
Abdominal Distension	3 (1.9)	4 (2.5)
Abdominal Discomfort	2 (1.3)	4 (2.5)
Flatulence	2 (1.3)	4 (2.5)
Mouth Ulceration	3 (1.9)	3 (1.9)
Ascites	3 (1.9)	1 (0.6)
Gastritis NOS	1 (0.6)	3 (1.9)
Abdominal Pain Lower	2 (1.3)	1 (0.6)
Aphthous Stomatitis	1 (0.6)	2 (1.2)
Gastroesophageal Reflux Disease	1 (0.6)	2 (1.2)
Rectal Hemorrhage	2 (1.3)	1 (0.6)
Toothache	2 (1.3)	1 (0.6)
Dysphagia	-	2 (1.2)
Hypoesthesia Oral	-	2 (1.2)
Loose Stools	2 (1.3)	-
Tongue Ulceration	2 (1.3)	-
General Disorders and Administration Site Conditions		
Fatigue	39 (24.5)	38 (23.5)
Pyrexia	14 (8.8)	21 (13.0)
Asthenia	14 (8.8)	8 (4.9)
Lethargy	9 (5.7)	12 (7.4)
Influenza like illness	7 (4.4)	13 (8.0)
Rigors	3 (1.9)	16 (9.9)
Pain NOS	5 (3.1)	12 (7.4)
Chest Pain	5 (3.1)	11 (6.8)
Chest Tightness	2 (1.3)	11 (6.8)
Edema Peripheral	8 (5.0)	5 (3.1)
Mucosal Inflammation NOS	4 (2.5)	5 (3.1)
Axillary Pain	4 (2.5)	-
Feeling Hot	1 (0.6)	2 (1.2)
Malaise	1 (0.6)	2 (1.2)
Chest Discomfort	-	2 (1.2)
Hyperpyrexia	-	2 (1.2)
Immune System Disorders		
Hypersensitivity NOS	1 (0.6)	5 (3.1)
Seasonal Allergy	1 (0.6)	2 (1.2)
Infections and Infestations		
Nasopharyngitis	11 (6.9)	15 (9.3)
Upper Respiratory Tract Infection NOS	9 (5.7)	4 (2.5)
Urinary Tract Infection NOS	6 (3.8)	6 (3.7)
Herpes Simplex	4 (2.5)	4 (2.5)
Pneumonia NOS	2 (1.3)	6 (3.7)
Lower Respiratory Tract Infection NOS	1 (0.6)	6 (3.7)
Influenza	4 (2.5)	2 (1. 2)
Pharyngitis	3 (1.9)	1 (0.6)
Viral Infection NOS	-	4 (2.5)
Gastroenteritis Viral NOS	1 (0.6)	2 (1.2)
Herpes Zoster	2 (1.3)	1 (0.6)
Oral Candidiasis	1 (0.6)	2 (1.2)
Tooth Abscess	2 (1.3)	1 (0.6)
Infection NOS	-	2 (1.2)
Neutropenic Sepsis	2 (1.3)	-

	Incidence	
	CVP N=159	R-CVP N=162
Body System	**N (%)**	**N (%)**
Respiratory Tract Infection NOS	-	2 (1.2)
Sinusitis NOS	2 (1.3)	-
Injury, Poisoning and Procedural Complications		
Excoriation	3 (1.9)	1 (0.6)
Joint Sprain	2 (1.3)	1 (0.6)
Investigations		
Weight Increased	2 (1.3)	6 (3.7)
Weight Decreased	4 (2.5)	3 (1.9)
Blood Glucose Increased	2 (1.3)	-
Blood Lactate Dehydrogenase Increased	2 (1.3)	-
Metabolism and Nutrition Disorders		
Anorexia	5 (3.1)	2 (1.2)
Appetite Increased NOS	2 (1.3)	2 (1.2)
Hyperglycemia NOS	-	2 (1.2)
Musculoskeletal and Connective Tissue Disorders		
Back Pain	16 (10.1)	13 (8.0)
Arthralgia	11 (6.9)	14 (8.6)
Pain in Extremity	9 (5.7)	10 (6.2)
Myalgia	7 (4.4)	9 (5.6)
Muscle Cramp	3 (1.9)	10 (6.2)
Bone Pain	5 (3.1)	5 (3.1)
Groin Pain	5 (3.1)	2 (1.2)
Pain in Jaw	3 (1.9)	4 (2.5)
Neck Pain	6 (3.8)	-
Chest Wall Pain	2 (1.3)	3 (1.9)
Joint Swelling	3 (1.9)	2 (1.2)
Buttock Pain	2 (1.3)	-
Facial Pain	-	2 (1.2)
Nervous System Disorders		
Headache	30 (18.9)	29 (17.9)
Peripheral Neuropathy NOS	25 (15.7)	30 (18.5)
Paresthesia	25 (15.7)	28 (17.3)
Hypoesthesia	11 (6.9)	14 (8.6)
Dizziness	13 (8.2)	9 (5.6)
Dysgeusia	8 (5.0)	11 (6.8)
Peripheral Sensory Neuropathy	5 (3.1)	1 (0.6)
Polyneuropathy NOS	3 (1.9)	2 (1.2)
Neuropathy NOS	2 (1.3)	2 (1.2)
Parosmia	4 (2.5)	-
Dysphonia	2 (1.3)	1 (0.6)
Hyperesthesia	1 (0.6)	2 (1.2)
Paresthesia oral	-	3 (1.9)
Tremor	1 (0.6)	2 (1.2)
Burning Sensation NOS	-	2 (1.2)
Sinus Headache	2 (1.3)	-
Psychiatric Disorders		
Insomnia	16 (10.1)	20 (12.3)
Depression	7 (4.4)	4 (2.5)
Anxiety	4 (2.5)	3 (1.9)
Mood Alteration NOS	1 (0.6))	3 (1.9)
Sleep Disorder NOS	1 (0.6)	2 (1.2)

	Incidence	
	CVP N=159	R-CVP N=162
Body System	**N (%)**	**N (%)**
Irritability	-	2 (1.2)
Renal and Urinary Disorders		
Dysuria	4 (2.5)	2 (1.2)
Pollakiuria	2 (1.3)	4 (2.5)
Micturition Urgency	2 (1.3)	3 (1.9)
Cystitis NOS	2 (1.3)	2 (1.2)
Hematuria	-	2 (1.2)
Renal Failure Acute	-	2 (1.2)
Urinary Retention	-	2 (1.2)
Reproductive System and Breast Disorders		
Breast Pain	1 (0.6)	2 (1.2)
Vaginal Hemorrhage	2 (1.3)	1 (0.6)
Amenorrhea NOS	-	2 (1.2)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	8 (5.0)	25 (15.4)
Pharyngolaryngeal Pain	15 (9.4)	17 (10.5)
Dyspnea	9 (5.7)	14 (8.6)
Bronchitis NOS	3 (1.9)	6 (3.7)
Nasal Congestion	3 (1.9)	4 (2.5)
Throat Irritation	-	6 (3.7)
Asthma NOS	3 (1.9)	1 (0.6)
Dyspnea Exertional	3 (1.9)	1 (0.6)
Pleural Effusion	2 (1.3)	2 (1.2)
Rhinitis NOS	3 (1.9)	1 (0.6)
Throat Tightness	-	4 (2.5)
Bronchospasm NOS	-	3 (1.9)
Hiccups	2 (1.3)	1 (0.6)
Hoarseness	2 (1.3)	1 (0.6)
Productive Cough	1 (0.6)	2 (1.2)
Respiratory Tract Congestion	1 (0.6)	2 (1.2)
Wheezing	1 (0.6)	2 (1.2)
Sinus Pain	2 (1.3)	-
Skin and Subcutaneous Tissue Disorders		
Alopecia	21 (13.2)	22 (13.6)
Rash NOS	7 (4.4)	22 (13.6)
Pruritus	1 (0.6)	15 (9.3)
Night Sweats	8 (5.0)	5 (3.1)
Sweating Increased	5 (3.1)	6 (3.7)
Urticaria NOS	-	9 (5.6)
Erythema	-	5 (3.1)
Acne NOS	-	4 (2.5)
Dry Skin	1 (0.6)	3 (1.9)
Hypotrichosis	1 (0.6)	3 (1.9)
Rash Generalized	2 (1.3)	2 (1.2)
Contusion	2 (1.3)	1 (0.6)
Psoriasis	2 (1.3)	1 (0.6)
Rash Pruritic	1 (0.6)	2 (1.2)
Skin Lesion NOS	-	3 (1.9)
Pain of Skin	2 (1.3)	-
Vascular Disorders		
Flushing	4 (2.5)	21 (13.0)

	Incidence	
	CVP N=159	R-CVP N=162
Body System	**N (%)**	**N (%)**
Hypertension NOS	3 (1.9)	8 (4.9)
Hypotension NOS	1 (0.6)	6 (3.7)
Lymphedema NOS	2 (1.3)	-
Phlebitis NOS	-	2 (1.2)

RITUXAN in Combination with CHOP Chemotherapy

The following table shows all Grade 3 to 4 clinical adverse events, including Grade 2 infections, reported in ≥ 1% of patients in either treatment group (CHOP and RITUXAN plus CHOP [R-CHOP]) in a randomized phase III clinical trial in the total safety population (n=398). Adverse events were graded according to the four-scale National Cancer Institute of Canada (NCIC) Common Toxicity Criteria.

Table 10 Summary of Grade 3 and 4 Adverse Events (Including Grade 2 Infections) Reported in ≥ 1% of 398 Patients in Either Treatment Group (CHOP or R-CHOP)

	Incidence	
Any Grade 3 and 4 Adverse Event (including Grade 2 Infections)	**CHOP N=196**	**R-CHOP N=202**
	N (%)	**N (%)**
Body System	**148 (75.5)**	**164 (81.2)**
Blood and Lymphatic System Disorders		
Febrile neutropenia[#]	47 (24.0)	46 (22.8)
Neutropenia	10 (5.1)	11 (5.4)
Anemia	10 (5.1)	9 (4.5)
Pancytopenia	2 (1.0)	2 (1.0)
Thrombocytopenia	2 (1.0)	2 (1.0)
Cardiac Disorder		
Cardiac failure	11 (5.6)	9 (4.5)
Atrial fibrillation*	1 (0.5)	5 (2.5)
Pulmonary edema	2 (1.0)	4 (2.0)
Tachycardia	1 (0.5)	3 (1.5)
Cardiomyopathy	3 (1.5)	-
Left ventricular dysfunction	2 (1.0)	-
Endocrine Disorders		
Diabetes mellitus inadequate control	4 (2.0)	2 (1.0)
Gastrointestinal Disorders		
Vomiting	13 (6.6)	8 (4.0)
Abdominal pain*	9 (4.6)	13 (6.4)
Constipation	8 (4.1)	6 (3.0)
Nausea	9 (4.6)	4 (2.0)
Diarrhea	5 (2.6)	5 (2.5)
Gastrointestinal disorder	3 (1.5)	2 (1.0)
Abdominal pain upper	2 (1.0)	-
Dysphagia	2 (1.0)	-
Gastritis	2 (1.0)	-
Ileus paralytic	2 (1.0)	-

Any Grade 3 and 4 Adverse Event (including Grade 2 Infections)	Incidence	
	CHOP N=196	R-CHOP N=202
	N (%)	N (%)
Melaena	2 (1.0)	-
General Disorders and Administration Site Conditions		
Pyrexia	34 (17.3)	26 (12.9)
Fatigue	14 (7.1)	9 (4.5)
General physical health deterioration	10 (5.1)	10 (5.0)
Mucosal inflammation	5 (2.6)	8 (4.0)
Shivering*	2 (1.0)	7 (3.5)
Chest pain	4 (2.0)	4 (2.0)
Influenza-like illness	3 (1.5)	4 (2.0)
Fall	4 (2.0)	3 (1.5)
Malaise	4 (2.0)	2 (1.0)
Multi-organ failure	4 (2.0)	2 (1.0)
Asthenia	1 (0.5)	4 (2.0)
Edema lower limb	1 (0.5)	4 (2.0)
Edema	-	3 (1.5)
Ulcer	2 (1.0)	1 (0.5)
Hepato-Billiary Disorders		
Cholestasis	1 (0.5)	3 (1.5)
Infections and Infestations		
Bronchitis*	16 (8.2)	24 (11.9)
Urinary tract infection	18 (9.2)	20 (9.9)
Pneumonia	15 (7.7)	11 (5.4)
Sepsis	7 (3.6)	4 (2.0)
Septic shock	7 (3.6)	4 (2.0)
Herpes zoster*	3 (1.5)	8 (4.0)
Implant infection	5 (2.6)	4 (2.0)
Staphylococcal septicemia	3 (1.5)	5 (2.5)
Superinfection lung	4 (2.0)	5 (2.5)
Acute bronchitis*	1 (0.5)	5 (2.5)
Lung infection	4 (2.0)	2 (1.0)
Sinusitis*	-	5 (2.5)
Herpes simplex	3 (1.5)	3 (1.5)
Tonsillitis	3 (1.5)	3 (1.5)
Infection	3 (1.5)	2 (1.0)
Nasopharyngitis	3 (1.5)	2 (1.0)
Cystitis	2 (1.0)	1 (0.5)
Erysipelas	2 (1.0)	1 (0.5)
Gastroenteritis helicobacter	2 (1.0)	-
Septicemia escherichial	2 (1.0)	-
Tooth infection	2 (1.0)	-
Injury and Poisoning		
Femoral neck fracture	2 (1.0)	2 (1.0)
Investigations		
Abnormal ejection fraction	4 (2.0)	4 (2.0)
Positive blood cultures	4 (2.0)	1 (0.5)
Metabolism and Nutrition Disorder		
Anorexia	5 (2.6)	4 (2.0)
Dehydration	2 (1.0)	-
Hyperglycemia	2 (1.0)	-
Musculoskeletal, Connective Tissue and Bone Disorder		

Any Grade 3 and 4 Adverse Event (including Grade 2 Infections)	Incidence	
	CHOP N=196	R-CHOP N=202
	N (%)	N (%)
Back pain*	2 (1.0)	5 (2.5)
Sciatica	2 (1.0)	2 (1.0)
Nervous System Disorder		
Paresthesia	2 (1.0)	5 (2.5)
Dizziness (excluding vertigo)	3 (1.5)	2 (1.0)
Cerebrovascular accident	1 (0.5)	3 (1.5)
Polyneuropathy	2 (1.0)	2 (1.0)
Depressed level of consciousness	2 (1.0)	-
Psychiatric Disorders		
Confusion	5 (2.6)	-
Depression	2 (1.0)	2 (1.0)
Renal and Urinary Disorders		
Renal colic	2 (1.0)	2 (1.0)
Urinary retention	2 (1.0)	1 (0.5)
Renal failure	2 (1.0)	-
Respiratory, thoracic and mediastinal disorders		
Dyspnea*	7 (3.6)	18 (8.9)
Cough	7 (3.6)	8 (4.0)
Rhinitis	5 (2.6)	2 (1.0)
Rhinorrhea	4 (2.0)	1 (0.5)
Skin and Subcutaneous Tissue Disorders		
Pruritus	3 (1.5)	3 (1.5)
Vascular Disorders		
Venous thrombosis deep limb	6 (3.1)	6 (3.0)
Hypotension	3 (1.5)	5 (2.5)
Hypertension*	1 (0.5)	5 (2.5)
Pulmonary embolism	3 (1.5)	2 (1.0)
Venous thrombosis	1 (0.5)	4 (2.0)
Peripheral ischemia	2 (1.0)	-
Phlebitis	2 (1.0)	-

* Adverse events that were reported at a higher incidence (≥2% difference) in the R-CHOP group as compared to the CHOP group and, therefore, may be attributable to R-CHOP.

Febrile neutropenia as reported by investigators: Fever and neutropenia with or without documented infection (see below, subsection Infections).

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 RITUXAN-arms compared to control arms: Hematotoxicity, neutropenic infection, urinary tract infection, septic shock, superinfection lung, implant infection, septicemia staphylococcal, lung infection, rhinorrhea, pulmonary edema, cardiac failure, sensory disturbance, venous thrombosis, mucosal inflammation NOS, influenza-like illness, edema lower limb, abnormal ejection fraction, pyrexia, general physical health deterioration, fall, multi-organ failure, venous thrombosis deep limb, abnormal ejection fraction, positive blood culture, anorexia, diabetes mellitus inadequate control.

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

RITUXAN in Combination with FC Chemotherapy

The following table shows all Grade 3 to 4 clinical adverse events and serious adverse events reported with a ≥ 2% difference in frequency between either treatment group (R-FC and FC) in ML17102 and BO17072. Grade 1 and 2 adverse events and Grade 4 lymphocytopenia were not captured in study ML17102. A total of 550 SAEs in 344 patients were reported across the two arms in the primary analysis of ML17102. Infections and infestations (15% in FC vs 18% in R-FC) and blood and lymphatic system disorders (11% in FC vs 17% in R-FC) were reported at higher frequencies, as expected, for the RITUXAN-containing arm. One case of tuberculosis was recorded as an adverse event in the R-FC arm. In the updated overall survival results (final analysis) of study ML17102 after a median of 66.4 months of observation (additional four years of follow-up data beyond that for the primary analysis), the safety profile of rituximab in combination with FC remained unchanged compared with that reported at the time of the primary analysis.

Table 11 Summary of Grade 3 & 4 Adverse Events and Serious Adverse Events that Occurred with a Difference in Incidence of ≥ 2% Between Either the R-FC Arm or the FC Arm

	Incidence			
	ML17102 (previously untreated CLL)**		**BO17072 (previously treated CLL)**	
	FC N= 396	**R-FC N = 397**	**FC N=272**	**R-FC N =274**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Any Grade 3 and 4 Adverse Event*				
Blood and Lymphatic System Disorders				
Neutropenia	75 (18.9)	119 (30.0)	108 (39.7)	116 (42.3)
Leukopenia	46 (11.6)	93 (23.4)	-	-
Thrombocytopenia	39 (9.8)	26 (6.5)	-	-
Febrile neutropenia	22 (5.6)	37 (9.3)	32 (11.8)	40 (14.6)
Anemia	26 (6.6)	16 (4.0)	-	-
Pancytopenia	5 (1.3)	13 (3.3)	-	-
Granulocytopenia			12 (4.4)	18 (6.6)
General Disorders and Administration Site Conditions				
Pyrexia	21 (5.3)	12 (3.0)	-	-
Infections and infestations				
Hepatitis B	-	-	-	6 (2.2)
Any Serious Adverse Event*				
Blood and Lymphatic System Disorders				
Febrile neutropenia	22 (5.6)	30 (7.6)	21 (7.7)	29 (10.6)
Anemia	-	-	11 (4.0)	3 (1.1)

* Grade 1 and 2 adverse events and Grade 4 lymphocytopenia were not captured in ML17102.
** Primary analysis: 20.7 months median observation time.

Table 12 Summary of Grade 3 or 4 Adverse Events and Deaths by Binet Stage in ML17102 (Primary Analysis: 20.7 Months Median Observation Time)

Binet Stage	FC	R-FC
Overall Incidence	246 (62%)	304 (77%)
Binet Stage A		
N	20	18
Total patients with at least one AE (%)	14 (70%)	13 (72%)
Deaths (%)	3 (15%)	1(6%)
Binet Stage B		
N	253	256
Total patients with at least one AE (%)	144 (57%)	189 (74%)
Deaths (%)	32 (13%)	13 (5%)
Binet Stage C		
N	122	123
Total patients with at least one AE (%)	87 (71%)	102 (83%)
Deaths (%)	12 (10%)	19 (15%)

In the subgroup analysis of Binet stage, in both arms of ML17102, the rate of Grade 3 or 4 AEs slightly increased from Binet stage B to Binet stage C. In the Binet stage A subgroup, there was no difference in the incidence of Grade 3 or 4 AEs between the FC and R-FC arms. In Binet stage B and C patients, the rates of Grade 3 or 4 AEs were higher in the R-FC arm compared to the FC arm. Similar patterns were observed for SAEs.

Table 13 Summary of Grade 3 or 4 Adverse Events and Fatal AEs by Binet Stage in BO17072

Binet Stage	FC	R-FC
Binet Stage A		
N	31	24
Total patients with at least one Grade 3/4 AE (%)	20 (65%)	18 (75%)
Fatal AEs (%)	4 (13%)	4 (17%)
Binet Stage B		
N	157	164
Total patitents with at least one Grade 3/4 AE (%)	109 (69%)	127 (77%)
Fatal AEs (%)	12 (8%)	16 (10%)
Binet Stage C		
N	84	86
Total patients with at least one Grade 3/4 AE (%)	71 (85%)	74 (86%)
Fatal AEs (%)	10 (12%)	16 (19%)

Table 14 Summary of Grade 3 or 4 Adverse Events and Deaths by Age in ML17102 (Primary Analysis: 20.7 Months Median Observation Time)

Age (years old)	FC	R-FC
< 65		
N	280	275
Total patients with at least one AE (%)	168 (60%)	203 (74%)
Deaths (%)	31 (11%)	26 (9%)

≥ 65- ≤ 70		
N	91	90
Total patients with at least one AE (%)	59 (65%)	72 (80%)
Deaths (%)	15 (16%)	6 (7%)
> 70		
N	25	32
Total patients with at least one AE (%)	19 (76%)	29 (91%)
Deaths (%)	1 (4%)	1 (3%)

In the subgroup analysis of age in ML17102, Grade 3 or 4 AEs tended to increase with increasing age > 65 years, especially for > 70 years and more AEs were recorded in the R-FC arm compared with FC alone. Similar patterns were observed for SAEs.

Table 15 Summary of Grade 3 or 4 Adverse Events and Fatal AEs by Age in BO17072

Age (years old)	FC	R-FC
< 65		
N	159	154
Total patients with at least one Grade 3/4 AE (%)	105 (66%)	109 (71%)
Fatal AEs (%)	12 (8%)	5 (3%)
≥ 65- ≤ 70		
N	68	74
Total patients with at least one Grade 3/4 AE (%)	53 (78%)	67 (91%)
Fatal AEs (%)	6 (9%)	19 (26%)
> 70		
N	45	46
Total patients with at least one Grade 3/4 AE (%)	42 (93%)	43 (93%)
Fatal AEs (%)	8 (18%)	12 (26%)

Further Information on Selected, Serious Adverse Drug Reactions

Infusion-Related Reactions

Maintenance Treatment (NHL) up to 2 years
Non-serious signs and symptoms suggestive of an infusion-related reaction were reported in 41% of patients under general disorders (mainly asthenia, pyrexia, influenza-like illness, pain) and in 7% of patients for immune system disorders (hypersensitivity). Serious infusion-related reactions occurred in <1% of patients (see WARNINGS AND PRECAUTIONS: Infusion/Administration Related Events).

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 RITUXAN in combination with chemotherapy. The incidence of severe 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 WARNINGS AND PRECAUTIONS), but also included dyspepsia, rash, hypertension, tachycardia, features of tumour lysis syndrome. Additional reactions reported in isolated cases at the time of R-CHOP

therapy were myocardial infarction, atrial fibrillation, pulmonary edema and acute reversible thrombocytopenia.

Infections

Maintenance Treatment (NHL) up to 2 years
The proportion of patients with Grade 1 to 4 infections was 26% in the observation group and 47% in the RITUXAN group with severe (Grade 3/4) infections in 2% of patients on observation and 11% receiving RITUXAN maintenance treatment. Severe infections reported in ≥ 1% of patients in the RITUXAN 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%, RITUXAN 11%), viruses (observation 8%, RITUXAN 11%) and fungi (observation 3%, RITUXAN 4%). There was no cumulative toxicity in terms of infections reported over the 2-year maintenance period.

Data from a phase III clinical trial included two cases of fatal PML in NHL patients that occurred after disease progression and retreatment (see WARNINGS AND PRECAUTIONS).

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 localized 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 [20, 61]. 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 previously untreated (18% R-FC, 17% FC) and in the previously treated setting (19% R-FC, 18% FC). The incidence of Grade 3 or 4 hepatitis B infection (reactivation and primary infection) was 2% R-FC vs. 0% FC.

Hematologic Events

Maintenance Treatment (NHL) up to 2 years
Leucopenia (all grades) occurred in 26% of patients on observation vs 32% of patients in the RITUXAN arm, and neutropenia was reported in 14% of patients on observation and in 25% of patients on RITUXAN. There was a higher incidence of Grade 3-4 leucopenia (observation 2%, RITUXAN 5%) and neutropenia (observation 5%, RITUXAN 11%) in the RITUXAN arm compared to the observation arm. The incidence of Grade 3 to 4 thrombocytopenia (observation 1%, RITUXAN <1%) was low. In approximately half of the patients with available data on B-cell recovery after end of RITUXAN induction treatment, it took 12 months or more for their B-cell levels to return to normal values.

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)
Severe (Grade 3/4) Adverse Events Neutropenia: There was a higher incidence of Grade 3-4 neutropenia in the RITUXAN 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% 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 the R-CHOP study, the incidence of severe neutropenia was 97% in the R-CHOP arm versus 88% in the CHOP arm. In previously untreated patients with CLL, Grade 3/4 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 previously treated CLL, the incidence of Grade 3/4 neutropenia adverse events was slightly higher in the R-FC arm (42% R-FC) compared to FC arm (40%).

Severe (Grade 3/4) Adverse Events 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 previously untreated CLL, more patients receiving R-FC experienced Grade 3/ 4 adverse events of leucopenia (23%) compared with patients receiving FC (12%). In patients with previously treated CLL, the overall incidence of Grade 3/4 leucopenia adverse events was comparable between the treatment arms (4% R-FC, 3% FC).

Studies in previously untreated and relapsed refractory CLL have established that in some cases neutropenia was prolonged or with late onset following treatment in the RITUXAN plus FC group.

Severe (Grade 3/4) Adverse Events Anemia and Thrombocytopenia: No relevant difference between the treatment arms was observed with respect to Grade 3 and 4 anemia or thrombocytopenia. In the R-CVP study, the incidence of anemia 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 anemia 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 hematological abnormalities was comparable in the two treatment groups. In the CLL first-line study, grade 3/4 anemia was reported by 4% of patients treated with R-FC compared to 7% of patients receiving FC, and Grade 3/ 4 thrombocytopenia was reported by 7% of patients in the R-FC group

compared to 10% of patients in the FC group. In the previously treated CLL study, adverse events of Grade 3/4 anemia were reported in 12% of patients treated with R-FC compared to 13% of patients receiving FC and Grade 3/4 thrombocytopenia was reported by 11% of patients in the R-FC group compared to 9% of patients in the FC group.

Cardiovascular Events (see WARNINGS AND PRECAUTIONS)

Maintenance Treatment (NHL) up to 2 years
The incidence of Grade 3 to 4 cardiac disorders was comparable between the two treatment groups (5% in observation, 7% in RITUXAN). Cardiac events were reported as serious adverse event in <1% of patients on observation and in 3% of patients on RITUXAN: atrial fibrillation (1%), myocardial infarction (1%), left ventricular failure (<1%), myocardial ischemia (<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 RITUXAN infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease (see WARNINGS AND PRECAUTIONS). 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 and 4 cardiac disorders was low both in previously untreated patients (4% R-FC vs. 3% FC) and in previously treated patients (4% R-FC vs. 4% FC).

IgG Levels

Maintenance Treatment (NHL) up to 2 years
After induction treatment, median IgG levels were below the lower limit of normal (LLN) (<7 g/L) in both the observation and the RITUXAN groups. In the observation group, the median IgG level subsequently increased to above the LLN, but remained constant during RITUXAN treatment. The proportion of patients with IgG levels below the LLN was about 60% in the RITUXAN group throughout the 2-year treatment period, while it decreased in the observation group (36% after 2 years).

Neurologic Events

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)
During the treatment period, (2% of patients) in the R-CHOP group, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle.

There was no difference between the treatment groups in the incidence of other thromboembolic events. In contrast, (1.5% of patients) had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period.

In CLL, the overall incidence of Grade 3 and 4 nervous system disorders was low both in previously untreated patients (4% R-FC vs. 4% FC) and in previously treated patients (3% R-FC vs. 3% FC).

Pulmonary Events (see WARNINGS AND PRECAUTIONS)

Three pulmonary events have been reported in temporal association with RITUXAN infusion as a single agent: acute, infusion-related bronchospasm, an acute pneumonitis presenting 1-4 weeks post infusion with RITUXAN, and bronchiolitis obliterans. The bronchiolitis obliterans was associated with progressive pulmonary symptoms and culminated in death several months following the last infusion with RITUXAN. The safety of resumption or continued administration of RITUXAN in patients with pneumonitis or bronchiolitis obliterans is unknown.

Malignancy

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)
In the CLL previously untreated study, the incidence of malignancy following exposure to RITUXAN was 4.5% compared to 3.8% in patients not exposed to RITUXAN.

RITUXAN in Combination with FC Chemotherapy
The following table shows all serious clinical adverse events reported in ≥ 1% of patients in either treatment group (R-FC and FC) in ML17102 and BO17072. In ML17102 Grade 1 and 2 adverse events and Grade 4 lymphocytopenia were not captured in the study.

Table 16 Summary of Serious Adverse Events that Occurred with an Incidence of ≥ 1%

	Incidence			
	ML17102[#] (previously untreated CLL*)**		**BO17072 (previously treated CLL)**	
	FC N = 396	**R-FC N = 397**	**FC N = 272**	**R-FC N = 274**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Blood and Lymphatic System Disorders*				
Febrile neutropenia	22 (6)	30 (8)	21 (8)	29 (11)
Anemia	9 (2)	6 (2)	11 (4)	3 (1)
Anemia hemolytic autoimmune			5 (2)	2 (<1)
Hemolytic anemia			3 (1)	2 (<1)
Leukopenia	3 (<1)	9 (2)	1 (<1)	3 (1)
Neutropenia	3 (<1)	8 (2)	7 (3)	8 (3)
Thrombocytopenia	5 (1)	6 (2)		
Autoimmune thrombocytopenia			4 (1)	2 (<1)
Pancytopenia	3 (<1)	6 (2)	5** (2)	5 (2)
Febrile bone marrow aplasia			2 (<1)	3 (1)
Infections and Infestations				
Pneumonia	20 (5)	18 (5)	18 (7)	15 (5)

	Incidence			
	ML17102# (previously untreated CLL***)		BO17072 (previously treated CLL)	
	FC N = 396	R-FC N = 397	FC N = 272	R-FC N = 274
	N (%)	N (%)	N (%)	N (%)
Herpes Zoster	6 (2)	8 (2)	3 (1)	1 (<1)
Sepsis	8 (2)	5 (1)	3 (1)	4 (1)
Bronchitis	5 (1)	5 (1)	2 (<1)	6 (2)
Infection	2 (<1)	5 (1)		
Sinusitis	1 (<1)	4 (1)		
Septic shock			2 (<1)	5 (2)
Neutropenic sepsis			4 (1)	2 (<1)
Hepatitis B			0	5 (2)
Respiratory tract infection			3 (1)	2 (<1)
Pneumocystis jiroveci pneumonia			3 (1)	1 (<1)
General Disorders and Administration Site Conditions				
Pyrexia	20 (5)	18 (5)	9 (3)	14 (5)
Cardiac Disorders				
Angina Pectoris	2 (<1)	5 (1)		
Gastrointestinal Disorders				
Diarrhea	2 (<1)	5 (1)		
Vomiting			3 (1)	1 (<1)
Neoplasms, benign, malignant and unspecified (including cysts and polyps)				
Squamous cell carcinoma of skin			4** (1)	1(<1)
Tumor lysis syndrome			3 (1)	1 (<1)
Basal cell carcinoma			3 (1)	-

*Grade 4 lymphocytopenia was not captured in ML17102.
** Onset in one patient before starting study medication.
*** (Primary analysis: 20.7 months median observation time)
# Grade 1 and 2 adverse events and Grade 4 lymphocytopenia were not captured in the study.

Combination Therapy

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

Post-Market Adverse Drug Reactions

INTRAVENOUS FORMULATION

Information in this section reports data from a separate Product Monograph for RITUXAN IV.

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 RITUXAN[1] (see WARNINGS AND PRECAUTIONS). As part of the continuing post-marketing surveillance of the safety of RITUXAN, the following serious adverse reactions have been observed:

Blood and Lymphatic System
Neutropenia: Rarely, the onset of neutropenia has occurred more than four weeks after the last infusion of RITUXAN. Cases of infusion-related acute reversible thrombocytopenia have been reported.

In post-marketing studies of RITUXAN in patients with Waldenstrom's macroglobulinemia, 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 from the administration/start of RITUXAN treatment.

Body as a Whole
Anaphylaxis; mucositis and serum sickness-like reactions have been reported rarely.

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

Infections and Infestations
Cases of HBV reactivation, occasionally with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with RITUXAN. The majority of patients received RITUXAN in combination with chemotherapy (see WARNINGS AND PRECAUTIONS).

Other serious viral infections, either new, reactivation or exacerbation, some of which were fatal, have been reported with RITUXAN treatment. The majority of patients had received RITUXAN 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 **(**see WARNINGS AND PRECAUTIONS**).**

Progression of Kaposi's sarcoma has been observed in RITUXAN-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive.

Increase in fatal infections in HIV lymphoma has been reported very rarely when RITUXAN is used with chemotherapy.

Immune Phenomena
Paraneoplastic neuropathy, encephalomyelitis, polymyositis, have been rarely reported. Other possible rare adverse events include: optic neuritis, uveitis, vasculitis, serum sickness or a lupus-like syndrome, pleuritis and arthritis. Systemic vasculitis has been reported very rarely.

Nervous System
Cases of cranial neuropathy with or without peripheral neuropathy have been rarely reported. 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 RITUXAN therapy.

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

Respiratory System
Respiratory failure/insufficiency and lung infiltration in the context of infusion-related reactions (see WARNINGS AND PRECAUTIONS). In addition to pulmonary events associated with infusions interstitial lung disease, some with fatal outcome, has been reported; pleural effusions, and pneumonia.

Skin and Appendages
Severe bullous skin reactions (including Toxic Epidermal Necrolysis and Stevens-Johnson syndrome) and pemphigus, some with fatal outcome, have been reported rarely.

Urogenital System
Renal insufficiency/failure.

DRUG INTERACTIONS

Overview
There have been no formal drug interaction studies performed with RITUXAN (rituximab). However, the existing data suggest that RITUXAN does not affect the pharmacokinetics of drugs which are used in combination with RITUXAN.

Drug-Drug Interactions
There have been no formal drug interaction studies performed with RITUXAN. The tolerability of simultaneous or sequential combination of RITUXAN with chemotherapy other than CHOP and CVP or agents which are liable to cause depletion of normal B cells is not well defined.

Renal failure requiring dialysis has been observed in patients treated with the combination of RITUXAN and cisplatin. If this combination is used, extreme caution should be exercised and renal function should be monitored closely.

Based on information from the limited number of previously treated CLL patients in study BO17072, co-administration with RITUXAN did not appear to have an effect on the pharmacokinetics of fludarabine or cyclophosphamide.

Drug-Food Interactions
There have been no formal drug-food interaction studies performed with RITUXAN.

Drug-Herb Interactions
There have been no formal drug-herb interaction studies performed with RITUXAN.

Drug-Laboratory Test Interactions
There have been no formal drug-laboratory interaction studies performed with RITUXAN.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

- RITUXAN SC formulation is not intended for intravenous administration.
- RITUXAN SC is not intended for self-administration
- RITUXAN SC should be administered as a subcutaneous injection in an environment where full resuscitation facilities are immediately available and under the close supervision of an experienced healthcare professional (see Administration).
- RITUXAN SC 1400 mg is intended for use in non-Hodgkin's lymphoma (NHL) only.
- RITUXAN SC 1600 mg is intended for use in chronic lymphocytic leukemia (CLL) only.

Premedication
Premedication consisting of an analgesic/anti-pyretic (e.g. acetaminophen) and an antihistaminic drug (e.g. diphenhydramine) should always be given before each administration of RITUXAN SC.

Premedication with glucocorticoids should also be considered, particularly if RITUXAN SC is not given in combination with steroid-containing chemotherapy (see WARNINGS AND PRECAUTIONS, Infusion/Administration Related Events).

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

Initial treatment
All patients must always receive their first dose of RITUXAN by intravenous administration, using the RITUXAN IV formulation.

The subcutaneous formulation should only be given at the second or subsequent cycles. Patients, unable to receive the full RITUXAN IV infusion dose should continue to receive subsequent cycles with RITUXAN IV until a full IV dose is successfully administered.

In patients who are able to receive the full RITUXAN IV infusion dose, the second or subsequent RITUXAN dose can be given subcutaneously using the RITUXAN SC formulation (see WARNINGS AND PRECAUTIONS).

Please refer to the separate RITUXAN IV Product Monograph for full instructions on dosing and administration of the intravenous formulation.

Recommended Dosage Regimens

Follicular Non-Hodgkin's Lymphoma (FL)

Induction

RITUXAN should be administered on day 1 of each chemotherapy cycle, after the administration of the glucocorticoid component of the chemotherapy, for up to 8 cycles. The recommended dose of RITUXAN in combination with chemotherapy for induction treatment in previously untreated Stage III/IV follicular, CD20 positive, B-cell non-Hodgkin's lymphoma is:

- First cycle - RITUXAN intravenous formulation - 375 mg/m^2 administered as an IV infusion on day 1 of cycle 1 after IV administration of the corticosteroid component of chemotherapy. During their first cycle the patient is at the highest risk of experiencing an infusion/administration related reaction. Beginning therapy with RITUXAN IV infusion allows management of infusion/administration related reactions by slowing or stopping the intravenous infusion (see WARNINGS AND PRECAUTIONS, Infusion/Administration Related Events).
- Patients unable to receive the full RITUXAN intravenous dose should continue to receive subsequent cycles with RITUXAN IV until a full IV dose is successfully administered.

If the full intravenous infusion is tolerated, then:

- Subsequent cycles - RITUXAN SC subcutaneous formulation injected at a fixed dose of 1400 mg, irrespective of the patient's BSA, per cycle for up to 8 cycles total, including cycles administrated via IV infusion. RITUXAN SC should be administered on day 1 of each chemotherapy cycle, after administration of the glucocorticoid component of the chemotherapy.

Maintenance

For maintenance treatment after response to induction treatment, patients with follicular NHL may receive maintenance therapy with RITUXAN SC given subcutaneously at 1400 mg once every 2 months (previously untreated) or once every 3 months (relapsed/refractory) until disease progression or for a maximum period of two years.

Diffuse Large B-Cell Non-Hodgkin's Lymphoma (DLBCL)

RITUXAN should be administered on day 1 of each chemotherapy cycle (CHOP), after the administration of the glucocorticoid component of the chemotherapy, for up to 8 cycles. The recommended dose of RITUXAN in combination with chemotherapy for induction treatment of CD20 positive, DLBCL is:

- First cycle - RITUXAN intravenous formulation - 375 mg/m^2 administered as an IV infusion on day 1 of cycle 1 after IV administration of the glucocorticoid component of chemotherapy. During their first cycle the patient is at the highest risk of experiencing an infusion/administration related reaction. Beginning therapy with RITUXAN IV infusion allows management of infusion/administration related reactions by slowing or stopping the intravenous infusion (see WARNINGS AND PRECAUTIONS, Infusion/Administration Related Events).
- Patients unable to receive the full RITUXAN intravenous dose should continue to receive subsequent cycles with RITUXAN IV until a full IV dose is successfully administered.

If the intravenous infusion is tolerated, then:

- Subsequent cycles - RITUXAN SC subcutaneous formulation injected at a fixed dose of 1400 mg per cycle, irrespective of the patient's BSA. RITUXAN SC should be administered on day 1 of each chemotherapy cycle, after administration of the glucocorticoid component of the chemotherapy if applicable.

Chronic Lymphocytic Leukemia

Prophylaxis with adequate hydration and administration of uricostatics (such as allopurinol) starting 48 hours prior to start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome. For CLL patients whose lymphocyte counts are > 25 x10^9/L it is recommended to administer methylprednisolone IV shortly before administration with RITUXAN to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome. In study ML17102 an equivalent of 80 mg of methylprednisolone (100 mg prednisone IV) was given prior to infusions with RITUXAN. Seventy-four percent (74%) of patients in the R-FC arms of study ML17102 received at least one dose of corticosteroids, with 27% receiving two or more doses.

RITUXAN should be administered on day 1 of each chemotherapy cycle (FC), after the administration of the glucocorticoid component of the chemotherapy, for 6 cycles (1st cycle RITUXAN IV + 5 cycles RITUXAN SC). The chemotherapy should be given after RITUXAN administration. The recommended dose of RITUXAN in combination with FC for the treatment of CLL is:

- First cycle – RITUXAN intravenous formulation – 375 mg/m^2 BSA administered as an IV infusion on day 1 of cycle 1 after IV administration of the glucocorticoid component of chemotherapy. The recommended initial infusion rate is 50 mg/hour. If

hypersensitivity or infusion-related events do not occur after the first 30 minutes, the rate can be escalated in 50 mg/hour increments every 30 minutes to a maximum of 400 mg/hour. This rate corresponds to a total administration time of 4.25 hours. If hypersensitivity or an infusion-related event develops, the infusion should be temporarily slowed or interrupted (see WARNINGS AND PRECAUTIONS). The infusion can continue at one-half the previous rate upon improvement of patient symptoms. During their first cycle the patient is at the highest risk of experiencing an infusion/administration related reaction. Beginning therapy with RITUXAN IV infusion allows management of infusion/administration related reactions by slowing or stopping the intravenous infusion (see WARNINGS AND PRECAUTIONS, Infusion/Administration Related Events).

- Patients unable to receive the full RITUXAN intravenous dose should continue to receive subsequent cycles with RITUXAN IV until a full IV dose is successfully administered.

If the intravenous infusion is tolerated, then:

- Subsequent cycles – RITUXAN SC subcutaneous formulation injected at a fixed dose of 1600 mg per cycle, irrespective of the patient's BSA. RITUXAN SC should be administered on day 1 of each chemotherapy cycle, after administration of the glucocorticoid component of the chemotherapy if applicable (see WARNINGS AND PRECAUTIONS, Infusion/Administration Related Events).

Administration

Subcutaneous Formulation Injection
RITUXAN SC should be injected subcutaneously into the abdominal wall and never into areas where the skin is red, bruised, tender, hard, or areas where there are moles or scars. No data are available on performing the injection in other sites of the body; therefore, injections should be restricted to the abdominal wall. **RITUXAN SC 1400 mg injection should be administered over approximately 5 minutes for the treatment of non-Hodgkin's lymphoma and RITUXAN SC 1600 mg injection should be administered over approximately 7 minutes for the treatment of chronic lymphocytic leukemia.**

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

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

Missed Dose
Missed or delayed doses should not be omitted but administered at a later time point, based on professional judgment observing the total number of planned cycles and the planned interval between doses.

OVERDOSAGE

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

Three patients in the RITUXAN SC BO22334 (SABRINA) study were inadvertently administered the SC formulation through the IV route up to a maximum rituximab dose of 2780 mg, with no untoward effect. One patient in the RITUXAN SC BO25341 (SAWYER) study inadvertently received a rituximab dose of 2200 mg, with no untoward effect observed. Patients who experience overdose or medication error should be closely monitored. Consideration should be given to the need for regular monitoring of blood cell count and for increased risk of infections while patients are B cell-depleted.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Rituximab binds specifically to the antigen CD20 (human B-lymphocyte-restricted differentiation antigen, Bp35), a hydrophobic transmembrane protein with a molecular weight of approximately 35 kD located on pre-B and mature B lymphocytes. [2,3] The antigen is also expressed on >90% of B-cell non-Hodgkin's lymphomas (NHL)[4] but is not found on hematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissues.[5] CD20 regulates an early step(s) in the activation process for cell cycle initiation and differentiation,[5] and possibly functions as a calcium ion channel.[6] CD20 is not shed from the cell surface and does not internalize upon antibody binding.[7] Free CD20 antigen is not found in the circulation.[3]

Mechanism 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 *in vitro.* Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC)[8] and antibody-dependent cell-mediated cytotoxicity (ADCC). The antibody has been shown to induce apoptosis in the DHL-4 human B-cell lymphoma line.[9]

Pharmacodynamics

Normal Tissue Cross-reactivity: Rituximab binding was observed 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 binding was observed in non-lymphoid tissues examined.

Pharmacokinetics

Subcutaneous Formulation

Absorption

Study BP22333 (SparkThera)
SparkThera was a two-stage phase Ib trial to investigate the pharmacokinetics, safety and tolerability of RITUXAN SC in patients with follicular lymphoma (FL) as part of maintenance treatment. In stage 2, RITUXAN SC was administered subcutaneously at a fixed dose of 1400 mg during maintenance treatment, after at least one cycle of RITUXAN intravenous formulation (375 mg/m^2), to FL patients who had previously responded to RITUXAN intravenous formulation during induction.

Predicted median C_{max} values for maintenance cycle 2, based on population pharmacokinetic modeling, are presented in Table 17.

Table 17 SparkThera: Predicted Median C_{max} at Cycle 2 of Maintenance for RITUXAN SC Compared to RITUXAN Intravenous Formulation

	RITUXAN SC subcutaneous 1400 mg N=77	**RITUXAN intravenous 375 mg/m^2 N=76**
Predicted median C_{max} (%CV) mcg/mL q2m	209(34.2)	201(18.6)
Predicted median C_{max} (%CV) mcg/mL q3m	189(33.2)	184(17.9)

SC: Subcutaneous; Cmax: peak serum concentration; mcg/mL: micrograms per milliliter; CV – coefficient of variation; q2m – once every 2 months; q3m – once every 3 months

Median T_{max} after subcutaneous administration was approximately 3 days [range: 2.0 – 4.0 days] compared to occurring at or close to the end of infusion for RITUXAN intravenous formulation.

Study BO22334 (SABRINA)
In study BO22334 (SABRINA), previously untreated patients with follicular NHL were randomised 1:1 to receive RITUXAN SC as a 1400 mg subcutaneous injection (first cycle intravenous RITUXAN 375 mg/m^2 followed by 7 cycles of RITUXAN SC) or intravenous RITUXAN 375 mg/m^2 (8 cycles) in combination with up to 8 cycles of CHOP or CVP chemotherapy every three weeks as part of induction treatment (see also CLINICAL TRIALS). The serum rituximab geometric mean (CV%) values for C_{max} at Cycle 7 for RITUXAN intravenous formulation and RITUXAN SC, were 250.63 (19.01) µg/mL and 236.82 (29.41) µg/mL, respectively.

Based on a population pharmacokinetic model including 403 patients with FL that received single or multiple doses of RITUXAN SC or RITUXAN intravenous formulation as monotherapy or in combination with chemotherapy, the absolute bioavailability or RITUXAN SC was estimated to be 71%.

Study BO25341 (SAWYER)

In Part 2 of Study BO25341 (SAWYER), previously untreated CLL patients were randomised 1:1 to receive RITUXAN SC as a 1600 mg subcutaneous injection for 5 cycles at 4-weekly intervals, following a first cycle of RITUXAN IV at a dose of 375 mg/m^2, or intravenous RITUXAN IV at a dose of 375 mg/m^2 for the first cycle and then at a dose of 500 mg/m^2 for 5 cycles at 4-weekly intervals, both in combination with chemotherapy (fludarabine and cyclophosphamide [FC]). The serum rituximab C_{max} at Cycle 6 was lower in the RITUXAN SC arm than the RITUXAN IV arm (at a dose 500 mg/m^2 for Cycles 2 to 6), with geometric mean (CV%) values of 202 (36.1) µg/mL and 280 (24.6) µg/mL for RITUXAN SC and IV, respectively with the resulting geometric mean ratio ($C_{max,}$ SC/$C_{max,}$ IV) of 0.719 (90% CI: 0.653, 0.792). The geometric mean t_{max} in the RITUXAN SC group was approximately 3 days as compared to the t_{max} occurring at or close to the end of the infusion for the RITUXAN IV group.

Distribution

Study BP22333 (SparkThera)

The primary objective of SparkThera stage 2 was to demonstrate C_{trough} non-inferiority, as assessed by a non-inferiority test with a lower boundary of 0.8 for the two-sided 90% confidence interval around the predicted geometric mean ratio of C_{trough}, for RITUXAN SC maintenance compared to RITUXAN intravenous formulation maintenance administered once every 2 or 3 months. AUC_{tau} was investigated as a secondary endpoint. Table 18 presents the predicted geometric mean C_{trough} and geometric mean AUC_{tau} values with their respective geometric mean ratios and 90% confidence intervals.

Table 18 Predicted C_{trough} and AUC_{tau} for RITUXAN Intravenous Formulation Compared to RITUXAN SC at Cycle 2 of Maintenance Therapy (q2m or q3m)

	Geometric Mean Ctrough (q2m) mcg/mL (%CV)	Geometric Mean Ctrough (q3m) mcg/mL(%CV)	Geometric Mean AUCtau (q2m) mcg·day/mL(%CV)	Geometric Mean AUCtau (q3m) mcg·day/mL(%CV)
RITUXAN SC 1400 mg n = 77	32.2 (74.6)	12.1 (100)	5430 (42.7)	5320 (43)
RITUXAN Intravenous formulation 375 mg/m^2 n = 76	25.9 (52.5)	10.9 (68)	4012 (29.9)	3947(30.3)
GMR SC/IV (90% CI)	1.24 (1.02; 1.51)[a]	1.12 (0.86; 1.45)[a]	1.35 (1.23; 1.49)[b]	1.35 (1.23; 1.48)[b]

a – non-inferiority criteria met (lower bound of 90%CI > 0.8)

b – confidence interval not adjusted for multiplicity

AUC_{tau}: area under the serum-concentration curve for dosing interval; CV: coefficient of variation; q2m: once every 2 months; q3m: once every 3 months.

Study BO22334 (SABRINA)

Stage 1 of SABRINA was designed to demonstrate C_{trough} non-inferiority, as assessed by a non-inferiority test with a lower boundary of 0.8 for the two-sided 90% confidence interval around the observed geometric mean ratio for C_{trough} SC/IV, at induction Cycle 7, for RITUXAN

administered in combination with chemotherapy (CHOP or CVP). AUC_{tau} was investigated as a secondary endpoint. Table 19 presents the observed geometric mean C_{trough} and geometric mean AUC_{tau} values with their respective geometric mean ratios and 90% confidence intervals.

Table 19 Study BO22334 (SABRINA) – Observed C_{trough} (Stage 1) and AUC_{tau} (Stage 1) at Induction Cycle 7

	RITUXAN Intravenous			RITUXAN SC			Geometric Mean Ratio SC/IV (90% CI)
	N	Geometric Mean	CV (%)	N	Geometric Mean	CV (%)	
C_{trough} mcg/mL	48	83.1	36.7	54	134.6	43.2	1.62 (1.36; 1.94)[a]
AUC_{tau}[a] (mcg·day/mL)	58	2734.2	28.03	55	3778.9	33.72	1.38 (1.24; 1.53)[b]

a – non-inferiority criteria met (lower bound of 90% CI > 0.8)
b – confidence interval not adjusted for multiplicity.

Effect of Body Size on Exposure

In the final population pharmacokinetic analysis that included 403 FL patients who received single or multiple doses of RITUXAN as a single agent or in combination with chemotherapy, body size (BSA) was identified as the main covariate. Body size had a strong effect on 1400 mg q3w SC to 375 mg/m^2 q3w IV exposure ratios in cycle 7, with C_{trough} ratios of 2.25, 1.65, and 1.21 in patients with BSA of 1.4, 1.9, and 2.4 m^2, respectively. The corresponding AUCτ ratios were 1.96, 1.45, and 1.09. These BSA values correspond to the typical (1.9 m^2) and extreme (1.4 m^2 and 2.4 m^2) values in the analysis dataset. Similar differences in exposure were predicted for the maintenance part of the treatment.

Study BO25341 (SAWYER)

RITUXAN at a fixed dose of 1600 mg was administered as a subcutaneous injection, in the abdomen, at 4-weekly intervals. A total of 176 previously untreated patients with CD20+ CLL were randomized 1:1 to receive 6 cycles of RITUXAN SC (1st cycle RITUXAN IV at a dose of 375 mg/m^2 followed by 5 cycles of RITUXAN SC) or RITUXAN IV (1st cycle RITUXAN IV at a dose of 375 mg/m^2 followed by 5 cycles of RITUXAN IV at a dose of 500 mg/m^2) in combination with up to 6 cycles of FC chemotherapy administered every four weeks. The geometric mean C_{trough} values at Cycle 5 (pre-dose Cycle 6) observed in the pharmacokinetics (PK) evaluable population (n=134) were higher among the RITUXAN SC group than the RITUXAN IV group (97.5 µg/mL vs. 61.5 µg/mL, respectively). Similarly, the geometric mean AUC values at Cycle 6 (n=109) were higher among the RITUXAN SC group than the RITUXAN IV group (4088 µg•day/mL vs. 3630 µg•day/mL, respectively). Table 20 presents the observed geometric mean C_{trough} and geometric mean AUC_{tau} values with their respective geometric mean ratios and 90% confidence intervals.

Table 20 Study BO25341 (SAWYER) – Observed C_{trough} at Cycle 5 and AUC_{tau} at Cycle 6 (Part 2)

	Rituximab IV 500 mg/m2	Rituximab SC 1600 mg	
PK parameter	**Geometric Mean (CV%)**	**Geometric Mean (CV%)**	**Geometric Mean Ratio [90% CI]**
C_{trough} (µg/mL) at Cycle 5 [N]	61.50 (63.9) [69]	97.5 (42.6) [65]	1.53 [1.27-1.85]
AUC_{tau} (µg• day/mL) at Cycle 6 [N]	3630 (32.8) [58]	4088 (34.6) [51]	1.10 [0.98-1.24]

Intravenous Formulation
For information on the IV formulation, please refer to the separate Product Monograph for RITUXAN IV.

Special Populations and Conditions

Pediatrics
Age had no effect on the pharmacokinetics of rituximab.

Geriatrics
Age had no effect on the pharmacokinetics of rituximab.

Gender
Gender had no effect on the pharmacokinetics of rituximab.

Hepatic Insufficiency
No pharmacokinetic data are available in patients with hepatic impairment.

Renal Insufficiency
No pharmacokinetic data are available in patients with renal impairment.

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

From a microbiological point of view, the product should be used immediately. If not used immediately, preparation should take place in controlled and validated aseptic conditions. In-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 48 hours at 2°C - 8°C and subsequent 8 hours at 30°C in diffused daylight.

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

Incompatibilities

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

SPECIAL HANDLING INSTRUCTIONS

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater, and disposal through household waste should be avoided. Use established 'collection systems' if available in your location.

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

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

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Composition:
RITUXAN SC is a colorless to yellowish, clear to opalescent solution supplied in sterile, preservative-free, non-pyrogenic single-dose vials.

Non-Medicinal Ingredients:
In addition to the active ingredient rituximab, each vial contains the following non-medicinal ingredients (in alphabetical order): α,α-trehalose dihydrate, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, recombinant human hyaluronidase (rHuPH20), water for injection.

RITUXAN SC contains recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously (see WARNINGS AND PRECAUTIONS, Pregnant Women).

Packaging:
RITUXAN SC (rituximab) for subcutaneous injection is supplied as either a single dose vial containing 1400 mg/11.7 mL (in a 15 mL vial) for use in patients with non-Hodgkin's lymphoma or a single dose vial containing 1600 mg/13.4 mL (in a 20 mL vial) for use in patients with chronic lymphocytic leukemia.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

The RITUXAN (rituximab) antibody 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 an IgG_1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analysis) and has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 11 nM by Scatchard analysis.

The chimeric anti-CD20 antibody is produced by mammalian cell (Chinese hamster ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. The anti-CD20 antibody is purified by affinity and ion exchange chromatography. The purification process includes specific viral inactivation and removal procedures. Molecular Weight Determination: The molecular weight of IDEC-C2B8 is calculated as 144, 544 Daltons from the primary sequence of the reduced, nonglycosylated form. The light chain consists of 213 amino acids and the heavy chain consists of 451 amino acids.

CLINICAL TRIALS

SUBCUTANEOUS FORMULATION

Previously Untreated Follicular Non-Hodgkin's Lymphoma: Study BO22334 (SABRINA)

A two-stage phase III, international, multi-center, randomized, controlled, open-label study was conducted in patients with previously untreated follicular lymphoma, to investigate the non-inferiority of the pharmacokinetic profile, together with efficacy and safety of RITUXAN SC in combination with CHOP or CVP vs. RITUXAN IV in combination with CHOP or CVP, followed by RITUXAN maintenance therapy.

The objective of the first stage was to determine whether 1400 mg rituximab SC resulted in non-inferior rituximab serum C_{trough} levels compared with 375 mg/m^2 rituximab IV, when given as part of induction treatment every 3 weeks for 8 cycles (see ACTION AND CLINICAL PHARMACOLOGY). Stage 1 enrolled previously untreated patients with CD20-positive, follicular lymphoma (FL) Grade 1, 2 or 3a (n=127). Patients with a response at the end of induction therapy received maintenance therapy with the corresponding formulation (intravenous or subcutaneous) used in the induction treatment, every 8 weeks for 24 months.
The objective of Stage 2 was to provide additional efficacy and safety data for RITUXAN SC compared with RITUXAN IV using the 1400 mg subcutaneous dose established in Stage 1. Previously untreated patients with CD20-positive, follicular lymphoma Grade 1, 2 or 3a (n=283) were enrolled in Stage 2.

The overall study design was identical across Stage 1 and Stage 2. Patients were randomized into the following two treatment groups:

- RITUXAN SC arm (n=205): 1st cycle RITUXAN IV plus 7 cycles of RITUXAN SC in combination with up to 8 cycles of CHOP or CVP chemotherapy, administered every 3 weeks. RITUXAN IV was given at the standard dose of 375 mg/m^2. RITUXAN SC was administered subcutaneously at a fixed dose of 1400 mg. Patients achieving at least partial response (PR) at the end of induction treatment were entered on to RITUXAN SC maintenance therapy administered once every 8 weeks for up to 24 months.
- RITUXAN IV arm (n=205): 8 cycles of RITUXAN IV in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks. RITUXAN IV was given at the standard dose of 375 mg/m^2. Patients achieving at least PR at the end of induction were entered on to RITUXAN IV maintenance therapy administered once every 8 weeks for up to 24 months.

Overall response rate (ORR, comprising complete response [CR], unconfirmed response [CRu], and partial response [PR]) at the end of induction treatment was calculated using investigator assessment of response in the ITT population based on pooled data from Stages 1 and 2. Additionally, ORR and complete response rate (CRR, comprising CR and CRu) at the end of maintenance treatment and time to event endpoints (progression-free survival [PFS] and overall survival [OS]) were analyzed. Efficacy results are presented in Table 21 based on a median observation time of approximately 37 months.

Table 21 Efficacy Results for Study BO22334 (SABRINA)

	RITUXAN Intravenous formulation n = 205	**RITUXAN Subcutaneous formulation n = 205**
Overall Response Rate at End of Induction [a]		
Overall response (%, [95% CI])	84.9 [79.2; 89.5]	84.4 [78.7; 89.1]
Complete response rate (%, [95% CI])	32.2 25.9; 39.1	32.2 25.9; 39.1
Overall Response Rate at End of Maintenance		
Overall response (%, [95% CI])	78.1 [71.3; 83.9]	77.9 [71.0; 83.9]
Complete response rate (%, [95% CI]	56.2 [48.6; 63.6]	50.6 [42.9; 58.3]
Progression-free Survival		
Number of patients with event	57 (27.8%)	50 (24.4%)
Hazard Ratio [95% CI] (unstratified Cox model)	0.84 [057; 1.23]	
Overall Survival		
Number of patients with event	20 (9.8%)	16 (7.8%)
Hazard Ratio [95% CI] (unstratified Cox model)	0.81 [0.42; 1.57]	

[a] Stage 2 primary efficacy endpoint was ORR at the end of induction, however pooled results which were preplanned are presented in this Table.
Response rates based on investigator assessment

Response rates at end of maintenance based on patients who received at least one cycle of maintenance treatment (n).

Chronic Lymphocytic Leukemia: Study BO25341 (SAWYER)

A two-part phase Ib, multicenter, randomized, open-label, parallel-group study was conducted in patients with previously untreated CLL to investigate the non-inferiority of the pharmacokinetic profile, together with efficacy and safety of RITUXAN SC in combination with chemotherapy (fludarabine and cyclophosphamide [FC]) vs. RITUXAN IV in combination with FC.

The objective of Part 1 was to select a RITUXAN SC dose that resulted in non-inferior rituximab serum C_{trough} levels compared with RITUXAN IV (500 mg/m^2). Previously untreated CLL patients (n=64) were enrolled at any point prior to Cycle 5 during their treatment with RITUXAN IV in combination with chemotherapy. The dose of 1600 mg of RITUXAN SC was selected for Part 2 of the study.

The objective of Part 2 was to establish non-inferiority in observed rituximab C_{trough} levels between the selected RITUXAN SC dose and the reference RITUXAN IV dose.

Previously untreated CLL patients (n=176) were randomized into the following two treatment groups:

- RITUXAN SC arm (n=88): 1st cycle of RITUXAN IV 375 mg/m^2 in combination with chemotherapy plus subsequent cycles (Cycle 2 to 6) of RITUXAN SC 1600 mg in combination with chemotherapy (FC).

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

The pharmacokinetic (PK) evaluation was based on the PK evaluable population that included n=69 patients from the IV arm and n=65 patients from the SC arm. A total of 42 patients were excluded from the PK evaluable population (n=19 IV arm and n=23 SC arm) due to no Cycle 5 administered (n=24), PK sample taken outside of the allowed time window at Cycle 5 (n=15), no PK sample taken at Cycle 5 (n=2) or PK sample taken after Cycle 6 was administered (n=1).

The PK results demonstrated that RITUXAN SC 1600 mg yielded serum rituximab Ctrough levels that were non-inferior compared with RITUXAN IV (500 mg/m^2) in patients receiving combination treatment with chemotherapy (FC) as the lower bound of the two-sided 90% CI of the geometric mean ratio (GMR) for Ctrough(SC)/Ctrough (IV) was above the pre-specified inferiority boundary of 0.8 (GMR 1.53; 90% CI: 1.27 – 1.85).

Exploratory assessment of the efficacy of SC rituximab compared with IV rituximab was evaluated as secondary objectives of the study. Response rates were 80.7% (95% CI: 70.9; 88.3) and 85.2% (95% CI: 76.1; 91.9) in the RITUXAN IV and SC arms, respectively. Complete response rate point estimates were 33.0% (95% CI: 23.3; 43.8) and 26.1% (95% CI: 17.3;

36.6) in the RITUXAN IV and SC arms respectively. Given that Study BO25341 (SAWYER) was not powered for efficacy assessment, however, interpretation of the efficacy results should be made with caution.

INTRAVENOUS FORMULATION

Information in this section reports data from a separate Product Monograph for RITUXAN IV formulation.

*The median time of all clinical time-to-event endpoints (e.g. progression free survival – PFS or overall survival – OS) was calculated by applying the Kaplan-Meier method (see table of trial results below)

NON-HODGKIN'S LYMPHOMA

Follicular Non-Hodgkin's Lymphoma, Initial Treatment in Combination with CVP

In an open-label randomized trial, a total of 322 previously untreated low-grade or follicular B cell NHL patients were randomized 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 RITUXAN 375 mg/m^2 in combination with CVP (R-CVP). RITUXAN was administered on the first day of each treatment cycle. The results are presented in Table 22. A total of 321 patients (162 R-CVP, 159 CVP) received therapy and were analyzed for efficacy. At the time of the analysis, the median observation time was 42 months. R-CVP led to a significant benefit over CVP for the primary endpoint, time to treatment failure (27 months vs. 6.6 months, $p < 0.0001$, log-rank test). The risk of experiencing a treatment failure event was reduced by 66% (95% CI: 55% - 74%) with R-CVP compared with CVP alone, using a Cox regression analysis. The Kaplan-Meier estimated event free rate at 36 months was 44% in the R-CVP group compared with 11% in the CVP group. The proportion of patients with a tumour response (CR, CRu, PR) was significantly higher ($p < 0.0001$ Chi-Square test) in the R-CVP group (81%) than the CVP group (57%). The median duration of response was 37.7 months in the R-CVP group and was 13.5 months in the CVP group ($p < 0.0001$, log-rank test). Amongst responding patients, Cox regression analysis showed that the risk of relapse was reduced by 65% (95% CI: 51% - 75%) in the R-CVP group compared to the CVP group.

The time to institution of new lymphoma treatment or death was significantly longer in the R-CVP group (not estimable), compared to the CVP group (12.3 months) ($p < 0.0001$, log-rank test). Treatment with R-CVP significantly prolonged the time to disease progression compared to CVP, 31.9 months and 14.5 months, respectively. At 36 months, 49% in the R-CVP group had not progressed, relapsed or died compared to 20% of patients receiving CVP.

A subsequent analysis of the primary and all secondary parameters, carried out with a median observation time of approximately 42 months, confirmed the benefit of R-CVP over CVP.

The rate of cause-specific deaths (death due to lymphoma) was significantly lower in the R-CVP arm when compared to the CVP arm ($p=0.02$ with stratification by center, log-rank test; 3 -year event-free rate 93% for R-CVP versus 85% for CVP).

Treatment with R-CVP compared with CVP resulted in a consistent and positive treatment effect in the following subgroups: BNLI criteria, age, extra-nodal sites, bone marrow involvement, elevated LDH, elevated ß2 microglobulin, International Prognostic Index, B symptoms, bulky disease, nodal disease, and Follicular Lymphoma Prognostic Index.

Table 22 Follicular Non-Hodgkin's Lymphoma, Initial Treatment in Combination with CVP

Trial design	Dosage	Number of study subjects	Mean age (Range)	Gender	Results (42 months median observation time)			
Open-label, randomized, phase III trial	CVP[1]	N= 159	53.9 (29-80)	Male: 85 (53.5%) Female: 74 (46.5%)		Kaplan-Meier Estimate of Median Time to Event (Months)[3*]		
						CVP	R-CVP	log-rank p-value (treatment effect)[4]
					Median observation time (months)	41.3	42.1	
					Time to treatment failure	6.6	27.0	<0.0001 (66%)
	R-CVP[2]	N= 162	52.6 (27-79)	Male: 88 (54.3%) Female: 74 (45.7%)	Time to disease progression or death	14.5	33.6	<0.0001 (58%)
					Overall survival	NR	NR	0.0700 (38%)
					Overall tumour response (CR, CRu, PR)[5]	57%	81%	<0.0001[6] (3.2)[7]
					Duration of response	13.5	37.7	<0.0001 (65%)
					Disease-free survival	20.5	44.8	0.0005 (71%)
					Time to new lymphoma treatment or death	12.3	46.3	<0.0001 (63%)

1 CVP = cyclophosphamide (750 mg/m^2 i.v. on day 1), vincristine (1.4 mg/m^2 i.v. up to a maximum of 2 mg on day 1), prednisolone (40 mg/m^2 p.o. on days 1-5).
2 R-CVP = RITUXAN (375 mg/m^2 i.v., every 3 weeks, on day 1 of the treatment cycle for 8 cycles) plus CVP chemotherapy.
3 According to investigator's assessment, all data stratified by center.
4 Treatment effect: for event-free parameters, estimates were calculated by risk reduction; for tumour response, odds ratio was used. NR: not reached since the Kaplan-Meier estimates of event-free rates were above 50% during the entire observation period of the study.
5 Overall response rate is calculated from the tumour response as assessed at the end of trial treatment.
6 Chi-square test
7 Odds ratio

Abbreviations: CR, complete response; CRu, complete response unconfirmed; PR, partial response; NR, not reached.

Follicular Non-Hodgkin's Lymphoma, Maintenance Therapy (previously untreated and relapsed refractory patients)

Previously Untreated Advanced High-Tumor Burden Follicular Non-Hodgkin's Lymphoma

In a prospective open-label, international, multicenter, randomized phase III trial (MO18264) 1193 patients with previously untreated advanced follicular lymphoma received induction therapy (phase one). During this phase, patients with advanced follicular lymphoma were evaluated for response to different RITUXAN plus chemotherapy induction regimens: R-CHOP (n=881), R-CVP (n=268) or R-FCM (n=44), according to the investigators' choice. The benefit-risk profile of induction therapy with R-FCM could not be determined due to the small number of patients treated with this chemotherapy regimen. Patients who responded to induction treatment (ie, achieved a confirmed or unconfirmed complete response [CR/CRu] or partial response [PR] at the end of induction), see Table 24, were randomized in the second phase to receive either RITUXAN maintenance therapy or no further treatment (observation). All randomized patients were treated or observed for two years or until disease progression, whichever occurred first.

Table 23 Summary of Demographics and Characteristics

	R-CHOP N=881	**R-CVP N=268**	**R-FCM N=44**
Sex			
Male	463 (53%)	134 (51%)	22 (50%)
Female	418 (47%)	131 (49%)	22 (50%)
Age			
≤ 40	96 (11%)	34 (13%)	7 (16%)
40 – 50	194 (22%)	42 (16%)	16 (36%)
50 – 60	286 (32%)	83 (31%)	12 (27%)
60 – 70	221 (25%)	68 (25%)	6 (14%)
> 70	84 (10%)	41 (15%)	3 (7%)
Mean	55.4	57.0	51.3
SD	11.47	12.66	10.87
Min-Max	22 - 80	22 - 87	29 - 74
Height (cm)			
Mean	168.46	169.00	164.70
SD	9.56	10.07	9.54
Min-Max	141.0 – 197.0	140.0 – 191.0	147.0 - 185
Weight (kg)			
Mean	73.27	76.00	73.50
SD	15.02	15.73	18.92
Min-Max	35.00 – 143.00	43.00 – 146.00	34.00 – 130.00

A total of 1078 patients responded to induction therapy, 35.5% had complete response, 28.3% had unconfirmed complete response and 26.5% had partial response. The table below provides responses for the R-CHOP and R-CVP regimens.

Table 24 Response at End of Induction Phase*

	R-CHOP (N=881)	R-CVP (N=268)
Responders	818 (92.8%)	227 (84.7%)
CR	326 (37.0%)	77 (28.7%)
CRu	267 (30.3%)	65 (24.3%)
PR	225 (25.5)	85 (31.7%)
Non-Responders[1]	63 (7.2%)	41 (15.3%)

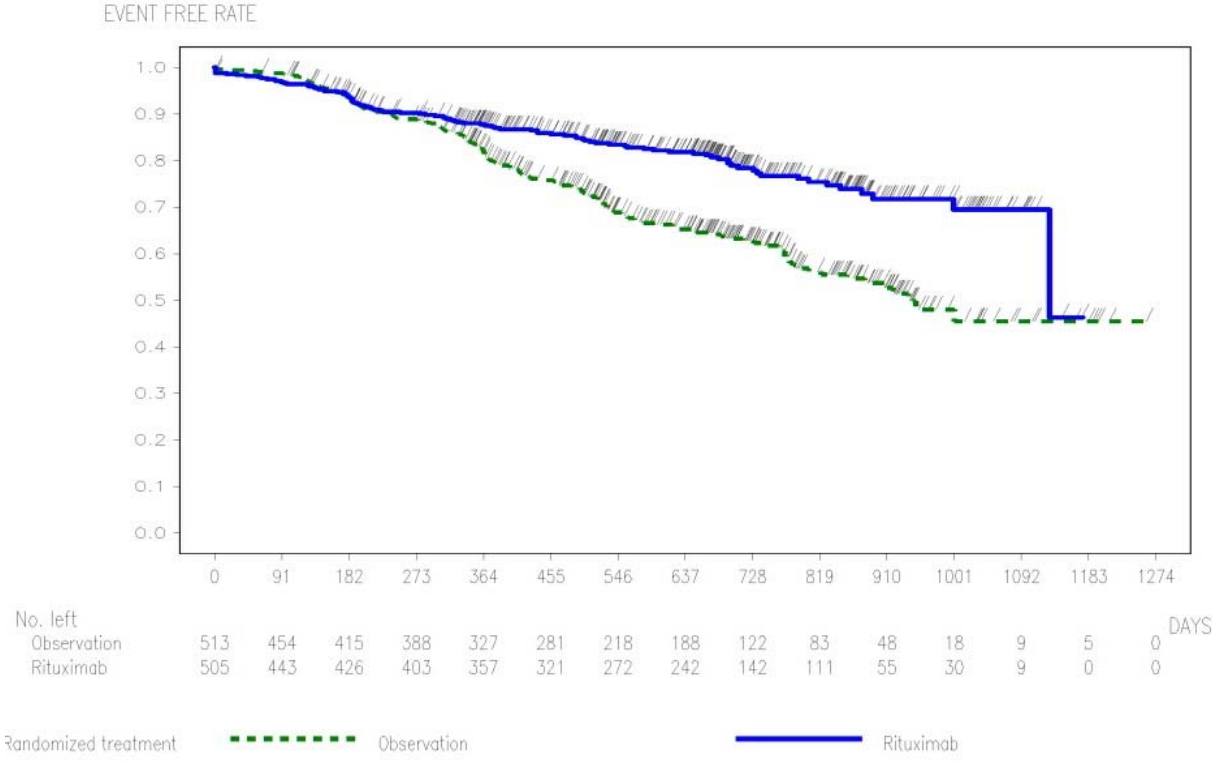
* patients treated with R-FCM were not included in the table as the benefit/risk profile of this induction chemotherapy regimen could not be determined due to the small number of patients

[1] non-responders including stable disease, progressive disease, not evaluated and missing (i.e., no response assessment)

Following induction therapy, 1018 were randomized to RITUXAN maintenance therapy (n=505) or observation (n=513). The number of patients 65 years of age or older that were included within the maintenance therapy or observation arm were 123 and 124 respectively. The two treatment groups were well-balanced with regards to baseline characteristics and disease status. RITUXAN was administered on Day 1 of each cycle of chemotherapy. RITUXAN maintenance treatment consisted of a single infusion of RITUXAN at 375 mg/m^2 body surface area given every 2 months until disease progression or for a maximum of 12 infusions (2 years).

After a median observation time of 25 months from randomization, maintenance therapy with RITUXAN resulted in an improvement in the primary endpoint of progression-free survival (PFS) based on independent review assessment (stratified log-rank p-value < 0.0001; stratified by induction treatment and response to induction treatment), refer to Figure 1.

Figure 1 Kaplan–Meier Plot of Independent Review Assessed PFS



RITUXAN maintenance treatment provided benefit in PFS in all subgroups tested: gender (male, female), age (<60 years, ≥ 60 years), FLIPI score (1, 2 or 3), induction therapy (R-CHOP, R-CVP) and regardless of the quality of response to induction treatment (CR or PR). The results of RITUXAN maintenance treatment in patients older than 75 years of age should be interpreted with caution due to the small number of patients in this subgroup.

The difference in overall survival between the two treatment arms was not conclusive. A longer follow-up is required to obtain mature overall survival results.

Relapsed/Refractory Follicular Non-Hodgkin's Lymphoma

Table 25 Relapsed/Refractory Follicular Non-Hodgkin's Lymphoma, Maintenance Therapy

Induction Phase: Overview of Efficacy Results for CHOP vs R-CHOP									
Trial design	**Dosage**	**Number of study subjects**	**Mean age (Range)**	**Gender**	**Results (50 months median observation time)**				
Prospective, open label, international, multi-centre, phase III trial	[3)]CHOP	N= 231	54.1 (27-78)	Male: 118 (51%) Female: 113 (49%)		**CHOP**	**R-CHOP**	**RR[1)]**	**p-value (log-rank)**
					Primary Efficacy ORR[2)] CR[2)] PR[2)]	 74% 16% 58%	 87% 29% 58%	 Na Na Na	 0.0003 0.0005 0.9449

	[4)]R-CHOP	N= 234	54.1 (26-80)	Male: 107 (46%) Female: 127 (54%)	Second. Efficacy OS (median) PFS (median)	NR 20.8 mo	NR 32.2 mo	31% 36%	0.0267 <0.0001

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 ($p < 0.0001$)
3) CHOP = cyclophosphamide (750 mg/m^2 i.v., day 1), doxorubicin (50 mg/m^2 i.v., day 1), vincristine (1.4 mg/m^2 i.v., (max. 2 mg) day 1) and prednisone (100 mg orally, days 1-5, every 21 days for 6 cycles).
4) R-CHOP = RITUXAN (375 mg/m^2 i.v. infusion, on day 1 of each cycle for 6 cycles) plus CHOP chemotherapy.

Abbreviations: RR, risk reduction; 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

Maintenance Phase: Overview of Efficacy Results RITUXAN vs Observation (47.2 months median observation time)

Demographics	**Observation**	**RITUXAN**
Mean age (range)	54.6 (27-80)	53.3 (29-76)
Gender	Male: 83 (50%); Female: 84 (50%)	Male: 78 (47%); Female: 89 (53%)

Efficacy Analyses	**Progression-Free Survival**		**Overall Survival**	
	Observation (N=167)	**RITUXAN** (N=167)	**Observation** (N=167)	**RITUXAN** (N=167)
Patients with event	124 (74.3 %)	95 (56.9 %)	52 (31.1 %)	37 (22.2 %)
Patients without events[1)]	43 (25.7 %)	72 (43.1 %)	115 (68.9 %)	130 (77.8 %)
Time to event (days)				
Median[2)*]	476.0	1304.0	NR	NR
95% CI for Median[2)*]	[375 ; 632]	[1072 ; 1605 -]	[- ; -]	[- ; -]
25% and 75%-ile	203 ; 1623	432 ; -	1287; -	1885 - ; -
Range[3)]	20 to 2407	19 to 2429	127 to 2671	50 to 2688
p-value (Log-Rank Test)	<0.0001		0.0229	
Hazard Ratio	0.49		0.61	
95% CI	[0.37 ; 0.64]		[0.40 ; 0.94]	
p-value (Wald Test)	< 0.0001		0.0243	
Month 12				
Patients remaining at risk	97	131	155	161
Event free rate	0.59	0.78	0.93	0.96
95% CI for rate	[0.51 ; 0.66]	[0.72 ; 0.85]	[0.90 ; 0.97]	[0.94 ; 0.99]

Exploratory Analysis	**Time to New Lymphoma Treatment or Death**		**Disease-Free Survival[4)]**	
	Observation (N=167)	**RITUXAN** (N=167)	**Observation** (N=48)	**RITUXAN** (N=49)
Patients with event	112 (67.1 %)	90 (53.9 %)	36 (75.0 %)	27 (55.1 %)
Patients without events[1)]	55 (32.9 %)	77 (46.1 %)	12 (25.0 %)	22 (44.9 %)
Time to event (days)				
Median[2)*]	659.0	1547.0	515.0	1591.0
95% CI for Median[2)*]	[568 ; 814]	[1143 ; 1750]	[450 ; 751]	[1120 ; -]
25% and 75%-ile	326; 2062 -	573 ; -	331 ; 1408	564 ; -

Efficacy Analyses	Progression-Free Survival		Overall Survival	
	Observation (N=167)	**RITUXAN** (N=167)	**Observation** (N=167)	**RITUXAN** (N=167)
Range[3)]	36 to 2407	27 to 2364	78 to 2144	76 to 2221
p-value (Log-Rank Test)	0.0003		0.0014	
Hazard Ratio	0.60		0.44	
95% CI	[0.46; 0.80]		[0.26 ; 0.74]	
p-value (Wald Test)	0.0004		0.0018	
Month 12				
Patients remaining at risk	120	137	35	40
Event free rate	0.72	0.82	0.75	0.82
95% CI for rate	[0.66 ; 0.79]	[0.76 ; 0.88]	[0.62 ; 0.87]	[0.71 ; 0.92]

[1)] Censored
[2)] Kaplan-Meier estimates
[3)] Including censored observations
[4)] Only applicable to patients achieving a CR.
[5)] RITUXAN (375 mg/m^2 i.v., once every 3 months, until disease progression or for a maximum period of 24 months).

Abbreviations: NR, not reached

Follicular Non-Hodgkin's Lymphoma, Maintenance Therapy

In a prospective, open-label, international, multi-centre, phase III trial, 465 patients with relapsed/refractory follicular NHL were randomized in a first step to induction therapy with either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone; n=231) or RITUXAN plus CHOP (R-CHOP, n=234). The two treatment groups were well-balanced with regard to baseline characteristics and disease status. The results are presented in Table 26. A total of 334 patients achieving a complete or partial remission following induction therapy were randomized in a second step to maintenance therapy with RITUXAN (n=167) or observation (n=167). Maintenance treatment with RITUXAN consisted of a single infusion of RITUXAN at 375 mg/m^2 body surface area given every 3 months until disease progression or for a maximum period of two years.

The final efficacy analysis included all patients randomized to both parts of the study. After a median observation time of 50 months for patients randomized to the induction phase, R-CHOP significantly improved the outcome of patients with relapsed or refractory follicular NHL when compared to CHOP.

For patients randomized to the maintenance phase of the trial, the median observation time was 47.2 months from maintenance randomization. Maintenance treatment with RITUXAN led to a clinically relevant and statistically significant improvement in the primary endpoint, PFS, (time from maintenance randomization to relapse, disease progression or death) when compared to observation alone ($p<0.0001$ log-rank test). The median PFS was 42.9 months (range: 0.6 to 80.1 months) in the RITUXAN maintenance arm compared to 15.7 months (range: 0.6 to 79.4 months) in the observation arm. Using a cox regression analysis, the risk of experiencing progressive disease or death was reduced by 51% with maintenance treatment with RITUXAN when compared to observation (95% CI; 36 %-63 %). Kaplan-Meier estimated progression-free rates at 12 months were 78% in the RITUXAN maintenance group vs 59% in the observation group. An analysis of overall survival suggested a benefit of maintenance treatment with RITUXAN over observation ($p=0.0229$ log-rank test). The significance level for this analysis was set at 0.001.

The median time to new anti-lymphoma treatment was significantly longer with RITUXAN maintenance treatment than with observation (50.9 months (range 0.9 to 77.9 months) vs. 21.7 months (range 1.2 to 79.4 months), p=0.0003 log-rank test). The risk of starting a new treatment was reduced by 40% (95% CI; 20 %-54 %).

Table 26 Patients Starting New Lymphoma Treatment (NLT) / Reporting Disease Progression (PD)

	Observation (n=167)	RITUXAN (n=167)
Total Patients reporting NLT (n)	85 (100%)	56 (100%)
No PD reported before initiation of NLT	-	2 (3.6%)
PD reported before initiation of NLT	85 (100%)	54 (96.4%)
PD reported during maintenance/observation phase		
PD > 3 months before NLT	27 (31.8%)	12 (21.4%)
PD ≤ 3 months before NLT	54 (63.5%)	30 (53.6%)
PD reported after maintenance/observation phase (follow-up)		
PD > 3 months before NLT	1 (1.2%)	4 (7.2%)
PD ≤ 3 months before NLT	3 (3.5%)	8 (14.3%)

In patients achieving a CR/CRu (complete response unconfirmed) as best response during induction treatment, maintenance treatment with RITUXAN significantly prolonged the median disease free survival (DFS) compared to the observation group (52.3 (range 2.5 to 73.2 months) vs 16.9 months (range 2.6 to 70.7 months), p=0.0014) log-rank test. The risk of relapse in complete responders was reduced by 56 % (95% CI; 26 %-74 %).

The benefit of maintenance treatment with RITUXAN was confirmed in all subgroups analysed, regardless of induction regimen (CHOP or R-CHOP) or quality of response to induction treatment (CR or PR) (refer to Overview of Clinical Trials). Maintenance treatment with RITUXAN significantly prolonged median PFS in patients responding to CHOP induction therapy (median PFS 36.9 months (range 0.7 to 80.1 months) vs 11.6 months (range 0.7 to 67.5 months), p<0.0001). The risk of experiencing progressive disease or death was reduced by 64% with maintenance treatment with RITUXAN when compared to observation (95% CI; 46%-75%). Maintenance treatment with RITUXAN also prolonged median PFS in patients responding to R-CHOP induction (median PFS 51.6 months (range 0.6 to 77.9 months) vs 23.1 months (range 1.4 to 79.4 months), p=0.0273). The risk of experiencing progressive disease or death was reduced by 35% with maintenance treatment with RITUXAN when compared to observation (95% CI; 4 %-55%). Since subgroup analysis based on induction therapy was not pre-specified in the protocol, the results should be interpreted with caution.

Maintenance treatment with RITUXAN provided consistent benefit in all subgroups tested [gender (male, female), age (≤ 60 years, > 60 years), stage (III, IV), WHO performance status (0 versus 1 or 2), 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), hemoglobin (< 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.

Table 27 Diffuse Large B-cell Non-Hodgkin's Lymphoma:

Trial design	Dosage	Number of study subjects	Mean age (Range)	Gender	Results (24 months median follow-up)				
Randomized open-label, phase III trial	[1)]CHOP	N= 197	68.9 (60-80)	Male: 107 (54%) Female: 90 (46%)	**24 month survival rate**	**CHOP**	**R-CHOP**	**Risk ratio**	**p-value (log-rank)**
					Event-free survival[3) *]	37.3%	57%	0.58	0.0001
	[2)]R-CHOP	N= 202	69.5 (59-80)	Male: 92 (46%) Female: 110 (54%)	Overall survival[3) *]	57.3%	70.2%	0.63	0.0072

1) CHOP = cyclophosphamide (750 mg/m^2 i.v.), doxorubicin (50 mg/m^2 i.v.), vincristine (1.4 mg/m^2 up to a maximum of 2 mg on day 1), prednisone (40 mg/m^2/day on days 1-5, every 3 weeks for 8 cycles).
2) R-CHOP = RITUXAN (375 mg/m^2 i.v., every 3 weeks, on day 1 of the treatment cycle for 8 cycles) plus CHOP chemotherapy.
3) Kaplan-Meier estimate.

Diffuse Large B-cell Non-Hodgkin's Lymphoma

In a randomized, open-label trial, a total of 399 previously untreated elderly patients (age 60 to 80 years) with diffuse large B-cell lymphoma received standard CHOP chemotherapy (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisone 40 mg/m^2/day on days 1-5) every 3 weeks for eight cycles, or RITUXAN 375 mg/m^2 plus CHOP (R-CHOP). RITUXAN was administered on the first day of the treatment cycle. In a planned interim analysis, a total of 328 patients (159 CHOP, 169 R-CHOP) were analyzed for efficacy. After a median follow up of approximately 12 months, R-CHOP led to a highly statistically significant increase in event-free survival compared to CHOP (p=0.0002), where events were death, relapse or progression of lymphoma, or institution of a new anti-lymphoma treatment; R-CHOP treatment reduced the risk of an event by 48%. Lower rates of disease progression during treatment and of relapse after complete response accounted for this difference. Overall survival was statistically significantly prolonged in the R-CHOP group compared to CHOP (p = 0.0055), with a 49% reduction in the risk of death. R-CHOP treatment was also associated with a statistically significant benefit, compared to CHOP, for complete response rate at the end of treatment (71% vs 59%; p = 0.0176), progression-free survival (p = 0.0001), and disease-free survival (p = 0.0048). The risk of disease progression was reduced by 54% and the risk of relapse after complete response by 51%. R-CHOP treatment benefited both low-risk and high-risk patients (age-adjusted International Prognostic Index score

0-1 and 2-3, respectively): the risk of an event was reduced by 69% in the low-risk group and 36% in the high-risk group.

An updated efficacy analysis including the total study population of 399 patients (197 CHOP, 202 R-CHOP), with a median follow-up of 24 months, presented in table 27, confirmed that R-CHOP significantly prolongs both event-free survival (p=0.0001) and overall survival (p=0.0072). R-CHOP treatment reduced the risk of an event by 42% and the risk of death by 37%. Kaplan Meier estimates of event-free survival at 24 months were 57.0% in the R-CHOP arm compared to 37.3% in the CHOP arm and of overall survival were 70.2% in the R-CHOP arm compared to 57.3% in the CHOP arm.

CHRONIC LYMPHOCYTIC LEUKEMIA ***(previously untreated and previously treated patients)***:

In two open-label randomized phase 3 trials, a total of 817 previously untreated patients and 552 previously treated patients with CLL were randomized to receive either FC chemotherapy (fludarabine 25 mg/m^2, cyclophosphamide 250 mg/m^2, days 1-3) every 4 weeks for 6 cycles or RITUXAN in combination with FC (R-FC)**.** RITUXAN 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 each subsequent treatment cycle.

A total of 810 previously untreated patients (primary analysis: 403 R-FC, 407 FC; updated OS (final) analysis: 408 R-FC, 409 FC) and 552 previously treated patients (276 R-FC, 276 FC) were analyzed for efficacy.

Previously Untreated CLL

Table 28 Study ML17102 Treatment of Previously Untreated Chronic Lymphocytic Leukemia (CLL) Overview of Efficacy Results for RITUXAN Plus FC vs. FC alone

Efficacy Parameter	Primary Analysis[a]		Final Analysis[b]	
	Analyses at the time of primary PFS analysis (20.7 months median observation time)		Analyses at the time of final OS analysis (66.4 months median observation time)	
	FC N = 407	R-FC N = 403	FC N = 409	R-FC N = 408
Progression-free Survival				
Median time to event (months)	32.2	39.8	32.8	56.0
p value (log-rank test)	p < 0.0001		p < 0.0001	
adjusted HR [95% CI], p value (Wald test)	0.56 [0.43;0.72], p< 0.0001		0.57 [0.48;0.67], p< 0.0001	
Overall Survival				
Median time to event (months)	NR	NR	85.8	NR
p value (log-rank test)	p = 0.0427		p = 0.0010	
adjusted HR [95% CI], p value (Wald test)	0.64 [0.41;1.00], p = 0.0487		0.68 [0.54;0.86], p = 0.0015	
Event-free Survival				

Median time to event (months)	31.1 39.8	31.2 54.7
p value (log-rank test)	p < 0.0001	p < 0.0001
adjusted HR [95% CI], p value (Wald test)	0.55 [0.43;0.70], p < 0.0001	0.57 [0.48;0.67], p < 0.0001
End of Treatment Response Rate[c]		
Responders (CR + PR/nPR)	72.7% 86.1%	72.4% 85.8%
Patients with		
complete response (CR)	17.2% 36.0%	16.9% 36.0%
partial response (PR/nPR)	55.5% 50.1%	55.5% 49.8%
stable disease (SD)	7.6% 4.7%	7.6% 4.7%
progressive disease (PD)	7.6% 3.5%	7.8% 3.7%
missing	12.0% 5.7%	12.2% 5.9%
Disease-free Survival[d]		
Median time to event (months)	NR NR	48.9 60.9
p value (log-rank test)	p = 0.7882	p = 0.0523
adjusted HR [95% CI], p value (Wald test)	0.93 [0.44;1.96], p = 0.8566	0.73 [0.52;1.02], p = 0.0689
Duration of Response[e]		
Median time to event (months)	34.7 40.2	36.2 56.4
p value (log-rank test)	p = 0.0040	p < 0.0001
adjusted HR [95% CI], p value (Wald test)	0.61 [0.43;0.85], p = 0.0036	0.58 [0.48;0.71], p < 0.0001
Time to New Treatment		
Median time to event (months)	NR NR	47.8 68.4
p value (log-rank test)	p = 0.0052	p < 0.0001
adjusted HR [95% CI], p value (Wald test)	0.65 [0.47;0.90], p = 0.0082	0.59 [0.49;0.72], p < 0.0001

NR: not reached; nPR: nodular partial response. Hazard ratios are from non-stratified (adjusted) analyses. 1 month = 30.4375 days.

a Clinical cut-off July 04, 2007. Informed consent forms for seven patients (2 FC, 5 R-FC) were missing at the time of the primary analysis; hence, these patients were excluded from the analysis. Informed consent forms were later collected from those seven patients, and their data were added to the database ahead of the first updated analysis of efficacy.

b Last patient visit October 31, 2011.

c The response for one patient with PR at the time of the primary and updated analyses has changed to missing (and hence non-responder) at the time of this final analysis.

d Based on patients with confirmed CR (including late responders).

e Based on patients with confirmed response (CR, PR, nPR).

Table 29 Summary of Progression-Free Survival According to Binet Stage (ITT) Primary Analysis (20.7 Months Median Observation Time)

	FC N = 407	R-FC N = 403
Binet Stage A		
N	22	18
Progression Free Survival –Median (months)	31.6	Not Reached
Log Rank p-value	0.0099	
Hazard Ratio (95% CI)	0.13 (0.03; 0.61)	
p-value (Wald test, not adjusted)	0.0093	
Binet Stage B		
N	257	259
Progression Free Survival –Median (months)	32.3	43.3
Log Rank p-value	< .0001	
Hazard Ratio (95% CI)	0.45 (0.32; 0.63)	
p-value (Wald test, not adjusted)	< 0.0001	
Binet Stage C		
N	126	125
Progression Free Survival –Median (months)	33.4	38.0
Log Rank p-value	0.4671	
Hazard Ratio (95% CI)	0.88 (0.58; 1.33)	
p-value (Wald test, not adjusted)	0.5406	

Table 30 Summary of Progression-Free Survival According to Age (ITT) Primary Analysis (20.7 Months Median Observation Time)

	FC N = 407	R-FC N = 403
Age <65		
N	288	279
Progression Free Survival –Median (months)	31.7	43.3
Log Rank p-value	< .0001	
Hazard Ratio (95% CI)	0.54 (0.40;0.72)	
p-value (Wald test, not adjusted)	<.0001	
Age >=65 - <=70		
N	94	91
Progression Free Survival –Median (months)	27.4	39.9
Log Rank p-value	0.0037	
Hazard Ratio (95% CI)	0.45 (0.26;0.78)	
p-value (Wald test, not adjusted)	0.0046	
Age >70		
N	25	33
Progression Free Survival –Median (months)	Not Reached	38.0
Log Rank p-value	0.3787	
Hazard Ratio (95% CI)	1.61 (0.55;4.74)	

	FC N = 407	R-FC N = 403
p-value (Wald test, not adjusted)	0.3832	

In the primary analysis of the study in previously untreated patients (see Table 28) the median PFS, calculated by applying the Kaplan-Meier method, was 39.8 months in the R-FC group and 32.2 months in the FC group ($p < 0.0001$, log-rank test). The primary analysis that led to the stopping of the study based on crossing the statistical boundary for PFS, showed an improvement of R-FC over FC for the secondary endpoint overall survival (p=0.0427). In updated overall survival results (final analysis) after a median of 64.4 months of observation, overall survival was significantly prolonged in the R-FC group compared with the FC group ($p = 0.0010$, log-rank test; adjusted HR 0.68 (95% CI [0.54, 0.86], $p = 0.0015$, Wald test). Although based on small numbers of patients, hazard ratios were greater than 1 (with wide confidence intervals) for the > 70 and ≥ 75 year age subgroups, and in the subgroup of patients who were diagnosed 6 to <12 months before entering the study. Due to the exploratory nature of subgroup analyses, these results need to be interpreted with caution. The benefit in terms of PFS was consistently observed in most patient subgroups analyzed according to disease risk at baseline, although it was not statistically significant in patients with Stage C disease or for patients > 70 years (see Tables 29 and 30).

Study ML17102 was initially open to all symptomatic patients in need of treatment, regardless of stage. From amendment #1 onwards, however, new patients in the lowest risk group (Binet A) were excluded from the study. A total of 40 patients (22 FC arm, 18 R-FC arm) had been enrolled at that time, which represents 5% of the overall intent-to-treat (ITT) population. Within the Binet A patients, patients who received R-FC had a better outcome compared to those who received FC. If Binet A patients were to be excluded from the ITT analysis of ML17102, the overall results of the remaining Binet B and C patients would be slightly lower to the current overall results, but, due to the small numbers, would not change any of the overall results and conclusions of the study.

In all subgroups analyzed according to Binet stage, the median PFS in the primary analysis was increased or not yet reached in Binet A for R-FC and the risk of disease progression or death [(Hazard Ratio (HR)] was decreased by the addition of RITUXAN to FC when compared to FC alone, although not statistically significantly decreased in patients with stage C disease. The effect was most pronounced in the group of patients with stage A disease, and least in patients in stage C disease.

The effect of RITUXAN when added to FC seems to be most pronounced with younger age. Due to the small size of the subgroup of patients over the age of 70 (FC n=25, R-FC n=33), no meaningful conclusion can be drawn for the effect RITUXAN might have in this age category.

180/403 (45%) of patients in the R-FC arm received Colony Stimulating Factors vs. 95/407 (23%) in the FC arm. A comparison with regards to the primary endpoint, PFS, yields a result favoring the R-FC arm: HR=0.59, 95% CI [0.43;0,81]. This outcome is similar to the overall study results. As is also true for the overall population, and as expected, in the subgroups more AEs were found in the R-FC arm compared to FC regardless if G-CSF was given or not.

Previously Treated CLL

Table 31 Treatment of Previously Treated[6] Chronic Lymphocytic Leukemia (CLL) Overview of Efficacy Results for RITUXAN plus FC vs. FC Alone

Trial design	Dosage	Number of study subjects	Mean age (Range)	Gender	Efficacy Results (25.3 months mean observation time)								
					Analysis	Investigator-Assessed Results[3)*]				IRC Results[3)*]			
Randomized open-label, phase III trial	FC[1)]	N = 276	61.3 (35-81)	Male: 181 (66%) Female: 95 (34%)		FC	R-FC	Log rank p-value	Hazard Ratio	FC	R-FC	Log rank p-value	Hazard Ratio
					Progression-free Survival (PFS) (months)	20.6 (18.1; 24.0)[5)]	30.6 (26.0; 38.1)[5)]	0.0002	0.65 (0.51; 0.82)[5)]	21.7 (18.3; 24.1)[5)]	26.7 (22.0; 31.1)[5)]	0.0218	0.76 (0.60; 0.96)[5)]
	R-FC[2)]	N = 276	62.1 (35-83)	Male: 187 (68%) Female: 89 (32%)	PFS with censoring of new CLL treatment[7)] (months)	22.5 (18.3; 29.0)[5)]	31.5 (26.2; 42.2)[5)]	0.0012	0.69 (0.53; 0.86)[5)]	22.6 (18.8; 25.2)[5)]	28.0 (22.9; 32.3)[5)]	0.0439	0.78 (0.61; 0.99)[5)]
					Overall Survival (months)	51.9 (46.3; ...)[5)]	NR (51.0; ...)[5)]		0.83 (0.59; 1.17)[5)]				
					Response rate[4)] (CR, nPR, PR)	58.0% (51.9; 63.9%)[5)]	69.9% (64.1; 75.3%)[5)]		NA	48.6% (42.5; 54.6%)[5)]	60.5% (54.5; 66.3%)[5)]		NA

1) FC = (fludarabine 25 mg/m^2, cyclophosphamide 250 mg/m^2, days 1-3) every 28 days for 6 cycles
2) R-FC = RITUXAN (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 each subsequent treatment cycle with FC chemotherapy.
3) Kaplan-Meier estimate.
4) Response rate is based on the Best Overall Response
5) 95% CI
6) Previous treatment included one of the following chemotherapy regimens:
single agent chlorambucil +/- prednisone/ prednisolone, single agent fludarabine (or other nucleoside analogue), or alkylator containing combination therapy (e.g. CHOP/CVP)
7) These results are based on a sensitivity analysis with censoring of new CLL treatment before documented disease progression
NR: not reached.
NA: not applicable.

Table 32 Summary of Progression-Free Survival According to Age (ITT) as Assessed by IRC*

Age Subgroup	N	HR (95% CI)	FC		R-FC	
			Patients (N)	Median PFS (months)	Patients (N)	Median PFS (months)
<65	317	0.61 [0.44;0.84]	162	22.5	155	30.2
≥ 65 to ≤ 70	142	0.94 [0.60;1.47]	68	23.3	74	26.1
> 70	93	1.10 [0.63;1.91]	46	18.8	47	15.5

* These results are based on exploratory analyses

Table 33 Summary of Progression-Free Survival According to Binet Stage (ITT) as Assessed by IRC*

Binet Stage	N	HR (95% CI)	FC		R-FC	
			Patients (N)	Median PFS (months)	Patients (N)	Median PFS (months)
Binet A	55	0.68 [0.29;1.57]	31	22.8	24	51.0
Binet B	326	0.79 [0.58;1.09]	160	24.6	166	30.2
Binet C	171	0.70 [0.47;1.03]	85	15.8	86	21.3

* These results are based on exploratory analyses

In the previously treated CLL study (see Table 31), the investigator-assessed median progression-free survival (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 risk of having a PFS event (progression or death, whichever occurred first) was statistically significantly decreased by 35% (HR = 0.65; 95% CI: [0.51, 0.82]; p=0.0002, Wald test) for patients in the R-FC arm compared to the FC arm (see Table 31). 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.

Based on Independent Review Committee (IRC) assessments, the median PFS was 21.7 months in the FC arm and 26.7 months in the R-FC arm (p = 0.0218, non-stratified Log-Rank test). The addition of RITUXAN to FC reduced the risk of disease progression or death by 24% (HR = 0.76; 95% CI [0.60, 0.96]; p = 0.0222, Wald test) compared to FC alone. Forty-three percent of patients in the FC arm and 54% of patients in the R-FC arm were progression-free at 2 years using Kaplan-Meier estimates. Please see Tables 32 and 33 for a summary of progression-free survival according to Age and Binet stage respectively, as assessed by IRC. These results are based on exploratory analyses.

In this open-label randomized trial, the discordance between investigators' efficacy results and IRC's assessments were due to differences in assessing disease status (progression or not) and in determining the time of progression. The discordance observed reflects the subjectivity of PFS assessment in open-labeled trials. The results should be interpreted cautiously.

OS benefit has not been demonstrated and follow-up is needed to draw meaningful conclusions about the treatment effect of R-FC compared to FC in terms of OS.

DETAILED PHARMACOLOGY

In Vitro

The binding affinity of RITUXAN (rituximab) for the CD20 antigen is approximately $11x10^{-9}$ M, by Scatchard analysis.

RITUXAN antibody bound to CD20-positive cells also binds complement component C1q. The complement cascade is thereby activated, causing lysis of the CD20 target cell by complement dependent cellular cytotoxicity.[2] The antibody also induces programmed cell death (apoptosis) in human B-cell lymphoma lines.[3]

In vitro studies suggest that RITUXAN sensitizes drug-resistant human B-cell lymphoma lines to the cytotoxic effects of some chemotherapeutic agents.[9] In human tissue, CD20 antigen binding with RITUXAN is highly restricted; binding to CD20 was found only on lymphoid cells in the thymus, the white pulp of the spleen, and a majority of peripheral blood and lymph node lymphocytes.

In Vivo

In macaque cynomolgus monkeys, doses of 269 mg/m^2 produced high plasma levels of RITUXAN (186 - 303 µg/mL) 24 hours after each of four infusions, which persisted at significant levels for two weeks after the last infusion. Weekly IV doses of 269 mg/m^2 of RITUXAN reduced B lymphocytes in both follicular and non-follicular areas of lymph nodes in 50% of monkeys treated for four weeks and in 67% of animals treated for eight weeks. CD20-antigen positive cells in the spleen were markedly reduced after eight weeks. In animals infused with lower doses of antibody, bone marrow and lymph node B cells were depleted by as much as 95%. In these animals the recovery of peripheral blood B cells usually started two weeks after treatment and was complete from 60 to greater than 90 days thereafter.

TOXICOLOGY

Subcutaneous Formulation

The subcutaneous formulation contains recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-

administered drugs when administered subcutaneously. Systemic absorption of rHuPH20 after subcutaneous administration is unlikely to occur. However, pharmacokinetic and toxicology studies in animals demonstrate reductions in foetal weight and increases in the number of resorptions following injection of rHuPH20, at maternal systemic exposure levels comparable to those that could occur after accidental bolus IV administration of a single vial of the RITUXAN SC formulation in humans. No evidence of teratogenicity was observed in an embryo-fetal development study in which mice were administered rHuPH20, via the subcutaneous route, at doses up to 18 mg/kg/day.

Intravenous formulation

Immunohistology Studies with Human Tissues

The tissue reactivity of the chimeric mouse/human antibody rituximab was evaluated using a panel of 32 different human tissues fixed with acetone. The antibody was biotinylated to avoid background staining. No loss of immunoreactivity, as determined by FACS (fluorescence activated cell sorter) analysis using antigen-positive cells, was observed following biotinylation.

Biotinylated rituximab exhibited a highly restricted pattern of tissue reactivity, binding to antigen was found only on a subset of cells of lymphoid origin. Immunoreactivity was noted in the white pulp of the spleen, the lymphoid follicles of the tonsil, and in some, but not all, of the B lymphocytes present in the lymph node. Also, lymphoid cells present in other organs, e.g., large and small intestines and stomach, were immunoreactive with rituximab.

All simple epithelial cells, as well as the stratified epithelia and squamous epithelia of different organs, were found to be unreactive. Similarly, no reactivity was seen with neuroectodermal cells, including those in the brain, spinal cord and peripheral nerves. Mesenchymal elements, such as skeletal and smooth muscle cells, fibroblasts, endothelial cells, and polymorphonuclear inflammatory cells were found to be negative.

***In Vitro* Testing for Cross-Reactivity with Human Tissues: Rituximab Lot 0111**

The human tissue specificity of biotinylated rituximab antibody Lot 0111 was evaluated using immunoperoxidase staining of formalin-fixed, normal adult human tissues obtained at autopsy. Biotinylated rituximab was used to avoid background reactivity caused by use of anti-human secondary reagents. CD20-positive (SB) and CD20-negative (HSB) human cell lines were used as controls, as was an irrelevant biotinylated mouse/human chimeric antibody termed S-004. The molar ratio of biotin-to-protein was approximately 10:1 for both antibodies; no loss of immunoreactivity was observed by flow cytometry using CD20-positive SB cells and the biotinylated rituximab antibody. Positive reactivity with staining intensity of 2+ to 3+ was observed with >90% of the CD20-positive control (SB) cells. No reactivity was observed with the CD20-negative cell line HSB.

The CD20 antigen exhibited a highly restricted pattern of distribution in the normal human tissues analyzed, and was mostly found on a subset of cells of lymphoid origin. Immunoreactivity was observed in the bone marrow, lymph node, peripheral blood B cells, white pulp of the spleen and in the lymphoid follicles of the tonsil. Some lymphoid nodules in other organ tissues, e.g., esophagus, kidney, small intestine, pancreas and stomach were also reactive.

All simple epithelial cells, and stratified epithelia and squamous epithelia of different organs were unreactive except for two specimens of large intestine with staining patterns of focal to diffuse. Reactivity was not seen in most neuroectodermal cells, including those of the brain and peripheral nerves; weak reactivity was observed in 30% of microglial cells present in 1 of 3 spinal cord specimens. Mesenchymal elements such as skeletal and smooth muscle cells, fibroblasts, and endothelial cells were unreactive.

Plasma Sample Analysis from Lot 0111 of Rituximab

Rituximab was evaluated in cynomolgus monkeys in a high-dose pathology/toxicology study designed to evaluate the safety of rituximab antibody Lot 0111 produced in suspension culture. Additionally, plasma samples from monkeys infused with this lot of

rituximab antibody were analyzed for rituximab antibody levels as well as for the presence of anti-rituximab antibody: monkey anti-murine (MAMA) and monkey anti-rituximab (MACA). Groups 1 and 2, consisting of two animals each, received only vehicle; Groups 3 and 4, consisting of 6 animals each divided equally by sex, received rituximab (20 mg/kg). Groups 1 and 3 were dosed for four consecutive weeks; Groups 2 and 4 were dosed for eight consecutive weeks. Preliminary results from Groups 1 and 3 are available.

Plasma clearance study results indicate that high rituximab plasma levels (186 - 303 μg/mL) were achieved in all treated monkeys 24 hours after the first and second infusions. Plasma antibody levels achieved 24 hours after the third and fourth antibody injections were similar to those detected after the first two injections in three Group 3 monkeys. Further, concentrations persisted at significant levels for two weeks after the last infusion in these animals. In the other three Group 3 animals, rituximab levels were markedly reduced at both the 24 hours and seven day time points after the third and fourth infusions; results correlated with the production of a MAMA response.

As seen in previous monkey studies, marked B-cell depletion occurred in all animals after each of the four infusions of rituximab antibody. However, the level of B-cell depletion was more marked in three of the six monkeys on day 36.

Three of the six Group 3 monkeys produced anti-rituximab antibodies that were detected two weeks after the last antibody injection. Results are confirmed by the rapid recovery of B lymphocytes in the peripheral blood of the three animals at time points that correlate with the appearance of the potentially neutralizing anti-chimeric antibody responses. None of the other Group 3 monkeys showed an anti-rituximab immune response greater than 0.2 μg/mL on day 36. Results indicate that certain monkeys with competent immune systems may respond to multiple antibody exposures by producing significant amounts of neutralizing antibodies that alter the efficacy (depleting capability) of the antibody.

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16.

PART III: CONSUMER INFORMATION

[Pr]RITUXAN® SC
rituximab
1400 mg (120 mg/mL) Solution for Subcutaneous Injection
***Pronounced*: rih TUCKS en**

Single Use Vial for Non-Hodgkin's Lymphoma

This leaflet is part III of a three-part "Product Monograph" published when RITUXAN SC was authorized for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about the subcutaneous formulation of RITUXAN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
RITUXAN SC (also known as rituximab) is a cancer medicine that is used to stop cancer cell growth and ideally cause the death of cancer cells. It must be prescribed by a doctor.

It is used to treat patients with certain types of non-Hodgkin's lymphoma (NHL).

What is non-Hodgkin's lymphoma?
Non-Hodgkin's lymphoma is a cancer of the lymph cells (lymphocytes), which are found in the blood and in the lymph nodes. Lymph nodes are located in the head and neck area, under the arms, in the groin and throughout the chest and abdomen. Lymphocytes are a type of white blood cell. There are two types: B lymphocytes and T lymphocytes. B lymphocytes produce antibodies or proteins that help our immune system to fight foreign substances which enter the body. All B-cells have a marker on their surface. This marker is called CD20.

What RITUXAN SC does:
Our bodies have a natural defence system against cancer cells. When cancer cells appear, our bodies respond by making special proteins called antibodies. Researchers studied this response and learned how to create antibodies outside the body that help with cancer treatment. These are called monoclonal antibodies.

Monoclonal antibodies are now made to target tumours in an effort to control the growth of cancer.

RITUXAN SC belongs to a family of medicine called monoclonal antibodies. It is an antibody that targets the CD-20 B-cell lymphocyte to stop its activity. RITUXAN SC attaches to the CD20 marker that is located on the B-cell. When in place, it works to stop the growth of the cancer cells and may destroy them.

RITUXAN SC is most active in patients whose lymphomas are of the B-cell type.

Who should take RITUXAN SC?

RITUXAN SC is given to patients with low-grade CD20 antigen positive B-cell non-Hodgkin's lymphoma, who have not received prior treatment or who are no longer responding to their current anti-cancer treatment or where the lymphoma has returned despite previous anti-cancer treatment.

Depending on the type of lymphoma, RITUXAN SC is given in combination with chemotherapy regimens called CHOP or CVP. CHOP stands for the following drugs: cyclophosphamide, doxorubicin, vincristine and prednisone while CVP stands for cyclophosphamide, vincristine and prednisolone.

RITUXAN SC may also be used as a continuous (maintenance) treatment for patients who have responded to initial therapy.

When it should not be used:
If you are allergic to rituximab or proteins of similar mouse or human origin or any other ingredient in RITUXAN SC or if you have ever had a rare infection of the brain called progressive multifocal leukoencephalopathy (PML) you should not take RITUXAN SC.

What should you tell your doctor before you start taking RITUXAN SC?
Before beginning treatment with the subcutaneous formulation of RITUXAN, make sure your doctor knows if:

- You ever had a bad reaction to RITUXAN or any of the non-medicinal ingredients.
- You are allergic to rituximab, other proteins which are like rituximab, or any of the other ingredients of this medicine
- You are allergic to hyaluronidase (an enzyme that is part of the formulation that helps to increase the absorption of injected active substance)
- You have a history of heart attack or stroke.
- You are taking any other medicines (including those not prescribed by the doctor).
- If you are taking medication to reduce blood pressure.
- If you are planning to be immunized with a vaccine during or after the completion of your RITUXAN SC therapy.
- If you have ever taken medicines which affect your immune system – such as chemotherapy or immune-suppressive medicines
- You have a pre-existing lung disease as you may have a greater chance of breathing difficulties during your RITUXAN SC treatment injection.
- You have a history of hepatitis B, current hepatitis B or tuberculosis infection.
- You are pregnant or could become pregnant or are breast-feeding a child.

This information will help your doctor and you decide whether you should use RITUXAN SC and what extra care may need to be taken while you are on the medication.

What the medicinal ingredient is:

RITUXAN SC contains the active ingredient rituximab.

What the non-medicinal ingredients are (in alphabetical order):
α,α-trehalose dihydrate, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, recombinant human hyaluronidase (rHuPH20), water for injection.

What dosage forms it comes in:

RITUXAN SC has been prescribed for you as a medicine for injection under your skin (called RITUXAN SC 1400 mg, solution for subcutaneous injection).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Some side effects associated with RITUXAN are severe and may be life-threatening. This drug should only be used by health professionals experienced in treating cancer in a facility where sudden and life-threatening reactions can be immediately treated.

Fatal allergic reactions and tumour lysis syndrome (TLS) causing fatal kidney damage have occurred.

Repeat and sometimes fatal attacks of hepatitis have occurred. Recurrence of hepatitis B virus infection has occurred in patients who show evidence of the virus in a blood test. It is advised that all patients be tested for hepatitis B virus infection before starting treatment with RITUXAN.

Patients with NHL who received treatment with RITUXAN may have an increased risk of JC virus infection resulting in progressive multifocal leukoencephalopathy (PML), which is a condition that leads to nerve damage within the brain. PML can cause disability, and deaths have been reported in patients with NHL. It is hard to predict who will get PML, but it is more common in people with weakened immune systems.

Severe skin reactions such as Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have been reported very rarely. Some cases have resulted in death.

Serious and potentially fatal cardiovascular events have been reported rarely following treatment with RITUXAN.

RITUXAN has not been studied in pregnant or breast-feeding women. If you are pregnant, could become pregnant or are breast-feeding, be sure to discuss with your doctor whether RITUXAN is right for you. Women should avoid pregnancy and use effective birth control methods during treatment with RITUXAN and for one year after treatment. Patients who are pregnant or become pregnant should not receive or continue to receive RITUXAN SC.

If you have ever had heart disease [for example angina (heart pain), arrhythmia (palpitations/ irregular heartbeat), or heart failure] or breathing problems, your doctor will take special care of you during therapy with RITUXAN.

In some cases, patients who have had hepatitis B might have a repeat attack of hepatitis. Tell the doctor if you think you have had hepatitis in the past.

Infection with hepatitis B virus causes inflammation of the liver which may show as mild fever, feeling of sickness, fatigue, loss of appetite, joint and/or abdominal pain and yellowing of whites of the eyes, skin and tongue. If you experience any of these symptoms immediately contact your doctor. If you show evidence of hepatitis B virus infection you may be referred to a liver disease expert for ongoing monitoring and management.

RITUXAN is not to be used in patients with active hepatitis B viral disease. Tell your doctor if you think you have hepatitis B.

Live viral vaccines should not be given with RlTUXAN. Your doctor will check if you should have any vaccines before or after you receive RITUXAN.

Cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported during use of RITUXAN in NHL. PML is a condition that causes nerve damage within the brain. Tell your doctor immediately if you have memory loss, trouble thinking, and difficulty with walking, clumsiness, falls or weakness on one side of the body, changes in mood or loss of vision. Your doctor will check if you need to see a neurologist.

Cases of Tumour Lysis Syndrome (TLS) have been reported during the use of RITUXAN. TLS is a condition that causes sudden kidney failure and abnormal heart rhythms due to changes in blood chemistry, which may be fatal. Tell your doctor immediately if you have palpitations/irregular heartbeats; vomiting; fatigue/weakness; difficulty concentrating/trouble thinking; swelling, numbness or tingling in hands, face or feet; back pain; muscle cramps; fainting or trouble breathing.
Some patients with TLS in its early stages have no symptoms, and your doctor will be performing blood tests for this and other side effects.

Bowel problems, including blockage or tears in the bowels that can sometimes lead to death can happen if you receive RITUXAN with chemotherapy medicines to treat non-Hodgkin's lymphoma. Tell your doctor immediately if you have any abdominal pain during treatment with RITUXAN.

INTERACTIONS WITH THIS MEDICATION

Before starting treatment, make sure your doctor knows if you are taking or have recently taken any other medicines (including those you have bought for yourself from a pharmacy, supermarket or health store). This is extremely important, as using more than one medicine at the same time can strengthen or weaken their effect. RITUXAN should not be used with other drugs unless your doctor has told you it is safe to do so.

PROPER USE OF THIS MEDICATION

Your doctor has prescribed RITUXAN SC after carefully studying your case. Other people may not benefit from taking this medicine, even though their problems may seem similar to yours.

RITUXAN SC will be given to you by a doctor or nurse who is experienced in the use of this treatment. Before you are given RITUXAN SC, you will be given other medicines (pre-medication) to prevent or reduce possible side effects.

You will always be given RITUXAN as a drip (intra-venous infusion) at the start of your treatment. After this, you may be given RITUXAN SC as an injection under your skin) over approximately 5 minutes.

Your doctor or nurse will watch you closely while you are being given this medicine. This is in case you get any side effects.

Your doctor will decide when to start RITUXAN SC injections.

When injected under your skin, RITUXAN SC is given in the stomach area, not in other sites of the body, and not into areas of the stomach where the skin is red, bruised, tender, hard or where there are moles or scars. You will be observed for at least 15 minutes after your injection. The observation period may be longer if you are at risk of hypersensitivity reactions.

RITUXAN SC will be given to you on the same day as your chemotherapy. This is usually given every 3 weeks up to 8 times. If you respond well to treatment, you may be given RITUXAN SC as a maintenance treatment every 2 or 3 months for two years. Your doctor may change this, depending on how you respond to the medicine.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Missed Dose
If you miss a dose of RITUXAN SC, contact your physician immediately. Your physician will decide when you should receive your next dose.

Overdose
It is unlikely that you will receive too much RITUXAN SC as you will be closely monitored by Healthcare Professionals during your administration. However, if you suspect you received too much RITUXAN SC contact your physician and poison control centre immediately.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Unwanted effects are possible with all medicines. Tell your doctor, nurse or pharmacist immediately if you do not feel well while you are receiving treatment with RITUXAN SC.

Many patients get some local side effects where RITUXAN is subcutaneously injected. These include: pain, swelling, bruising, bleeding, skin redness, itching and rash.

Your doctor may decide to stop your RITUXAN SC treatment if these reactions are serious.

Tell your doctor immediately if you get signs of an infection including:

- fever, cough, sore throat, burning pain when passing urine or feeling weak or generally unwell
- memory loss, trouble thinking, difficulty walking or sight loss - these may be due to a very rare, serious brain infection, which has been fatal (Progressive Multifocal Leukoencephalopathy or PML).

You might get infections more easily during your treatment with RITUXAN SC. These are often colds, but there have been cases of pneumonia or urinary infections.

There are also possible unwanted effects which could be serious but occur less commonly:

- Chest pain, fast or irregular or uneven heartbeat.
- Decreased white blood cells, red blood cells and platelets in the blood, infection and bleeding.
- Rapid destruction of cells sometimes leading to kidney, heart or breathing problems (Tumour Lysis Syndrome).
- Redness or blistering of the skin and the inside of the mouth.
- Recurrence of Hepatitis B infection. Signs and symptoms of Hepatitis B include mild fever, feeling of sickness, fatigue, loss of appetite, joint and/or abdominal pain and yellowing of whites of the eyes, skin and tongue.
- Increasing weakness on one side of the body, clumsiness or falls, trouble with thinking or memory, changes in mood, change in vision.

If you have been given RITUXAN SC in combination with chemotherapy, the following additional unwanted effects may occur:

- Sudden loss of speech, weakness or numbness of part or all of one side of the body, loss of vision or blurred vision, unexplained dizziness and/or sudden falls.
- Herpes zoster also known as shingles. Symptoms of shingles include itching, tingling or severe burning pain with red patches that develop into blisters and are grouped in a cluster usually on the trunk of the body.

Please consult your doctor, nurse or pharmacist for possible unwanted effects that may be caused by CHOP, CVP

chemotherapy.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Common (1% to less than 10% of patients)	New fever or if your temperature becomes higher than 38ºC		✓	
	Shortness of breath, difficulty breathing, wheezing, coughing		✓	
	Symptoms of infection that include: -fever, temperature at 38ºC or higher. -Sore throat -Cough -Any redness or swelling -Pain when you pass your urine		✓	
	Any bleeding or unusual bruising		✓	
	Skin rash, itching, hives or sore joints		✓	
	Swelling of the face, lips, mouth or throat which may cause difficulty in swallowing or breathing, swelling of the hands, feet or ankles		✓	
	Symptoms of Hepatitis B such as mild fever, feeling of sickness, fatigue, loss of appetite, joint and/or abdominal pain and yellowing of whites of the eyes, skin and tongue.		✓	
Uncommon (0.1% to less than 1% of patients)	Chest pain, fast heart rate or an irregular or uneven heart rate		✓	
	Kidney problems such as lower back or side pain, swelling of feet or lower legs, numbness or tingling in feet or hands.		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
	Redness or blistering of the skin and the inside of the mouth		✓	✓
	Sudden loss of speech, increasing weakness or numbness of part or all of one side of the body, loss of vision or blurred vision, unexplained dizziness and/or clumsiness or sudden falls, trouble with thinking or memory, changes in mood, change in vision, change in mental status (for example, confusion), seizures.		✓	✓
	Symptoms of shingles such as itching, tingling, or severe burning pain with red patches that develop into blisters and are grouped in a cluster usually on the trunk of the body.		✓	

This is not a complete list of side effects. For any unexpected effects while taking RITUXAN SC, contact your doctor or pharmacist.

This document does not provide all known information about RITUXAN SC. If you have any questions or concerns about your treatment, please speak with your doctor, nurse or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  Fax toll-free to 1-866-678-6789, or Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 1908C
  Ottawa, Ontario
  K1A 0K9
  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Hoffmann-La Roche Limited at: www.rochecanada.com or by contacting the sponsor, Hoffmann-La Roche Limited, at: 1-888-762-4388.

This leaflet was prepared by Hoffmann-La Roche Limited.

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Roche

Hoffmann-La Roche Limited
Mississauga, ON L5N 5M8

PART III: CONSUMER INFORMATION

[Pr]RITUXAN® SC
rituximab
1600 mg (120 mg/mL) Solution for Subcutaneous Injection
***Pronounced*: rih TUCKS en**

Single Use Vial for Chronic Lymphocytic Leukemia

This leaflet is part III of a three-part "Product Monograph" published when RITUXAN SC was authorized for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about the subcutaneous formulation of RITUXAN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
RITUXAN SC (also known as rituximab) is a cancer medicine that is used to stop cancer cell growth and ideally cause the death of cancer cells. It must be prescribed by a doctor.

It is used to treat patients with certain types of chronic lymphocytic leukemia (CLL).

What is chronic lymphocytic leukemia?
Chronic lymphocytic leukemia is a cancer of the bone marrow (spongy tissue inside bones where blood cells are made). It affects lymph cells (lymphocytes) which are a type of white blood cell. There are two types: B lymphocytes and T lymphocytes. B lymphocytes produce antibodies or proteins that help our immune system to fight foreign substances which enter the body. All B-cells have a marker on their surface. This marker is called CD20.

What RITUXAN SC does:
Our bodies have a natural defence system against cancer cells. When cancer cells appear, our bodies respond by making special proteins called antibodies. Researchers studied this response and learned how to create antibodies outside the body that help with cancer treatment. These are called monoclonal antibodies.

Monoclonal antibodies are now made to target tumours in an effort to control the growth of cancer.

RITUXAN SC belongs to a family of medicine called monoclonal antibodies. It is an antibody that targets the CD-20 B-cell lymphocyte to stop its activity. RITUXAN SC attaches to the CD20 marker that is located on the B-cell. When in place, it works to stop the growth of the cancer cells and may destroy them. RITUXAN SC is most active in patients whose lymphomas are of the B-cell type.

Who should take RITUXAN SC?
RITUXAN SC is used to treat patients with moderate or severe [stage B or C] B-cell chronic lymphocytic leukemia. In the CLL trial RITUXAN was used with 2 other chemotherapy drugs FC [which stands for fludarabine and cyclophosphamide].

When it should not be used:
If you are allergic to rituximab or proteins of similar mouse or human origin or any other ingredient in RITUXAN SC or if you have ever had a rare infection of the brain called progressive multifocal leukoencephalopathy (PML) you should not take RITUXAN SC.

What should you tell your doctor before you start taking RITUXAN SC?
Before beginning treatment with the subcutaneous formulation of RITUXAN, make sure your doctor knows if:

- You ever had a bad reaction to RITUXAN or any of the non-medicinal ingredients.
- You are allergic to rituximab, other proteins which are like rituximab, or any of the other ingredients of this medicine
- You are allergic to hyaluronidase (an enzyme that is part of the formulation that helps to increase the absorption of injected active substance)
- You have a history of heart attack or stroke.
- You are taking any other medicines (including those not prescribed by the doctor).
- If you are taking medication to reduce blood pressure.
- If you are planning to be immunized with a vaccine during or after the completion of your RITUXAN SC therapy.
- If you have ever taken medicines which affect your immune system – such as chemotherapy or immune-suppressive medicines
- You have a pre-existing lung disease as you may have a greater chance of breathing difficulties during your RITUXAN SC treatment injection.
- You have a history of hepatitis B, current hepatitis B or tuberculosis infection.
- You are pregnant or could become pregnant or are breast-feeding a child.

This information will help your doctor and you decide whether you should use RITUXAN SC and what extra care may need to be taken while you are on the medication.

What the medicinal ingredient is:
RITUXAN SC contains the active ingredient rituximab.

What the non-medicinal ingredients are (in alphabetical order):
α,α-trehalose dihydrate, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, recombinant human hyaluronidase (rHuPH20), water for injection.

What dosage forms it comes in:

RITUXAN SC has been prescribed for you as a medicine for injection under your skin (called RITUXAN SC 1600 mg, solution for subcutaneous injection).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Some side effects associated with RITUXAN are severe and may be life-threatening. This drug should only be used by health professionals experienced in treating cancer in a facility where sudden and life-threatening reactions can be immediately treated.

Fatal allergic reactions and tumour lysis syndrome (TLS) causing fatal kidney damage have occurred.

Repeat and sometimes fatal attacks of hepatitis have occurred. Recurrence of hepatitis B virus infection has occurred in patients who show evidence of the virus in a blood test. It is advised that all patients be tested for hepatitis B virus infection before starting treatment with RITUXAN.

Patients with CLL who received treatment with RITUXAN may have an increased risk of JC virus infection resulting in progressive multifocal leukoencephalopathy (PML), which is a condition that leads to nerve damage within the brain. PML can cause disability and death. It is hard to predict who will get PML, but it is more common in people with weakened immune systems.

Severe skin reactions such as Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have been reported very rarely. Some cases have resulted in death.

Serious and potentially fatal cardiovascular events have been reported rarely following treatment with RITUXAN.

RITUXAN has not been studied in pregnant or breast-feeding women. If you are pregnant, could become pregnant or are breast-feeding, be sure to discuss with your doctor whether RITUXAN is right for you. Women should avoid pregnancy and use effective birth control methods during treatment with RITUXAN and for one year after treatment. Patients who are pregnant or become pregnant should not receive or continue to receive RITUXAN SC.

If you have ever had heart disease [for example angina (heart pain), arrhythmia (palpitations/ irregular heartbeat), or heart failure] or breathing problems, your doctor will take special care of you during therapy with RITUXAN.

One patient with CLL who had a tuberculosis infection had repeat and severe attacks when treated with RITUXAN. Tell the doctor if you think you had tuberculosis; you will be carefully checked for signs of tuberculosis infection.

In some cases, patients who have had hepatitis B might have a repeat attack of hepatitis. Tell the doctor if you think you have had hepatitis in the past.

Infection with hepatitis B virus causes inflammation of the liver which may show as mild fever, feeling of sickness, fatigue, loss of appetite, joint and/or abdominal pain and yellowing of whites of the eyes, skin and tongue. If you experience any of these symptoms immediately contact your doctor. If you show evidence of hepatitis B virus infection you may be referred to a liver disease expert for ongoing monitoring and management.

RITUXAN is not to be used in patients with active hepatitis B viral disease. Tell your doctor if you think you have hepatitis B.

Live viral vaccines should not be given with RITUXAN. Your doctor will check if you should have any vaccines before or after you receive RITUXAN.

Cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported during use of RITUXAN in CLL. PML is a condition that causes nerve damage within the brain. Tell your doctor immediately if you have memory loss, trouble thinking, and difficulty with walking, clumsiness, falls or weakness on one side of the body, changes in mood or loss of vision. Your doctor will check if you need to see a neurologist.

Cases of Tumour Lysis Syndrome (TLS) have been reported during the use of RITUXAN. TLS is a condition that causes sudden kidney failure and abnormal heart rhythms due to changes in blood chemistry, which may be fatal. Tell your doctor immediately if you have palpitations/irregular heartbeats; vomiting; fatigue/weakness; difficulty concentrating/trouble thinking; swelling, numbness or tingling in hands, face or feet; back pain; muscle cramps; fainting or trouble breathing.
Some patients with TLS in its early stages have no symptoms, and your doctor will be performing blood tests for this and other side effects.

Bowel problems, including blockage or tears in the bowels that can sometimes lead to death can happen if you receive RITUXAN with chemotherapy medicines to treat non-Hodgkin's lymphoma. Tell your doctor immediately if you have any abdominal pain during treatment with RITUXAN.

INTERACTIONS WITH THIS MEDICATION

Before starting treatment, make sure your doctor knows if you are taking or have recently taken any other medicines (including those you have bought for yourself from a pharmacy, supermarket or health store). This is extremely important, as using more than one medicine at the same time can strengthen or weaken their effect. RITUXAN should not be used with other drugs unless your doctor has told you it is safe to do so.

PROPER USE OF THIS MEDICATION

Your doctor has prescribed RITUXAN SC after carefully studying your case. Other people may not benefit from taking this medicine, even though their problems may seem similar to yours.

RITUXAN SC will be given to you by a doctor or nurse who is experienced in the use of this treatment. Before you are given RITUXAN SC, you will be given other medicines (pre-medication) to prevent or reduce possible side effects.

You will always be given RITUXAN as a drip (intra-venous infusion) at the start of your treatment. After this, you may be given RITUXAN SC as an injection under your skin) over approximately 7 minutes.

Your doctor or nurse will watch you closely while you are being given this medicine. This is in case you get any side effects.

Your doctor will decide when to start RITUXAN SC injections.

When injected under your skin, RITUXAN SC is given in the stomach area, not in other sites of the body, and not into areas of the stomach where the skin is red, bruised, tender, hard or where there are moles or scars. You will be observed for at least 15 minutes after your injection. The observation period may be longer if you are at risk of hypersensitivity reactions.

RITUXAN SC will be given to you on the same day as your chemotherapy. This is usually given every 4 weeks up to 5 times.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Missed Dose
If you miss a dose of RITUXAN SC, contact your physician immediately. Your physician will decide when you should receive your next dose.

Overdose
It is unlikely that you will receive too much RITUXAN SC as you will be closely monitored by Healthcare Professionals during your administration. However, if you suspect you received too much RITUXAN SC contact your physician and poison control centre immediately.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Unwanted effects are possible with all medicines. Tell your doctor, nurse or pharmacist immediately if you do not feel well while you are receiving treatment with RITUXAN SC.

Many patients get some local side effects where RITUXAN is subcutaneously injected. These include: pain, swelling, bruising, bleeding, skin redness, itching and rash.

Your doctor may decide to stop your RITUXAN SC treatment if these reactions are serious.

Tell your doctor immediately if you get signs of an infection including:

- fever, cough, sore throat, burning pain when passing urine or feeling weak or generally unwell
- memory loss, trouble thinking, difficulty walking or sight loss - these may be due to a very rare, serious brain infection, which has been fatal (Progressive Multifocal Leukoencephalopathy or PML).

You might get infections more easily during your treatment with RITUXAN SC. These are often colds, but there have been cases of pneumonia or urinary infections.

There are also possible unwanted effects which could be serious but occur less commonly:

- Chest pain, fast or irregular or uneven heartbeat.
- Decreased white blood cells, red blood cells and platelets in the blood, infection and bleeding.
- Rapid destruction of cells sometimes leading to kidney, heart or breathing problems (Tumour Lysis Syndrome).
- Redness or blistering of the skin and the inside of the mouth.
- Recurrence of Hepatitis B infection. Signs and symptoms of Hepatitis B include mild fever, feeling of sickness, fatigue, loss of appetite, joint and/or abdominal pain and yellowing of whites of the eyes, skin and tongue.
- Increasing weakness on one side of the body, clumsiness or falls, trouble with thinking or memory, changes in mood, change in vision.

If you have been given RITUXAN SC in combination with chemotherapy, the following additional unwanted effects may occur:

- Sudden loss of speech, weakness or numbness of part or all of one side of the body, loss of vision or blurred vision, unexplained dizziness and/or sudden falls.
- Herpes zoster also known as shingles. Symptoms of shingles include itching, tingling or severe burning pain with red patches that develop into blisters and are grouped in a cluster usually on the trunk of the body.

Please consult your doctor, nurse or pharmacist for possible unwanted effects that may be caused by FC chemotherapy.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM		
Symptom / effect	**Talk with your doctor or pharmacist**	**Stop taking drug and call your**

		Only if severe	In all cases	doctor or pharmacist
Common (1% to less than 10% of patients)	New fever or if your temperature becomes higher than 38ºC		✓	
	Shortness of breath, difficulty breathing, wheezing, coughing		✓	
	Symptoms of infection that include: -fever, temperature at 38ºC or higher. -Sore throat -Cough -Any redness or swelling -Pain when you pass your urine		✓	
	Any bleeding or unusual bruising		✓	
	Skin rash, itching, hives or sore joints		✓	
	Swelling of the face, lips, mouth or throat which may cause difficulty in swallowing or breathing, swelling of the hands, feet or ankles		✓	
	Symptoms of Hepatitis B such as mild fever, feeling of sickness, fatigue, loss of appetite, joint and/or abdominal pain and yellowing of whites of the eyes, skin and tongue.		✓	
Uncommon (0.1% to less than 1% of patients)	Chest pain, fast heart rate or an irregular or uneven heart rate		✓	
	Kidney problems such as lower back or side pain, swelling of feet or lower legs, numbness or tingling in feet or hands.		✓	
	Redness or blistering of the skin and the inside of the mouth		✓	✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
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	Symptoms of shingles such as itching, tingling, or severe burning pain with red patches that develop into blisters and are grouped in a cluster usually on the trunk of the body.		✓	

This is not a complete list of side effects. For any unexpected effects while taking RITUXAN SC, contact your doctor or pharmacist.

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  Health Canada
  Postal Locator 1908C
  Ottawa, Ontario
  K1A 0K9
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