PRODUCT MONOGRAPH

PrRITUXAN®

rituximab

10 mg/mL Intravenous Infusion

Professed Standard

Antineoplastic

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rituximab

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Injection- 10 mg/mL	Not applicable *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION
RITUXAN 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 relapsed or refractory low-grade or follicular, CD20 positive, B-cell non-Hodgkin's lymphoma.
- the treatment of patients with CD20 positive, diffuse large B-cell non-Hodgkin's lymphoma 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 rituximab.

Chronic Lymphocytic Leukemia (CLL)
RITUXAN (rituximab) is indicated for:
- The treatment of patients with previously untreated B-cell chronic lymphocytic leukemia (B-CLL), 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.

Rheumatoid Arthritis (RA)
RITUXAN in combination with methotrexate is indicated to reduce signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more tumour necrosis factor (TNF) inhibitor therapies**.**

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 any component of this product (See WARNINGS AND PRECAUTIONS).

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

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Progressive Multifocal Leukoencephalopathy

Patients with Rheumatoid Arthritis, Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia who received treatment with RITUXAN may have an increased risk of Progressive Multifocal Leukoencephalopathy (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).

Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia

RITUXAN (rituximab) is a potent drug. Several adverse reactions are associated with RITUXAN, some of which are severe and life-threatening. This drug should only be used by health professionals experienced in treating cancer in a setting where full resuscitation facilities are immediately available (see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

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).

Severe, including fatal, adverse reactions have occurred in patients receiving RITUXAN including: Acute renal failure and Tumor Lysis Syndrome (TLS); mucocutaneous reactions; hepatitis reactivation and JC virus infection resulting in Progressive Multifocal Leukoencephalopathy (PML). Patients should be screened for infectious disease history (see WARNINGS AND PRECAUTIONS).

Rheumatoid Arthritis

Several adverse reactions are associated with RITUXAN, some of which are severe and life-threatening (see WARNINGS AND PRECAUTIONS: RHEUMATOID ARTHRITIS). This drug should only be used by health professionals experienced in treating rheumatoid arthritis in a setting where medications and supportive care measures for the treatment of hypersensitivity reactions (eg., epinephrine, antihistamines, glucocorticoids) are immediately available in the event of an allergic reaction during administration (see DOSAGE AND ADMINISTRATION).

NON-HODGKIN'S LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA

Infusion-Related Events

RITUXAN is associated with infusion-related reactions, which may be related to release of cytokines and/or other chemical mediators. Severe infusion-related reactions might be clinically indistinguishable from hypersensitivity reactions or cytokine release syndrome. Severe infusion-related reactions with fatal outcome have been reported during post-marketing use. Severe 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 IN HEMATO-ONCOLOGY).

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 and mantle cell lymphoma, 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; 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. acetominophen and diphenhydramine) should always be administered before each infusion of RITUXAN. 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 trial, most patients received high-dose boluses intravenous corticosteroids [100 mg Prednisone IV] before each RITUXAN infusion.

Patients should be monitored closely throughout the infusion. Patients with a high tumour burden or with a high number (>25 x 109/L) of circulating malignant cells such as patients with CLL and mantle cell lymphoma 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 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.

Pulmonary events: Pulmonary events have included hypoxia, pulmonary infiltrates, 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 their infusion 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 occur.

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 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 x 109/L) of circulating malignant cells such as patients with CLL and mantle cell lymphoma). These patients should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should be provided for patients who develop signs and symptoms consistent with rapid tumour lysis. Following treatment for and complete resolution of signs and symptoms, subsequent RITUXAN 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, or to determine its effects on fertility in males or females. Individuals of childbearing potential should use effective contraceptive methods during treatment and for up to 12 months following therapy with RITUXAN.

Cardiovascular
Since transient hypotension may occur during infusion with RITUXAN, consideration should be given to withholding anti-hypertensive medications 12 hours prior to and throughout infusion with RITUXAN. Serious and potentially fatal cardiovascular events have been reported rarely following administration of RITUXAN. These events included: cardiac arrhythmias such as atrial flutter and fibrillation, cardiac failure and cardiogenic shock. Infusions with 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 infusions of RITUXAN. Patients with preexisting cardiac conditions including arrhythmias and angina have had recurrences of these events during therapy with RITUXAN and should be monitored throughout the infusion and immediate post-infusion 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 rituximab 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 $< 1.5 \times 10^9$/L and/or platelet counts of $<75 \times 10^9$/L, as clinical experience with such patients is limited. RITUXAN 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 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 this or other murine or chimeric monoclonal antibodies.

Immunization: The safety of immunization with any vaccine, particularly live viral vaccines, following therapy with RITUXAN has not been studied. The ability to generate a primary or anamnestic humoral response to any vaccine has also not been studied.

Infections

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

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 postmarketing reports. The majority of patients were profoundly immune-suppressed. These viral infections included JC virus [progressive multifocal leukoencephalopathy (PML) (see WARNINGS AND PRECAUTIONS: NON-HODGKIN'S LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA, Progressive Multifocal Leukoencephalopathy)], 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.

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 rituximab 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 TIA (duration of signs/symptoms <24 hours) is applied, then one of the four patients with reported stroke experienced a TIA.

Progressive Multifocal Leukoencephalopathy

Very rare cases of Progressive Multifocal Leukoencephalopathy have been reported during post-marketing use of RITUXAN in hematologic malignancies. The majority of patients had received RITUXAN 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, lichenoid dermatitis, vesiculobullous dermatitis, toxic epidermal necrolysis 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 interrupt treatment with RITUXAN and seek prompt medical evaluation. Skin biopsy may help to establish a diagnosis and guide subsequent treatment. The safety of re-administration of RITUXAN in these patients has not been determined.

RHEUMATOID ARTHRITIS

Infusion-Related Events

RITUXAN is associated with infusion-related reactions, which may be related to release of cytokines and/or other chemical mediators. Premedication with IV glucocorticoid significantly reduced the incidence and severity of these events (See ADVERSE REACTIONS: RHEUMATOID ARTHRITIS).

RITUXAN has caused severe infusion reactions. In spontaneous reports, fatal infusion reactions were reported very rarely in patients with autoimmune diseases and other co-morbidities (e.g. pulmonary fibrosis and SLE). The co- morbidities may have contributed to the fatal outcome. (see WARNINGS AND PRECAUTIONS: NON-HODGKIN'S LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA).

In clinical studies, 10/990 (1 %) patients with rheumatoid arthritis who received a first infusion of RITUXAN at any dose experienced a serious reaction during the infusion. Four out of 10 patients that experienced serious infusion reactions did not receive premedication with i.v. steroids. No infusion reactions in the RA population were fatal. Most infusion events reported were mild to moderate in severity. The proportion of affected patients decreases with subsequent infusions. The infusion-related reactions reported with RITUXAN were usually reversible with a reduction in rate, or interruption, of the infusion and administration of appropriate symptomatic treatment, if required. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved**.**

Anaphylaxis

Anaphylactic and other hypersensitivity reactions have been reported following the IV administration of proteins to patients. Medicinal products for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of RITUXAN.

In clinical studies 10/990 (1%) patients with rheumatoid arthritis who received a first infusion of RITUXAN at any dose experienced a serious reaction during the infusion. Four out of 10 patients that experienced serious infusion reactions did not receive premedication with i.v. steroids. Infusions with RITUXAN should be administered in an environment where full resuscitation facilities (see Serious Warnings and Precautions) are immediately available, and under the close supervision of an experienced health-professional.

Carcinogenesis and Mutagenesis

See WARNINGS AND PRECAUTIONS: NON-HODGKIN'S LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA.

Cardiovascular

Since hypotension may occur during infusion with RITUXAN, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the infusion of RITUXAN.

Angina pectoris, or cardiac arrhythmias such as atrial flutter and fibrillation heart failure have

occurred in patients treated with RITUXAN. Patients who develop clinically significant arrythmias should undergo cardiac monitoring during and after subsequent infusions of RITUXAN. Patients with a history of cardiac disease such as angina and arrhythmias should be monitored during and after infusions (see DOSAGE AND ADMINISTRATION).

Concomitant use with Biologic Agents and DMARDs other than Methotrexate in RA
Limited data are available on the safety of the use of biologic agents or DMARDs other than methotrexate in patients exhibiting peripheral B cell depletion following treatment with rituximab. Patients should be closely observed for signs of infection if biologic agents and/or DMARDs are used concomitantly.

Effects on Ability to Drive and Use Machines
See WARNINGS AND PRECAUTIONS: NON-HODGKIN'S LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA.

Immune
A total of 96/1039 (9.2%) patients with rheumatoid arthritis tested positive for HACA in clinical studies. The emergence of HACA was not associated with clinical deterioration or with an increased risk of reactions to subsequent infusions in the majority of patients. The presence of HACA could be associated with worsening of infusion or allergic reactions after the second infusion of subsequent courses. Such events could include hypersensitivity or anaphylactic reactions or anaphylactic shock. Failure to deplete B cells after receipt of further treatment courses has also been observed rarely.

Immunization: There are no data concerning the use of vaccines while patients are B cell depleted following therapy with RITUXAN (see CLINICAL TRIALS). Physicians should review the vaccination status of patients being considered for treatment with RITUXAN and follow local/national guidance for adult vaccination against infectious disease. Vaccination should be completed at least 4 weeks prior to first administration of RITUXAN. Live vaccines are not recommended in patients while B cell depleted.

Infections
Serious infections can occur during therapy with RITUXAN. RITUXAN should not be administered to patients with an active and/or severe infection or severely immuno-compromised patients (e.g. in hypogammaglobulinemia or AIDS where levels of CD4 or CD8 are very low). Physicians should exercise caution when considering the use of RITUXAN in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection (see ADVERSE REACTIONS: RHEUMATOID ARTHRITIS). Patients who develop infection following therapy with RITUXAN should be promptly evaluated and treated appropriately.

Hepatitis B Reactivation: In patients with NHL receiving rituximab in combination with cytotoxic chemotherapy, very rare cases of hepatitis B reactivation have been reported (see WARNINGS AND PRECAUTIONS: NON-HODGKIN'S LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA).

HBV screening should be considered for patients before initiation of treatment with RITUXAN.

Progressive Multifocal Leukoencephalopathy: Cases of fatal progressive multifocal leukoencephalopathy have been reported following use of RITUXAN for the treatment of autoimmune diseases (including RA). Several, but not all of the reported cases had multiple risk factors for PML, including the underlying disease, long-term immunosuppressive therapy or chemotherapy. PML has also been reported in patients with autoimmune disease not treated with RITUXAN.

Patients being treated with RITUXAN should be instructed to report any new neurological signs or symptoms to their physician. Physicians treating patients with autoimmune diseases 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.

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

Retreatment in Patients with RA

Safety and efficacy of retreatment have not been established in controlled trials. A limited number of patients have received two to five courses (two infusions per course) of treatment in an uncontrolled setting. In clinical trials in patients with RA, most of the patients who received additional courses did so 24 weeks after the previous course and none were retreated sooner than 16 weeks.

Use in Patients with RA who had no Prior Inadequate Response to TNF Antagonists

While efficacy of RITUXAN was supported in two well-controlled trials in patients with RA with prior inadequate responses to non-biologic DMARDs, a favourable risk benefit relationship has not been established in this population. The use of RITUXAN in patients with RA who have no prior inadequate response to one or more TNF antagonists is not recommended.

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 rituximab 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 should employ effective contraceptive methods during and for up to 12 months after treatment with RITUXAN.

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

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.

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 CLL trial M17102, 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 rituximab 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 rituximab might have in this age category.

In RA clinical studies, adverse reactions, including incidence, severity and type of adverse reaction were similar between older and younger patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview- HEMATO-ONCOLOGY

Clinical trials have been conducted in patients with various malignancies and benign disorders in hematology treated with RITUXAN, 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 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 IN HEMATO-ONCOLOGY

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 the table below 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 166 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 (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 1 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% - < 10%)	Uncommon (≥0.1% - < 1%)
Infections and infestations	bacterial infections , viral infections ,	sepsis , [+]pneumonia, [+]febrile infection, [+]herpes zoster, [+]respiratory tract infection, fungal infections, infections of unknown etiology	
Blood and the lymphatic system disorders	neutropenia , leucopenia	anemia , thrombocytopenia	coagulation 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	pruritis , rash	urticaria , [+]alopecia, sweating, night sweats	
Musculoskeletal, connective tissue and		hypertonia, myalgia , arthralgia , back pain , neck pain, pain	

bone disorders			
General disorders and administration site conditions	fever , chills , asthenia , headache	tumour pain, flushing, malaise, cold syndrome	pain at the infusion site
Investigations	decreased IgG levels		
For each term, the frequency count was based on reactions of all grades (from mild to severe), except for terms marked with "+" where the frequency count was based only on severe (≥ grade 3 NCI common toxicity criteria) reactions. Only the highest frequency observed in either trial is reported.			

RITUXAN as Monotherapy

The adverse events listed below were considered by the investigator to be related or of unknown relationship to RITUXAN and were reported during or up to 12 months after treatment. Adverse events were graded according to the four scale National Cancer Institute (NCI) Common Toxicity Criteria.

Table 2 Summary of Adverse Events Reported in ≥ 1% of 356 NHL Patients Receiving RITUXAN Monotherapy in Clinical Trials

	All grades		Grade 3 and 4	
Body system Adverse event	**N**	**%**	**N**	**%**
Any adverse event	324	91.0	63	17.7
Blood and lymphatic system				
Leukopenia	44	12.4	10	2.8
Neutropenia	40	11.2	15	4.2
Thrombocytopenia	34	9.6	6	1.7
Anemia	13	3.7	4	1.1
Body as a whole				
Fever	172	48.3	2	0.6
Chills	113	31.7	8	2.2
Asthenia	64	18.0	1	0.3
Headache	45	12.6	2	0.6
Throat irritation	27	7.6	-	-
Abdominal pain	25	7.0	2	0.6
Back pain	16	4.5	1	0.3
Flushing	15	4.2	-	-
Pain	15	4.2	-	-
Chest pain	8	2.2	-	-
Infection	7	2.0	2	0.6
Malaise	7	2.0	-	-
Tumour pain	6	1.7	-	-
Cold syndrome	5	1.4	-	-
Neck pain	4	1.1	-	-
Cardiovascular system				
Hypotension	35	9.8	3	0.8
Hypertension	16	4.5	1	0.3
Arrhythmia	5	1.4	2	0.6
Tachycardia	5	1.4	-	-
Hypotension orthostatic	4	1.1	-	-
Digestive system				
Nausea	61	17.1	1	0.3
Vomiting	24	6.7	1	0.3
Diarrhea	15	4.2	-	-

	All grades		Grade 3 and 4	
Body system Adverse event	**N**	**%**	**N**	**%**
Anorexia	10	2.8	-	-
Dyspepsia	10	2.8	-	-
Dysphagia	5	1.4	1	0.3
Stomatitis	5	1.4	-	-
Constipation	4	1.1	-	-
Metabolic and nutritional disorders				
Angioedema	38	10.7	1	0.3
Hyperglycemia	19	5.3	1	0.3
Peripheral edema	17	4.8	-	-
Hypocalcemia	8	2.2	-	-
Increased lactate-dehydrogenase	8	2.2	-	-
Face edema	4	1.1	-	-
Decreased weight	4	1.1	-	-
Musculoskeletal system				
Myalgia	29	8.1	1	0.3
Arthralgia	21	5.9	2	0.6
Hypertonia	5	1.4	-	-
Pain	4	1.1	1	0.3
Nervous system				
Dizziness	26	7.3	-	-
Paresthesia	9	2.5	-	-
Anxiety	8	2.2	-	-
Insomnia	8	2.2	-	-
Vasodilatation	6	1.7	-	-
Agitation	5	1.4	-	-
Hypesthesia	5	1.4	-	-
Respiratory system				
Bronchospasm	28	7.9	5	1.4
Rhinitis	26	7.3	1	0.3
Increased cough	18	5.1	1	0.3
Dyspnea	8	2.2	3	0.8
Pneumonia	7	2.0	1	0.3
Infection	6	1.7	1	0.3
Sinusitis	6	1.7	-	-
Pharyngitis	5	1.4	-	-
Bronchitis	4	1.1	-	-
Chest pain	4	1.1	-	-
Respiratory disease	4	1.1	-	-
Skin and appendages				
Pruritus	44	12.4	1	0.3
Rash	40	11.2	1	0.3
Urticaria	26	7.3	3	0.8
Sweat	10	2.8	-	-
Night sweat	10	2.8	-	-
Herpes zoster	8	2.2	1	0.3
Herpes simplex	5	1.4	1	0.3
Special senses				
Lacrimation disorder	11	3.1	-	-
Conjunctivitis	5	1.4	-	-
Ear pain	4	1.1	-	-
Tinnitus	4	1.1	-	-

Less Common Clinical Trial Adverse Drug Reactions (<1%)
The following adverse events were also reported: coagulation disorders, asthma, lung disorder, bronchiolitis obliterans, hypoxia, abdominal enlargement, pain at the infusion site, bradycardia, lymphadenopathy, nervousness, depression, dysgeusia.

Subpopulations
Elderly patients (≥ 65 years): The incidence of any adverse event and of grade 3 and 4 adverse events was similar in elderly (N=94) and younger (N=237) patients (88.3% versus 92.0% for any adverse event and 16.0% versus 18.1% for grade 3 and 4 adverse events).

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

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

RITUXAN Maintenance Treatment
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 3 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)
Febrile neutropenia*	8 (4)	14 (6)
Hematotoxicity	12 (5)	9 (4)

System Organ Class	Incidence N (%)	
	CHOP	R-CHOP
Adverse Event	**152 (67)**	**185 (79)**
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 observation, 166 rituximab) 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 4 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)

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 (%)
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				
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)	-

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 (%)
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)	-
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)	-	-	-

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 (%)
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)	-
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 rituximab-arm data from controlled clinical trials that occurred in addition to those seen with monotherapy/maintenance therapy and/or at a higher frequency grouping: 202 patients with diffuse large B-cell lymphoma (DLBCL) treated with R-CHOP, and from 234 and 162 patients with follicular lymphoma treated with R-CHOP or R-CVP, respectively and from 397 CLL patients treated with rituximab in combination with fludarabine and cyclophosphamide (R-FC) (see CLINICAL TRIALS for further details).

Table 5 Summary of 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 CLL (N= 397)

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

Frequency count was based on only severe reactions
Severe reactions were defined in clinical trials as ≥ grade 3 NCI common toxicity criteria

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 6 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)

	Incidence	
	CVP N= 159	**R-CVP N = 162**
Body System	**N (%)**	**N (%)**
Diarrhea NOS	19 (11.9)	19 (11.7)
Abdominal Pain Upper	10 (6.3)	11 (6.8)
Stomatitis	11 (6.9)	7 (4.3)
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)

	Incidence	
	CVP N= 159	R-CVP N = 162
Body System	**N (%)**	**N (%)**
Tooth Abscess	2 (1.3)	1 (0.6)
Infection NOS	-	2 (1.2)
Neutropenic Sepsis	2 (1.3)	-
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)

	Incidence	
	CVP N= 159	R-CVP N = 162
Body System	**N (%)**	**N (%)**
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)
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)

	Incidence	
	CVP N= 159	R-CVP N = 162
Body System	**N (%)**	**N (%)**
Pain of Skin	2 (1.3)	-
Vascular Disorders		
Flushing	4 (2.5)	21 (13.0)
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 7 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)

Any Grade 3 and 4 Adverse Event (including Grade 2 Infections)	Incidence	
	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)	-

Any Grade 3 and 4 Adverse Event (including Grade 2 Infections)	Incidence	
	CHOP N= 196	R-CHOP N = 202
	N (%)	N (%)
Gastritis	2 (1.0)	-
Ileus paralytic	2 (1.0)	-
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)	-

Any Grade 3 and 4 Adverse Event (including Grade 2 Infections)	Incidence	
	CHOP N= 196	R-CHOP N = 202
	N (%)	N (%)
Hyperglycemia	2 (1.0)	-
Musculoskeletal, Connective Tissue and Bone Disorder		
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 (exc 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. CHOP, MCP,

CHVP-IFN) is comparable to the safety profile as described for the combination of RITUXAN and CVP or CHOP.

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. Grade 1 and 2 adverse events and grade 4 lymphocytopenia were not captured in the study. A total of 550 SAEs in 344 patients were reported across the two arms in 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 rituximab-containing arm. One case of tuberculosis was recorded as an adverse event in the R-FC arm.

Table 8 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	
	FC N= 396	**R-FC N = 397**
	N (%)	**N (%)**
Any Grade 3 and 4 Adverse Event*		
Blood and Lymphatic System Disorders		
Neutropenia	75 (18.9)	119 (30.0)
Leukopenia	46 (11.6)	93 (23.4)
Thrombocytopenia	39 (9.8)	26 (6.5)
Febrile neutropenia	22 (5.6)	37 (9.3)
Anemia	26 (6.6)	16 (4.0)
Pancytopenia	5 (1.3)	13 (3.3)
General Disorders and Administration Site Conditions		
Pyrexia	21 (5.3)	12 (3.0)
Any Serious Adverse Event*		
Blood and Lymphatic System Disorders		
Febrile neutropenia	22 (5.6)	30 (7.6)

* Grade 1 and 2 adverse events and grade 4 lymphocytopenia were not captured in ML17102.

Table 9 Summary of Grade 3 or 4 Adverse Events and Deaths by Binet Stage

Binet Stage	FC	R-FC
Overall Incidence	246 (62%)	304 (77%)
Binet Stage A		
N	20	18
Total pts with at least one AE (%)	14 (70%)	13 (72%)
Deaths (%)	3 (15%)	1(6%)
Binet Stage B		
N	253	256

Total pts with at least one AE (%)	144 (57%)	189 (74%)
Deaths (%)	32 (13%)	13 (5%)
Binet Stage C		
N	122	123
Total pts 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 10 Summary of Grade 3 or 4 Adverse Events and Deaths by Age

Age (years old)	**FC**	**R-FC**
< 65		
N	280	275
Total pts with at least one AE (%)	168 (60%)	203 (74%)
Deaths (%)	31 (11%)	26 (9%)
≥ 65- ≤ 70		
N	91	90
Total pts with at least one AE (%)	59 (65%)	72 (80%)
Deaths (%)	15 (16%)	6 (7%)
> 70		
N	25	32
Total pts 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 yrs and more AEs were recorded in the R-FC arm compared with FC alone. Similar patterns were observed for SAEs.

Further information on selected, serious adverse drug reactions

Infusion-Related Reactions (see WARNINGS AND PRECAUTIONS)
Monotherapy – 4 weeks treatment
Hypotension, fever, chills, rigors, urticaria, bronchospasm, sensation of tongue or throat swelling (angioedema), nausea, fatigue, headache, pruritus, dyspnea, rhinitis, vomiting, flushing, and pain at disease sites have occurred in association with RITUXAN infusion as part of an infusion-related symptom complex. Such infusion-related symptoms occurred in the majority of patients during the first infusion with RITUXAN. The incidence of infusion-related symptoms decreased from 77% (7% Grade 3/4) with the first infusion to approximately 30% (2% Grade 3/4) with the fourth infusion and to 14% (no grade 3/4 events) with the eighth infusion.

Maintenance Treatment (NHL) up to 2 years

Non-serious signs and symptoms suggestive of an infusion-related reaction were reported in 41% of patients 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.

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)
The incidence of severe (grade 3/4) infusion-related reactions was consistent with those observed for monotherapy. Severe infusion-related reactions occurred in approximately 9% of all patients at the time of the first treatment cycle with rituximab 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-chemotherapy were myocardial infarction, atrial fibrillation and pulmonary edema.

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

Maintenance Treatment (NHL) up to 2 years
The proportion of patients with grade 1 to 4 infections was 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.

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 (18% R-FC, 17% FC).

Hematologic Events

Monotherapy 4 weeks

Hematologic adverse events occur in a minority of patients and are usually mild and reversible. Severe neutropenia was reported in 4.2% of patients, severe anemia was reported in 1.1% of patients and severe thrombocytopenia was reported in 1.7% of patients. A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following therapy with RITUXAN were reported.

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.

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

Severe (grade 3/4) 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 CLL patients, grade 3 or 4 neutropenia was reported in 30% of patients in the R-FC arm and in 19% of patients in the FC arm.

Severe (grade 3/4) Leucopenia: In the R-CHOP study, the incidence of severe leucopenia was 88% in the R-CHOP arm versus 79% in the CHOP arm. In CLL, more patients receiving R-FC experienced grade 3 or 4 leucopenia (23%) compared with patients receiving FC (12%).

Severe (grade 3/4) 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 or 4 anemia was reported by 4% of patients treated with R-FC compared to 7% of patients receiving FC, and grade 3 or 4 thrombocytopenia was reported by 7% of patients in the R-FC group compared to 10% of patients in the FC group.

Cardiovascular Events (see WARNINGS AND PRECAUTIONS)
Monotherapy 4 weeks treatment
Cardiovascular events were reported in 18.8% of patients during the treatment period. The most frequently reported events were hypotension and hypertension. Two patients (0.6%) experienced grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) during an infusion with RITUXAN and one patient with a history of myocardial infarction experienced angina pectoris, evolving into myocardial infarction 4 days later.

Maintenance Treatment (NHL) up to 2 years
The incidence of grade 3 to 4 cardiac disorders was comparable between the two treatment groups (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 inDLBCL, 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 the CLL first-line study, the overall incidence of grade 3 or 4 cardiac disorders was low (4% R-FC, 3% 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, four patients (2%) in the R-CHOP group, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment group in the incidence of other thromboembolic events. In contrast, three patients (1.5%) had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period.

In the CLL first-line study, the overall incidence of grade 3 or 4 nervous system disorders was low (4% R-FC, 4% 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

In the CLL first line study, the incidence of malignancy following exposure to RITUXAN was 4.5% compared to 3.8% in patients not exposed to RITUXAN.

Subpopulations

Monotherapy – 4 weeks treatment

Elderly patients (≥ 65 years): The incidence of any ADR and of grade 3 and 4 ADRs was similar in elderly (N=94) and younger (N=237) patients (88.3% versus 92.0% for any ADR and 16.0% versus 18.1% for grade 3 and 4 ADRs).

Bulky disease: Patients with bulky disease (N=39) had a higher incidence of grade 3 and 4 ADRs than patients without bulky disease (N=195; 25.6% versus 15.4%). The incidence of any ADR was similar in these two groups (92.3% in bulky disease versus 89.2% in non-bulky disease).
Retreatment with monotherapy: The percentage of patients reporting any ADR and grade 3 and 4 ADRs upon re-treatment (N=60) with further courses of RITUXAN was similar to the percentage of patients reporting any ADR and grade 3 and 4 ADRs upon initial exposure (N=203; 95.0% versus 89.7% for any ADR and 13.3% versus 14.8% for grade 3 and 4 ADRs).

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. Grade 1 and 2 adverse events and grade 4 lymphocytopenia were not captured in the study.

Table 11 Summary of Serious Adverse Events that occurred with an incidence of ≥ 1%

	Incidence	
	FC N= 396	**R-FC N = 397**
	N (%)	**N (%)**
Blood and Lymphatic System Disorders*		
Febrile neutropenia	22 (6)	30 (8)
Anemia	9 (2)	6 (2)
Leukopenia	3 (<1)	9 (2)
Neutropenia	3 (<1)	8 (2)
Thrombocytopenia	5 (1)	6 (2)
Pancytopenia	3 (<1)	6 (2)
Infections and Infestations		
Pneumonia	20 (5)	18 (5)
Herpes Zoster	6 (2)	8 (2)
Sepsis	8 (2)	5 (1)
Bronchitis	5 (1)	5 (1)
Infection	2 (<1)	5 (1)
Sinusitis	1 (<1)	4 (1)
General Disorders and Administration Site Conditions		
Pyrexia	20 (5)	18 (5)
Cardiac Disorders		
Angina Pectoris	2 (<1)	5 (1)
Gastrointestinal Disorders		
Diarrhea	2 (<1)	5 (1)

* Grade 4 lymphocytopenia was not captured in ML17102.

Post-Market Adverse Drug Reactions

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.

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: Very rare 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).

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

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 rituximab therapy.

Respiratory System: respiratory failure/insufficiency and pulmonary infiltrates in the context of infusion-related reactions (see WARNINGS AND PRECAUTIONS), pulmonary infiltrates outside of infusion-related reactions and interstitial pneumonitis have been reported rarely; pleural effusions, and pneumonia.

Skin and Appendages: severe bullous skin reactions (including toxic epidermal necrolysis) and pemphigus, some with fatal outcome, have been reported rarely.

Urogenital System: renal insufficiency/failure.

RHEUMATOID ARTHRITIS

The clinical efficacy of RITUXAN, given together with methotrexate was studied in three double blind controlled clinical trials (one phase III trial and two phase II trials) in patients with rheumatoid arthritis. More than 1000 patients received at least one treatment course and were followed for periods ranging from 6 months to over 3 years; approximately 600 patients received two or more courses of treatment during the follow up period.

Patients received 2 x 1000 mg of RITUXAN separated by an interval of two weeks; in addition to methotrexate (10-25 mg/week). Infusions of RITUXAN were administered after an IV infusion of 100 mg methylprednisolone; patients also received treatment with oral prednisolone for 15 days. Listed in Table 3 are ADRs that occurred with at least a 2% difference compared to the control arm and more frequently by patients who had received at least one infusion of RITUXAN than among patients that had received placebo in the phase III trial and the combined population included in phase II studies. In these studies, adverse reactions were more frequent in patients treated with RITUXAN than in patients treated with placebo. Frequencies are defined as very common (≥1/10) and common (≥1/100 to <1/10).

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

Table 12 Summary of Adverse Drug Reactions Occurring in Patients with Rheumatoid Arthritis Receiving RITUXAN During Phase II and III Clinical Studies

	Pooled Phase II Study Population		**Phase III Study Population**	
	Very Common (≥ 10%)	**Common** (≥1 % - < 10%)	**Very Common** (≥ 10%)	**Common** (≥1% - < 10%)
Acute Infusion reactions*		Hypertension , rash, pruritus, chills, pyrexia, rhinitis, throat irritation		Hypertension, nausea, rash, pyrexia, pruritus, urticaria, throat irritation, hot flush, hypotension
Gastrointestinal Disorders		Dyspepsia		Dyspepsia
Infections and Infestations	Any Infection	Urinary tract infections	Any infection, Upper respiratory tract infection	
Metabolism and Nutritional Disorders				Hypercholesterolemia
Musculo skeletal disorders		Arthralgia / musculoskeletal pain		Arthralgia / musculoskeletal pain, osteoarthritis
Nervous System disorders		Migraine		Paraesthesia
† This table include all events with an incidence difference of ≥ 2 % for rituximab compared to placebo * Reactions occurring during or within 24 hours of infusion				

Table 13 Adverse Reactions Occurring in at Least 1% of Patients and More Frequently in Rheumatoid Arthritis Patients Receiving RITUXAN During Phase II and III Clinical Studies

	Pooled Phase II Study Population		Phase III Study Population	
	MTX + Placebo N = 189 n (%)	RITUXAN + MTX N = 232 n (%)	MTX + Placebo N =209 n (%)	RITUXAN + MTX N = 308 n (%)
Acute Infusion reactions*				
Hypertension	10 (5%)	22 (9%)	11 (5%)	21 (7%)
Nausea	14 (7%)	19 (8%)	5 (2%)	22 (7%)
Rash	6 (3%)	18 (8%)	9 (4%)	17 (6%)
Pyrexia	1 (<1%)	12 (5%)	7 (3%)	15 (5%)
Pruritus	1 (<1%)	14 (6%)	4 (2%)	12 (4%)
Urticaria	0	2 (<1%)	3 (1%)	10 (3%)
Rhinitis	2 (1%)	6 (3%)	4 (2%)	8 (3%)
Throat irritation	0	5 (2%)	0	6 (2%)
Hot Flush	4 (2%)	2 (<1%)	0	6 (2%)
Hypotension	11 (6%)	10 (4%)	1 (<1%)	5 (2%)
Chills	3 (2%)	13 (6%)	6 (3%)	3 (<1%)
Gastrointestinal Disorders				
Dyspepsia	3 (2%)	9 (4%)	0	7 (2%)
Abdominal Pain Upper	3 (2%)	7 (3%)	1 (<1%)	4 (1%)
General Disorders				
Asthenia	0	3 (1%)	1 (<1%)	6 (2%)
Infections and Infestations				
Any infection	56 (30%)	85 (37%)	78 (37%)	127 (41%)
Urinary tract Infections	8 (4%)	14 (6%)	17 (8%)	15 (5%)
Upper Respiratory Tract	28 (15%)	31 (13%)	26 (12%)	48 (16%)
Lower Respiratory Tract Infection/Pneumonia	10 (5%)	9 (4%)	5 (2%)	8 (3%)
Metabolism and Nutritional Disorders				
Hypercholesterolemia	1 (<1%)	3 (1%)	0	6 (2%)
Musculo skeletal disorders				
Arthralgia/musculoskeletal pain	8 (4%)	18 (7%)	6 (3%)	17 (7%)
Muscle Spasms	0	1 (<1%)	2 (1%)	7 (2%)
Osteoarthritis	1 (<1%)	4 (2%)	0	6 (2%)
Nervous System				
Paresthesia	2 (1%)	4 (2%)	1 (<1%)	8 (3%)
Migraine	0	4 (2%)	2 (1%)	5 (2%)

* Reactions occurring within 24 hours of infusion

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

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

General Disorders: Generalized edema
Immune system Disorders: Anaphylaxis, anaphylactoid reaction

Respiratory Disorders: Bronchospasm, wheezing, laryngeal edema
Skin and Subcutaneous Disorders: Angioneurotic edema, generalized pruritis.

Multiple Courses: Multiple courses of treatment are associated with a similar ADR profile to that observed following first exposure. The incidence of acute infusion reactions following subsequent treatment courses was generally lower than the incidence following the first infusion of RITUXAN.

Acute Infusion reactions: Symptoms suggesting an acute infusion reaction (pruritis, fever, urticaria/rash, chills, pyrexia, rigors, sneezing, angioneurotic edema, throat irritation, cough and bronchospasm, with or without associated hypotension or hypertension) were observed in 79/540 (15%) patients with rheumatoid arthritis following their first exposure to RITUXAN compared to 19/398 (5%) patients receiving their first placebo infusion. In a study comparing the effect of glucocorticoid regimens, these events were observed in 5/149 (3%) of patients following their first placebo infusion and 42/192 (22%) of patients receiving their first infusion of 1000 mg rituximab. Premedication with IV glucocorticoid significantly reduced the incidence and severity of these events. Of the patients who received 1000 mg rituximab without premedication with glucocorticoids, 18/65 (28%) experienced an acute infusion reaction following the first infusion, compared with 24/127 (19%) in patients given IV glucocorticoid premedication and 2/63 (3%) in patients receiving their first placebo infusion, respectively.

Infections: The rate of infection was approximately 0.9 per patient year in patients treated with RITUXAN. The infections consisted mostly of upper respiratory tract infections and urinary tract infections. The incidence of clinically significant infections, some of which were fatal, was 0.07 per patient year in patients treated with RITUXAN.

Malignancies: In RA clinical studies, the incidence of malignancy following exposure to rituximab is 1.5 per 100 person years. On the basis of limited experience with RITUXAN in rheumatoid arthritis patients, a possible risk for the development of solid tumours cannot be excluded at this time, although present data do not seem to suggest any increased risk.

DRUG INTERACTIONS

Overview
There have been no formal drug interaction studies performed with RITUXAN (rituximab). However, the existing data suggest that rituximab 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 (rituximab). 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.

Co-administration with methotrexate had no effect on the pharmacokinetics of RITUXAN in rheumatoid arthritis patients.

Concomitant use with Biologic Agents and DMARDs other than Methotrexate in RA
Limited data are available on the safety of the use of biologic agents or DMARDs other than methotrexate in patients exhibiting peripheral B cell depletion following treatment with rituximab. Patients should be closely observed for signs of infection if biologic agents and/or DMARDs are used concomitantly.

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

RITUXAN (rituximab) infusions should be administered in a setting where full resuscitation facilities (see Serious Warnings and Precautions) are immediately available, and under the close supervision of someone experienced and capable of dealing with severe infusion-related reactions. RITUXAN should be administered as an IV infusion through a dedicated line**. Do not administer as an intravenous push or bolus (See Administration).**

Hypersensitivity reactions and severe infusion-related reaction may occur with administration of RITUXAN (see WARNINGS AND PRECAUTIONS). Since transient hypotension may occur during infusion with RITUXAN, consideration should be given to withholding anti-hypertensive medications 12 hours prior to and throughout infusion with RITUXAN. Premedication consisting of an analgesic/anti-pyretic (e.g. acetaminophen) and an antihistaminic drug (e.g. diphenhydramine) should always be administered before each infusion of RITUXAN. In the clinical trial for CLL ML17102, most patients also received high-dose IV corticosteroids before each dose.

Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of RITUXAN. Patients with pre-existing cardiac conditions such as angina and arrhythmias should be monitored during and after the infusion of RITUXAN.

Preparation for Administration
Use appropriate aseptic technique. RITUXAN does not contain any preservative or bacteriostatic agent. Withdraw the necessary amount of RITUXAN and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride Injection USP or 5%

Dextrose Injection USP. To avoid foaming, gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

NON-HODGKIN'S LYMPHOMA

Usual Dose

Low grade or follicular non-Hodgkin's lymphoma:

Initial treatment
The recommended dosage of RITUXAN as a single agent, is 375 mg/m^2 given as an IV infusion once weekly for four doses (days 1, 8, 15, and 22).

The recommended dosage of RITUXAN in combination with CVP chemotherapy is 375 mg/m^2 for 8 cycles (21 days/cycle), administered as an IV infusion on day 1 of each chemotherapy cycle after IV administration of the corticosteroid component of CVP.

Maintenance treatment
The recommended dose of RITUXAN for patients who have responded to induction treatment, is 375 mg/m^2 every 3 months until disease progression or for a maximum period of two years.

Diffuse large B-cell non-Hodgkin's lymphoma:
RITUXAN should be used in combination with CHOP chemotherapy. The recommended dosage of RITUXAN is 375 mg/m^2 administered on day 1 of each chemotherapy cycle after i.v. administration of the glucocorticoid component of CHOP. The other components of CHOP (cyclophosphamide, doxorubicin, vincristine) should be given after the administration of RITUXAN.

Chronic Lymphocytic Leukemia
The recommended dosage of RITUXAN in combination with chemotherapy is 375 mg/m^2 body surface area administered on day 1 of the first treatment cycle followed by 500mg/m^2 body surface area administered on day 1 of each subsequent cycle for 6 cycles in total. The chemotherapy should be given after RITUXAN infusion.

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 infusion with RITUXAN to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome. In ML17102 an equivalent of 80mg 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 ML17102 received at least one dose of corticosteroids, with 27% receiving two or more doses.

Dosage Adjustments During Treatment

No dose reductions of RITUXAN are recommended but 47% of patients in the clinical trial for CLL ML17102 required a delayed and/or slowed infusion, and 17% required their first dose split over two days. When RITUXAN is given in combination with CHOP chemotherapy, standard dose reductions for the chemotherapeutic drugs should be applied. When RITUXAN is given as maintenance treatment, treatment should be delayed in case of significant clinical toxicity according to standard practice.

RITUXAN as a Component of Zevalin®(Ibritumomab Tiuxetan) Therapeutic Regimen

As a required component of the Zevalin therapeutic regimen, RITUXAN is administered twice. The first administration of RITUXAN is a single infusion of 250 mg/m^2 and should precede the second administration by 7-9 days. At the second administration, RITUXAN 250 mg/m^2 should be infused within 4 hours prior to the administration of ^{90}Y-ibritumomab tiuxetan. Refer to the Zevalin product monograph for full prescribing information.

®Zevalin, Registered Trade-Mark of IDEC Corporation.

Administration

Do not administer as an intravenous push or bolus. Premedication with glucocorticoids should be considered, particularly if RITUXAN is not given in combination with steroid-containing chemotherapy. Premedication may attenuate infusion-related events. In the clinical trial for CLL ML17102, the equivalent of 80 mg methylprednisolone (100 mg prednisone IV) was given to most patients prior to each infusion.

First Infusion: The RITUXAN solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. RITUXAN should not be mixed or diluted with other drugs. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. 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.

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

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.

RHEUMATOID ARTHRITIS

Usual Dose

A course of RITUXAN consists of two 1000 mg IV infusions. The recommended dosage of RITUXAN is 1000 mg by IV infusion followed two weeks later by the second 1000 mg IV infusion.

Rheumatoid arthritis patients should receive treatment with 100 mg IV methylprednisolone 30 minutes prior to RITUXAN to decrease the rate and severity of acute infusion reactions (See WARNINGS AND PRECAUTIONS).

Retreatment in Patients with RA

Safety and efficacy of retreatment have not been established in controlled trials. A limited number of patients have received two to five courses (two infusions per course) of treatment in an uncontrolled setting. In clinical trials in patients with RA, most of the patients who received additional courses did so 24 weeks after the previous course and none were retreated sooner than 16 weeks.

Administration

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

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

OVERDOSAGE

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

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]

Type B lymphocytes are believed to play a central role in the pathogenesis of rheumatoid arthritis (RA) and associated chronic synovitis. In this setting, B cells may be acting at multiple sites in the autoimmune/inflammatory process, including through production of rheumatoid factor (RF) and other autoantibodies, antigen presentation, T cell activation, and/or pro-inflammatory cytokine production. Depletion of CD 20 surface antigen positive B cells was associated with reduction of pro-inflammatory cytokines in rheumatoid synovial tissue.

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

Non-Hodgkin's Lymphoma

In patients given single doses at 10, 50, 100, 250 or 500 mg/m^2 as an IV infusion, serum levels and the half-life of rituximab were proportional to dose. In 9 patients given 375 mg/m^2 as an IV infusion for four doses, the mean serum half-life was 59.8 hours (range 11.1 to 104.6 hours) after the first infusion and 174 hours (range 26 to 442 hours) after the fourth infusion. The wide range of half-lives may reflect the variable tumour burden among patients and the changes in CD20 positive (normal and malignant) B-cell populations upon repeated administrations.

Rituximab at a dose of 375 mg/m^2 was administered as an IV infusion at weekly intervals for four doses to 166 patients. The peak and trough serum levels of rituximab were inversely correlated with baseline values for the number of circulating CD20 positive B cells and measures of disease burden. Median steady-state serum levels were higher for responders compared to nonresponders; however, no difference was found in the rate of elimination as measured by serum half-life. Serum levels were higher in patients with International Working Formulation

(IWF) subtypes B, C, and D as compared to those with subtype A. Rituximab was detectable in the serum of patients three to six months after completion of treatment.

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

Administration of RITUXAN (rituximab) resulted in a rapid and sustained depletion of circulating and tissue-based B cells. Lymph node biopsies performed 14 days after therapy showed a decrease in the percentage of B-cells in seven of eight patients who had received single doses of rituximab ≥ 100 mg/m^2.[10] Among the 166 patients in the pivotal study, circulating B-cells (measured as CD19+ cells) were depleted within the first three doses with sustained depletion for up to 6 to 9 months post-treatment in 83% of patients. One of the responding patients (1%), failed to show significant depletion of CD19+ cells after the third infusion of rituximab as compared to 19% of the nonresponding patients. B-cell recovery began at approximately six months following completion of treatment. Median B-cell levels returned to normal by twelve months following completion of treatment.

There were sustained and statistically significant reductions in both IgM and IgG serum levels observed from 5 through 11 months following rituximab administration. However, only 14 % of patients had reductions in IgG and/or IgM serum levels, resulting in values below the normal range.

Peripheral B-cell counts declined to levels below normal following the first dose of RITUXAN. In patients treated for hematological malignancies, B cell repletion began within 6 months of treatment returning to normal levels between 9 and 12 months after completion of therapy. In rheumatoid arthritis patients, immediate depletion of B cells in the peripheral blood was observed following two infusions of 1000 mg of RITUXAN separated by a 14 day interval. Peripheral blood B cell counts begin to increase from week 24 and evidence of repopulation is observed in the majority of patients by week 40, whether RITUXAN was administered as monotherapy or in combination with methotrexate.

Diffuse large B-cell non-Hodgkin's lymphoma (DLCL): Elimination and distribution have not been extensively studied in patients with diffuse large B-cell non-Hodgkin´s lymphoma, but available data indicate that serum levels of rituximab in DLCL patients are comparable to those in patients with low-grade or follicular NHL following treatment with similar doses.

Chronic Lymphocytic Leukemia (CLL)
No pharmacokinetic information in the untreated CLL population is available.

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

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

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
RITUXAN (rituximab) vials are stable at 2 to 8ºC. Do not use beyond expiration date stamped on carton. Keep the vial in the outer carton to protect it from light.

As RITUXAN for infusion does not contain any antimicrobial preservative, it is essential to ensure that prepared solutions for infusion are not microbiologically compromised. RITUXAN solutions for infusion are stable at 2 to 8ºC for 24 hours and at room temperature for an

additional 12 hours. However, administration should take place as per standard practices after the aseptic preparation of intravenous admixtures.

Incompatibilities
No incompatibilities between RITUXAN and polyvinylchloride or polyethylene bags have been observed.

DOSAGE FORMS, COMPOSITION AND PACKAGING

RITUXAN (rituximab) is supplied as 100 mg and 500 mg single-use vials containing a sterile, preservative-free solution.

100 mg: each carton contains two 100 mg/10 mL vials (10 mg/mL).
500 mg: each carton contains one 500 mg/50 mL vial (10 mg/mL).

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.

RITUXAN is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration. RITUXAN is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for intravenous administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Sterile Water for Injection. The pH is adjusted to 6.5.

CLINICAL TRIALS

*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

Overview of Clinical Trials

Table 14 Follicular non-Hodgkin's Lymphoma, Monotherapy:

Trial design	Dosage	Number of study subjects	Mean age (Range)	Gender	Results			
					Complete Response (CR)	**Partial Response (PR)**	**Overall Response Rate (ORR)**	**95% CI (ORR)**
Multicenter, open-label, single arm, phase III trial	RITUXAN 375 mg/m^2 given as an i.v. infusion	N=166	58 (22-79)	Male: 105 (63%) Female:				

Trial design	Dosage	Number of study subjects	Mean age (Range)	Gender	Results			
					10/166 (6%)	70/166 (42%)	80/166 (48%)	41-56%

Table 15 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.

Table 16 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)				
						CHOP	**R-CHOP**	**RR[1)]**	**p-value (log-rank)**
Prospective, open label, international, multi-centre, phase III trial	[3)]CHOP	N= 231	54.1 (27-78)	Male: 118 (51%) Female: 113 (49%)	Primary Efficacy				
					ORR[2)]	74%	87%	Na	0.0003
					CR[2)]	16%	29%	Na	0.0005
					PR[2)]	58%	58%	Na	0.9449
	[4)]R-CHOP	N= 234	54.1 (26-80)	Male: 107 (46%) Female: 127 (54%)	Second. Efficacy				
					OS (median)	NR	NR	31%	0.0267
					PFS (median)	20.8 mo	32.2 mo	36%	<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**		**Rituximab**	
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)	**Rituximab** (N=167)	**Observation** (N=167)	**Rituximab** (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)	**Rituximab** (N=167)	**Observation** (N=48)	**Rituximab** (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 ; -
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

Table 17 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
					Overall survival[3)*]	57.3%	70.2%	0.63	0.0072
	[2)]R-CHOP	N= 202	69.5 (59-80)	Male: 92 (46%) Female: 110 (54%)					

[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.

Table 18 Chronic Lymphocytic Leukemia (CLL)

Trial design	Dosage	Number* of study subjects	Mean age (Range)	Gender	Results[3] * (20.7 months mean observation time)				
Randomized open-label, phase III trial	[1]FC F: 25mg/m^2 C: 250 mg/m^2, each on days 1-3) every 4 weeks for 6 cycles [2]R-FC F: 25mg/m^2 C: 250 mg/m^2, each on days 1-3) every 4 weeks for 6 cycle R: 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	N= 407 N= 403	59.3 (36-81) 59.6 (30-78)	Male: 302 (74%) Female: 105 (26%) Male: 298 (74%) Female: 105 (26%)		**FC**	**R-FC**	**Log rank p-value**	**Risk Reduction**
					Progression Free Survival	32.2	39.8	< 0.0001	44%
					Overall survival (at interim analysis)	NR	NR	0.0427	36%
					Overall survival (with an additional 4.8 months of median follow-up)	NR	52.4	0.1208	28%
					Event Free Survival	31.1	39.8	< 0.0001	45%
					[4]Response rate (CR, nPR, or PR)	72.7%	86.1%	< 0.0001	NA
					CR rates	17.2%	36.0%	< 0.0001	NA
					Duration of response	34.7	40.2	0.0040	39%
					Disease free survival (DFS)[5]	NR	NR	0.7882	7%
					Time to new CLL treatment	NR	NR	0.0052	35%

[1] FC = (fludarabine 25mg/m^2, cyclophosphamide 250 mg/m^2, days 1-3) every 4 weeks 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 and CR rates analysed using Chi-squared Test.
[5]: only applicable to patients achieving a CR;
NR: not reached
NA: not applicable
* after a severe allergic reaction to their first dose of RITUXAN, one patient in the R-FC was considered part of the FC arm for safety and efficacy assessments.

Table 19 Summary of Progression-Free Survival according to Binet Stage (ITT)

	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 20 Summary of Progression-Free Survival according to Age (ITT)

	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)	
p-value (Wald test, not adjusted)	0.3832	

Study Results

Follicular non-Hodgkin's Lymphoma, Monotherapy: A multicenter, open-label, single-arm study was conducted in 166 patients with relapsed or refractory low-grade or follicular B-cell NHL who received 375 mg/m^2 of RITUXAN given as an IV infusion weekly for four doses. Patients with tumour masses >10 cm or with > 5,000 lymphocytes/µL in the peripheral blood were excluded from the study. The overall response rate (ORR) was 48% (80/166) with a 6% (10/166) complete response (CR) and a 42% (70/166) partial response (PR) rate. Disease-related signs and symptoms (including B-symptoms) were present in 23% (39/166) of patients at study entry and resolved in 64% (25/39) of those patients. The median time to onset of response was 50 days and the median duration of response is projected to be 10 to 12 months.

In a multivariate analysis, the ORR was higher in patients with IWF B, C, and D histologic subtypes as compared to IWF A subtype (58% vs. 12%), higher in patients whose largest lesion

was <5 cm vs. >7 cm in greatest diameter (53% vs. 38%), and higher in patients with chemosensitive relapse as compared to chemoresistant (defined as duration of response <3 months) relapse (53% vs. 36%). ORR in patients previously treated with autologous bone marrow transplant was 78% (18/23). The following factors were not associated with a lower response rate: age ≥ 60 years, extranodal disease, prior anthracycline therapy, and bone marrow involvement.

In a second multicenter, multiple-dose study, 37 patients with relapsed or refractory B-cell NHL received 375 mg/m^2 of RITUXAN as an IV infusion once weekly for four doses.[11,12] The ORR was 46% with a median duration of response of 8.6 months (range 2.6 to 26.2+). Single doses of up to 500 mg/m^2 were well-tolerated in a phase I, dose escalation study.[10]

Twenty one patients who have responded to RITUXAN initially have been treated again with RITUXAN. Response rate seems to be comparable in these retreated patients. Twenty patients have received two courses and one patient has received three courses of RITUXAN as 4 weekly infusions of 375 mg/m^2 per infusion. The percentage of patients reporting adverse events upon retreatment was similar to that reported following the first course, although the incidence of specific adverse events differed (see ADVERSE REACTIONS). All patients had obtained an objective clinical response (CR or PR) to the first course of RITUXAN; upon retreatment, 6 of 12 patients evaluable for response obtained a complete or partial remission.

In another study with twenty-nine patients with relapsed or refractory, bulky (single lesion of >10 cm in diameter), low grade NHL received 375 mg/m^2 of RITUXAN as four weekly infusions. The overall incidence of adverse events and the incidence of Grade 3 and 4 adverse events was higher in patients with bulky disease than in patients with non-bulky disease (see ADVERSE REACTIONS). Ten of 21 patients evaluable for response have obtained a complete or partial remission.

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. 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.

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. 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/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 21: 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 4% 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.

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, 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: In an open-label randomized trial ML17102, a total of 817 previously untreated patients with CLL were randomized to receive either FC chemotherapy (fludarabine 25mg/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 patients (403 R-FC, 407 FC) were analyzed for efficacy.

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). Primary analysis that led to the termination of the study showed an improvement of R-FC over FC for the secondary endpoint overall survival (p=0.0427. An updated survival analysis with an additional 4.8 months

of follow-up information was consistent with the main analysis in showing a benefit in favor of the R-FC arm; however, the difference in OS between the treatment arms was not significant (p=0.1208, Log-rank test). Longer follow-up is needed to draw meaningful conclusions about the treatment effect of R-FC compared to FC in terms of OS. 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 19 and 20.)*

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 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 rituximab 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 rituximab 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 rituximab 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.

RHEUMATOID ARTHRITIS

The efficacy and safety of RITUXAN in alleviating the symptoms and signs of rheumatoid arthritis was demonstrated in three randomized, controlled, double-blind, multicenter studies.

Study 1 was a double blind comparative study which included 517 patients that had experienced an inadequate response or intolerance to one or more TNF inhibitor therapies. Eligible patients had severe active rheumatoid arthritis, diagnosed according to the criteria of the American College of Rheumatology (ACR). The primary endpoint was the percent of patients who achieved an ACR20 response at week 24. Patients received two 1000 mg IV infusions of RITUXAN, each following an IV infusion of 100 mg methylprednisone and separated by an interval of 15 days. Patients were also pre-medicated with acetaminophen and diphenhydramine before each infusion of RITUXAN. All patients received concomitant oral methotrexate (10-25 mg/week) and 60 mg oral prednisone on days 2-7 and 30 mg on days 8-14 following the first infusion.

Study 2 was a randomized, double-blind, double-dummy, controlled, 3 x 3 multifactorial study which compared two different dose levels of RITUXAN given with or without one of two per infusional corticosteroid regimens in combination with weekly methotrexate in patients with active rheumatoid arthritis which had not responded to treatment with 1 but no more than 5 other Disease-Modifying Anti-Rheumatic Drug (DMARD)s.

Study 3 was a double-blind, double-dummy, controlled study evaluating rituximab monotherapy, and rituximab in combination with either cyclophosphamide or methotrexate in patients with active rheumatoid arthritis which had not responded to one or more prior DMARDs.

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

Disease Activity Outcomes
In all three studies, RITUXAN 2 x 1000 mg significantly increased the proportion of patients achieving at least a 20% improvement in ACR score compared with patients treated with methotrexate alone (Table 10). The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, body surface area, race, number of prior treatments or disease status.

ACR20 response rates at week 24 in RF negative patients were significantly higher in patients receiving rituximab + MTX (40%) compared to those receiving placebo + MTX (12%, p=0.0009), although lower than among rheumatoid factor positive patients (54%). In HACA positive patients, a total of 61/96 patients (63.4%) achieved at least an ACR20 response following their first treatment course. Mean change from original baseline DAS in HACA positive patients and HACA negative patients are -2.36 and -2. 23 respectively.

The proportion of rituximab patients achieving an ACR20 response at week 24 in the US and non-US (including Canada) were 44% vs 61% respectively. ACR20 response in placebo patients was 18% in both regions. Treatment effect in favor of rituximab was statistically significant for both regions ($p < 0.001$).

Table 22 Cross-Study Comparison of ACR Responses at Week 24 (ITT Population)

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

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

In study 3, the ACR20 response in patients treated with RITUXAN alone was 65% compared with 38% on methotrexate alone (p=0.025).

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

Table 23 Components of ACR Response in Study 1

RITUXAN + MTX (N=122)	Study 1 [RF(+) and RF (-) Patients]					
	Placebo + MTX (N=201)			RITUXAN + MTX (N=298)		
	Wk 0	Wk 24	% mean change	Wk 0	Wk 24	% mean change
Tender Joint Count (68)	32.9	30.2	7.2	33.9	19.5*	-41.8
Swollen Joint Count (66)	22.9	20.3	-5.6	23.4	13.0*	-43.0
Physician Global Assessment[a]	6.7	6.1	-4.2	6.9	4.0*	-40.8
Patient Global Assessment[a]	7.0	6.4	-3.1	6.9	4.3**	-25.4
Pain[a]	6.5	6.2	2.8	6.4	4.1**	-23.8
Disability Index (HAQ)[b]	1.9	1.8	-2.0	1.9	1.4*	-24.3
CRP (mg/dL)	3.8	3.7	80.0	3.7	1.7*	-36.3

[a] Visual Analogue Scale: 0=best, 10=worst

[b] Disability Index of the Health Assessment Questionnaire: 0=best, 3=worst

* $p<0.0001$, ** $p<0.005$ RITUXAN + MTX minus Placebo + MTX stratified for rheumatoid factor, region and baseline ACR

Negative % change from baseline value indicates an improvement.

Patients treated with RITUXAN had a significantly greater reduction in disease activity score (DAS28) than patients treated with methotrexate alone. A good to moderate European League against Rheumatism (EULAR) response was achieved by significantly more patients treated with rituximab compared to patients treated with methotrexate alone (Table 24).

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

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

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

Quality of Life Outcomes

Patients treated with rituximab reported an improvement in all patient-reported outcomes (Health Assessment Questionnaire Disability Index (HAQ-DI), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and Short Form Health Survey (SF-36) questionnaires, (Tables 25 and 26). Significant reductions in disability index (HAQ-DI), fatigue (FACIT-F), and improvement in both the physical and mental health domains of the SF-36 were observed in patients treated with RITUXAN compared to patients treated with methotrexate alone.

Table 25 Short Form Health Survey (SF-36): Mean and Categorical Change from Baseline to Week 24

	Study 1		Study 2	
	Placebo+MTX N=197	**RITUXAN+MTX N=294**	**Placebo+MTX N=141**	**RITUXAN+MTX N=178**
Mental Health				
Mean change (SD)	1.3 (9.4)	4.7 (11.8)	1.8 (8.0)	3.2 (11.2)
p-value*	0.0002			
Improved	40 (20%)	111 (38%)	29 (21%)	60 (34%)
Unchanged	128 (65%)	144 (49%)	99 (70%)	90 (51%)
Worsened	29 (15%)	39 (13%)	13 (9%)	28 (16%)
p-value*	0.0015			
Physical Health				
Mean change (SD)	0.9 (5.7)	5.8 (8.5)	1.96 (6.3)	6.1 (8.2)
p-value*	<0.0001			
Improved	25 (13%)	141 (48%)	37 (26%)	88 (49%)
Unchanged	158 (80%)	136 (46%)	92 (65%)	81 (46%)
Worsened	14 (7%)	17 (6%)	12 (9%)	9 (5%)
p-value*	<0.0001			

*No test was performed on study 2 data
Mental Health Change Category: Change > 6.33 = improved, -6.33<= Change < 6.33 = unchanged, Change < -6.33 = worsened Physical Health Change Category: Change > 5.42 = improved, -5.42<= Change < 5.42 = unchanged, Change < -5.42 = worsened

Table 26 HAQ and FACIT –F Responses at Week 24 in Study 1

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

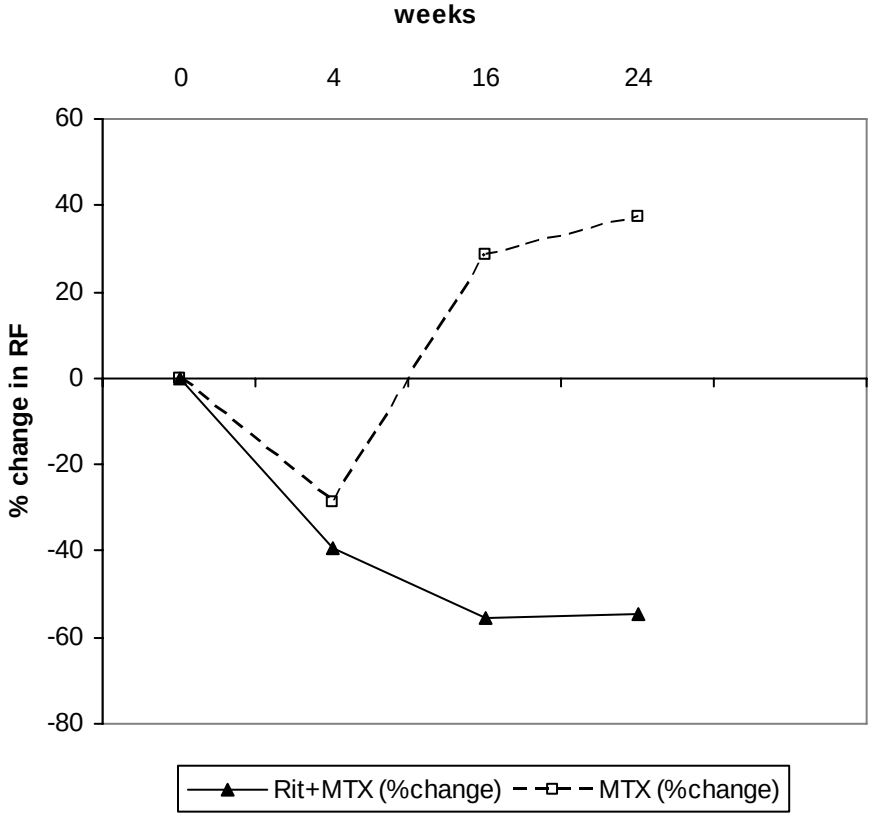
[1] MTX, [2] Health assessment questionnaire (HAQ), [3] Functional assessment of chronic illness therapy (FACIT-F)

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

Laboratory Evaluations

In rheumatoid factor (RF) positive patients, marked decreases were observed in rheumatoid factor concentrations following treatment with RITUXAN in all three studies (range 45-64%, Figure 1).

Figure 1 Percentage Change in Total RF Concentration Over Time in Study 1 (ITT Population, RF-Positive Patients)



Plasma total immunoglobulin concentrations, total lymphocytes counts, and white cells generally remained within normal limits following treatment with RITUXAN, with the exception of a transient drop in white cells counts over the first four weeks following therapy. Titers of IgG antigen specific antibody to mumps, rubella, varicella, tetanus toxoid, influenza and streptococcus pneumococci remained stable over 24 weeks following exposure to RITUXAN in rheumatoid arthritis patients.

Effects of RITUXAN on a variety of biomarkers were evaluated in patients enrolled into Study 3. This substudy evaluated the impact of a single treatment course of RITUXAN on levels of biochemical markers, including markers of inflammation [Interleukin 6, C Reactive protein, Serum amyloid type A protein, Protein S100 isotypes A8 and A9], autoantibody (RF and anti-cyclic citrullinated peptide immunoglobulin) production and bone turnover [osteocalcin and procollagen 1 N terminal peptide (P1NP). Rituximab treatment, whether as monotherapy or in combination with methotrexate or cyclophosphamide reduced the levels of inflammatory markers significantly, relative to methotrexate alone, over the first 24 weeks of follow-up. Levels of markers of bone turnover, osteocalcin and P1NP, increased significantly in the rituximab groups compared to methotrexate alone**.**

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

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 timepoints 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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PART III: CONSUMER INFORMATION

[Pr]RITUXAN®
Rituximab
***Pronounced*: rih TUCKS en**

Non-Hodgkin's Lymphoma& Chronic Lymphocytic Leukemia

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

ABOUT THIS MEDICATION

What the medication is used for:
RITUXAN (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 is a cancer medicine that must be prescribed by a doctor.

It is used to treat patients with certain types of non-Hodgkin's lymphoma and chronic lymphocytic leukemia.

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

Who should take RITUXAN?
RITUXAN is given alone for 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 may also be 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 may also be used as a continuous (maintenance) treatment for patients who have responded to initial therapy.

RITUXAN may also be 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 or if you have ever had a rare infection of the brain called progressive multifocal leukoencephalopathy (PML) you should not take RITUXAN.

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

- You ever had a bad reaction to rituximab or any of the non-medicinal ingredients.
- You are allergic to other medications, food or dyes.
- 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 therapy.
- You have a pre-existing lung disease as you may have a greater chance of breathing difficulties during your RITUXAN treatment infusion.
- You have a history of 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 and what extra care may need to be

taken while you are on the medication.

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

What the nonmedicinal ingredients are:
Hydrochloric acid, polysorbate 80, sodium chloride, sodium citrate, sodium hydroxide and water for injection.

What dosage forms it comes in:
Liquid concentrate for intravenous (IV) administration.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

-Some side effects associated with RITUXAN are severe and may be fatal. 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.
-A rare brain infection called JC virus causing progressive multifocal leukoencephalopathy (PML) and death has been reported in patients with non-Hodgkin Lymphoma (NHL) and ChronicLymphocytic Leukemia (CLL). It is hard to predict who will get PML, but it is more common in people with weakened immune systems.

RITUXAN has not been studied in pregnant or breast-feeding women. If you are pregnant, could become pregnant or are or 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.

RITUXAN is an infusion ("drip") which is given intravenously (into your veins). Very commonly patients being given RITUXAN have some side effects while the infusion is being given. Most patients are also given medication such as acetaminophen [TYLENOL®], antihistamines, and steroids for allergic reactions [such as prednisone] before the infusion to prevent these reactions. If you notice any trouble breathing, feel hot or shivery, have hives or an itchy rash, tell the person giving you the infusion immediately.

These side effects are more common with the first infusions of RITUXAN. If you develop any of these symptoms, the infusion will be slowed down or stopped for a while. Once these symptoms go away, or improve, the infusion can be continued.

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

A few patients with a history of hepatitis B and 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 hepatitis or tuberculosis; you will be carefully checked for signs of active hepatitis B or tuberculosis infection. Some vaccines should not be given with RITUXAN. Your doctor will check if you should have any vaccines before 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.

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

Usual Dose
The usual dose of RITUXAN is based on your body surface area which your doctor will calculate for you.

RITUXAN is not taken by mouth, but given with fluids through an intravenous line. An intravenous line, or I.V., is a thin, plastic tube placed in a vein in your hand or arm. When RITUXAN is given intravenously, it is called an infusion.

A healthcare professional in a healthcare facility will give you RITUXAN as prescribed by your doctor.

Your first RITUXAN infusion may take most of the day. Usually the remaining infusions will take less time.

Missed Dose

If you miss a dose of RITUXAN, 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 as you will be closely monitored by Healthcare Professionals during your infusion. However, if you suspect you received too much RITXUXAN contact your physician and poison control centre immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

The most common possible unwanted effects are infusion related events, and happen to more than 30% of patients treated with RITUXAN:

- Fever and chills
- Nausea, vomiting, fatigue (feeling tired or weak), headache, skin rash, redness of the skin, itchiness, wheezing or tightness in the chest, shortness of breath, difficulty breathing, sensation of the tongue or throat swelling, throat irritation, rhinitis (runny nose), temporary low blood pressure, flushing, dizziness on standing up, fast heart beat, chest pain, pain where the non-Hodgkin's lymphoma is located.

If these unwanted effects occur, it is most common within 30 minutes to 2 hours after starting the first infusion, but may also occur after the infusion has finished. The symptoms are usually mild to moderate, which can be easily treated. Rarely, these reactions can be severe. These unwanted effects are less common after the first treatment.

These unwanted effects can be prevented or managed by:

- Slowing or interrupting your infusion of RITUXAN. The treatment can be restarted once the symptoms have resolved.
- Giving a fever reducer, such as TYLENOL®, an antihistamine, such as BENADRYL®, and a steroid such as Prednisone which can be given for allergic reactions, before each infusion of RITUXAN. Sometimes additional medications are needed to be given to treat these unwanted effects.

Additionally:

- Your doctor may instruct you not to take your blood pressure medication 12 hours before and delay taking until after your infusion of RITUXAN is complete. Please ask your doctor for specific instructions.
- Because some of the medications given with RITUXAN may cause some dizziness or sleepiness, you should arrange for someone else to drive you home after each treatment.

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

- Chest pain, fast or irregular or uneven heart beat.
- Decreased of the 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 yellowing of the skin or eyes (jaundice), feeling of sickness, tiredness, loss of appetite, joint pain and abdominal pain.
- 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 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 or 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 doctor or pharmacist**
		Only if severe	**In all cases**	
Common (≥ 1% - <10%)	New fever or if your temperature becomes higher that 38ºC		✓	
	Shortness of breath, difficulty breathing, wheezing, coughing		✓	

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**	
	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		✓	
Uncommon (≥0.1% - <1%)	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		✓	
	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.		✓	✓

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**	
	Symptoms of shingles such as itching, tingling, or sever burning pain with red patches that develop into blisters and are grouped in a cluster usually on the trunk of the body.		✓	
	Symptoms of Hepatitis B such as yellowing of the skin or eyes (jaundice), feeling of sickness, tiredness, loss of appetite, joint pain and abdominal pain.		✓	

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

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

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

Online:	www.healthcanada.gc.ca/medeffect
Toll free phone:	1-866-234-2345
Toll free fax:	1-866-678-6789
Postage Paid Mail:	Canada Vigilance Program Health Canada AL 0701C Ottawa, Ontario K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider. 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.

This leaflet was prepared by Hoffmann-La Roche Limited.

Last revised:

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PART III: CONSUMER INFORMATION

[Pr]RITUXAN®
rituximab

Rheumatoid Arthritis

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

ABOUT THIS MEDICATION

What the medication is used for:
RITUXAN (also known as rituximab) is an injectable medicine that is used to reduce signs and symptoms of rheumatoid arthritis (in combination with methotrexate).

What is rheumatoid arthritis?
Rheumatoid Arthritis (RA) is an inflammatory disease of the joints. Characteristics of RA include redness, swelling, pain, and limited movement around joints of the hands, feet, elbows, knees and neck. It is considered an autoimmune disease, a disease which produces antibodies against its own immune system or against its own body proteins.

What RITUXAN does:
B cells are an important element in the immune system, helping the body to fight off infection. However in diseases such as RA, the immune system acts abnormally leading to an attack on normal healthy tissue such as the joints.

RITUXAN is a monoclonal antibody. Antibodies are proteins which are produced to bind to another protein called an antigen. RITUXAN binds to an antigen on the surface of a type of white blood cell, the B lymphocyte. When RITUXAN binds to the surface of this cell, it causes the cell to die.

Who should take RITUXAN?
RITUXAN is used to reduce signs and symptoms of rheumatoid arthritis in people who have tried other medicines already, but the other medicine has either stopped working or has not worked well enough. RITUXAN is taken together with another medicine called methotrexate.

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

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

- You ever had a bad reaction to rituximab or any of the non-medicinal ingredients.
- You are allergic to other medications, food or dyes.
- You have a history of heart disease, heart attack or stroke.
- You are taking any other medicines (including those not prescribed by the doctor). If you are taking or took another biologic medicine called a TNF inhibitor or a DMARD (disease modifying anti-rheumatic drug). 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 therapy.
- You have a pre-existing lung disease as you may have a greater chance of breathing difficulties during your RITUXAN treatment infusion.
- You have a history of hepatitis B infection.
- You have a history of chronic or recurrent infection.
- You are pregnant or plan on becoming pregnant or are breast-feeding a child.

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

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

What the nonmedicinal ingredients are:
Hydrochloric acid, polysorbate 80, sodium chloride, sodium citrate, sodium hydroxide and water for injection.

What dosage forms it comes in:
Injection.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Several side effects are associated with RITUXAN, some may be severe and life-threatening. This drug should only be used by health professionals experienced in treating rheumatoid arthritis in a setting where medication and supportive care measures are immediately available in the event of an allergic reaction during administration (see DOSAGE AND ADMINISTRATION).

A rare brain infection called JC virus causing progressive multifocal leukoencephalopathy (PML) and death has been reported in patients with autoimmune diseases treated with Rituxan. It is hard to predict who will get PML, but it is more common in people with weakened immune systems

RITUXAN has not been studied in pregnant or breast-feeding women. If you are pregnant or breast-feeding, be sure to discuss with your doctor whether RITUXAN is right for you. Women in whom there is a possibility of conceiving a child should avoid becoming pregnant and use effective contraceptive methods during and up to 12 months after treatment with RITUXAN.

RITUXAN is an infusion ("drip") which is given into your veins. Some patients being given RITUXAN have some side effects while the infusion is being given. If you notice any difficulty breathing, feel hot or shivery, have hives or an itchy rash, tell the person giving you the infusion immediately.
These effects mainly occur with the first infusion of RITUXAN. If you develop any of these symptoms, the infusion will be slowed down or stopped for a while. Some patients will need to take an antihistamine or acetaminophen. When these symptoms go away, or improve, the infusion can be continued.

If you have ever had heart disease (i.e. angina, palpitations, or heart failure) or a history of breathing problems, your doctor will take special care of you during therapy with RITUXAN.

The cells that are killed by RITUXAN help to fight infection. RITUXAN should not be given to people who have an active infection. Tell your doctor if you think you may have an infection, even a mild one like a cold, before he gives you the medicine. Also please tell your doctor if you have a lot of infections or suffer from severe infections.

You might get infections more easily following RITUXAN therapy. It is very important to tell your doctor if you get any symptoms of an infection, for example fever, cough, sore throat, burning pain when passing urine, or you start to feel weak or generally unwell.

In a few 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; patients with a history of hepatitis B infection will be carefully checked by their physician for signs of active hepatitis B. Some vaccines should not be given with RITUXAN. Your doctor will check if you should have any vaccines before you receive RITUXAN.

Cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported following use of RITUXAN for the treatment of autoimmune diseases. PML is a condition that causes nerve damage within the brain. Tell your doctor immediately if you have memory loss, trouble thinking, 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.

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

Before the infusion is given you will be given medicines to prevent or reduce possible reactions to RITUXAN.

RITUXAN is not taken by mouth, but given through an intravenous line. An intravenous line, or I.V., is a thin, plastic tube placed in a vein in your hand or arm. When RITUXAN is given intravenously, it is called an infusion.

Each course of treatment is made up of two separate infusions which are given at least 2 weeks apart. Repeated courses of treatment with RITUXAN are possible. Depending on the signs and symptoms of your disease, your doctor will decide when you should receive more RITUXAN.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

The most common possible unwanted effects are infusion related events:

- Fever and chills
- Nausea, vomiting, fatigue (feeling tired or weak), headache, skin rash, redness of the skin, itchiness, wheezing or tightness in the chest, shortness of breath, difficulty breathing, sensation of the tongue or throat swelling, throat irritation, rhinitis (runny nose), temporary low blood pressure, flushing, dizziness on standing up, fast heart beat.

If these unwanted effects occur, it is most common within 30 minutes to 2 hours after starting the first infusion, but may also occur after the infusion has finished. The symptoms are usually mild to moderate, and can be easily treated. Rarely, these reactions can be severe. These unwanted effects are less common after the first treatment.

These unwanted effects can be prevented or managed by:

- Slowing or interrupting your infusion of RITUXAN. The treatment can be restarted once the symptoms have resolved.
- Giving a fever reducer, such as TYLENOL®, and an antihistamine, such as BENADRYL® before each infusion of RITUXAN. Sometimes additional medications are needed to be given to treat these unwanted effects.

Additionally:

- Your doctor may instruct you not to take your blood pressure medication 12 hours before and delay taking until after your infusion of RITUXAN is complete. Please ask your doctor for specific instructions.
- Because some of the medications given with RITUXAN may cause some dizziness or sleepiness, you should arrange for someone else to drive you home after each treatment.

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

Some patients get infections after treatment. Often these are colds, but could be pneumonia or urinary infections. Some other effects might occur, but are less likely, including: pain in the tummy, back, chest, muscles and/or joints, at the infusion site, feeling unwell, changes in blood pressure, changes in heart rate, diarrhea, indigestion, cramp, dizziness, tingling or numbness, anxiety or nervousness, cough, watery or itchy eyes, runny or itchy nose, sweating, sinusitis.

Some patients also have some changes to blood tests including a fall in the number of red cells, white cells or both. Severe but rare reactions, in particular severe breathing difficulties and severe skin reactions including blistering, could be fatal. This is why your doctor will watch you closely, and why it is important for you to tell your doctor immediately if you experience any difficulty in breathing and any skin reactions.

Some patients also have increasing weakness on one side of the body, clumsiness or falls, trouble with thinking or memory, changes in mood, change in vision. You should report these to your doctor immediately.

If you are receiving RITUXAN in combination with other medicines, some of the side effects you may experience may be due to the other medicine.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM		
Symptom / effect		**Call your doctor or pharmacist immediately**
Common	New fever or if your temperature becomes higher that 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	✓
Uncommon	Changes in blood pressure, changes in heart rate	✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM		
Symptom / effect		**Call your doctor or pharmacist immediately**
	Redness or blistering of the skin	✓
	Symptoms of Hepatitis B such as yellowing of the skin or eyes (jaundice), feeling of sickness, tiredness, loss of appetite, joint pain and abdominal pain.	✓
	Increasing weakness on one side of the body, clumsiness or falls, trouble with thinking or memory, changes in mood, change in vision	✓

If you are concerned about these or any other unexpected effects while on treatment with RITUXAN, talk with your doctor, nurse or pharmacist.

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

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance by:

By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. 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**.**

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Last revised:

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