Rituximab (Rituxan)  

**Manufacturer:** Genentech, Inc., South San Francisco, CA  

**Indication:** On March 6, 2006, the U.S. Food and Drug Administration (FDA) approved, following Priority Review, the therapeutic antibody rituximab (Rituxan) in combination with methotrexate to reduce signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies.

In 1997, the FDA approved rituximab, the first monoclonal antibody, for the treatment of non-Hodgkin’s lymphoma (NHL), which is characterized by an overgrowth of B cells involved in about 85% of NHL malignancies. By binding the CD20 protein on the B cell, the antibody targets it for removal from the circulation.

Over the past nine years, rituximab has revolutionized the way oncologists have successfully treated NHL. Rituximab is therapeutic either alone or in combination with other chemotherapeutic drugs. Specifically, very good results have been observed when used in combination with the CHOP (cyclophosphamide, hydroxydaunorubicin, Oncovin [Vincristine], prednisone) chemotherapy regimen.

The Prescribing Information for rituximab in the treatment of RA reflects the majority of the findings with rituximab in treating patients with NHL. Because rituximab has been prescribed for nine years, the predominance of the warnings described in the Prescribing Information reflects the clinical experience and adverse effects found with the agent used in the treatment of NHL.

**Drug Class:** The genetically engineered chimeric murine/human monoclonal antibody is directed against the CD20 antigen, found on the surface of normal and malignant B lymphocytes. Rituximab may affect multiple pathways by which B cells are believed to contribute to the initiation and development of RA. The antibody is an IgG1 kappa immunoglobulin containing murine light-chain 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 complementary DNA analysis). The approximate molecular weight is 145 kilodaltons.

**Uniqueness of Product:** Rituximab reduces signs and symptoms of RA by targeting certain B cells that are also part of the inflammatory process in RA.

**Boxed Warnings:**

**Fatal Infusion Reactions:** Deaths within 24 hours of rituximab infusion have been reported. These fatal reactions followed an infusion reaction complex, which included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred in association with the first infusion (see Warnings).

Patients who develop severe infusion reactions should have the rituximab infusion discontinued and should receive medical treatment.

**Tumor Lysis Syndrome:** Acute renal failure requiring dialysis with instances of fatal outcomes has been reported in the setting of tumor lysis syndrome (TLS) following treatment of NHL patients with rituximab (see Warnings).

**Severe Mucocutaneous Reactions:** Severe mucocutaneous reactions, some with fatal outcome, have been reported in association with rituximab treatment (see Warnings).

**Warnings:**

**Severe Infusion Reactions:** Rituximab has caused severe infusion reactions. In some cases, these reactions were fatal. These severe reactions typically occurred during the first infusion with a time to onset of 30 to 120 minutes. Signs and symptoms of severe infusion reactions may include urticaria, hypotension, angioedema, hypoxia, or bronchospasm and may require interruption of rituximab administration. The most severe manifestations and sequelae include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and anaphylactic and anaphylactoid events. In the reported cases, the following factors were more frequently associated with fatal outcomes: female gender, pulmonary infiltrates, and chronic lymphocytic leukemia or mantle-cell lymphoma.

Management of severe infusion reactions: The rituximab infusion should be interrupted for severe reactions. Medications and supportive care measures, including, but not limited to, epinephrine, antihistamines, glucocorticoids, intravenous (IV) fluids, vasopressors, oxygen, bronchodilators, and acetaminophen, should be available and instituted as medically indicated for use in the event of a reaction during administration. In most cases, the infusion can be resumed at 50% reduction rate (e.g., from 100 mg/hour to 50 mg/hour) when symptoms have completely resolved. Patients requiring close monitoring during first and subsequent infusions include those with pre-existing cardiac and pulmonary conditions, those with prior clinically significant cardiopulmonary adverse events, and those with high numbers of circulating malignant cells (≥25,000/mm³) with or without evidence of high tumor burden.

**Tumor Lysis Syndrome:** Rapid reduction in tumor volume, followed by acute renal failure, hyperkalemia, hypercalcemia, hyperuricemia, or hyperphosphatasemia, has been reported within 12 to 24 hours after the first rituximab infusion. Rare instances of fatal outcome have been reported in the setting of TLS following treatment with rituximab in patients with NHL.
The risks of TLS appear to be greater in patients with high numbers of circulating malignant cells (≥25,000/mm³) or a high tumor burden. Prophylaxis for TLS should be considered for patients at high risk. Correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care, including dialysis, should be initiated as indicated. Following complete resolution of the complications of TLS, rituximab has been tolerated when re-administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

**Hepatitis B Reactivation with Related Fulminant Hepatitis and Other Viral Infections.** Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death have been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately four months after the initiation of rituximab and approximately one month after the last dose.

Patients at high risk of HBV infection should be screened before rituximab therapy begins. Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and up to several months after rituximab therapy. In patients who develop viral hepatitis, rituximab and any concomitant chemotherapy should be discontinued, and appropriate treatment, including antiviral therapy, should be initiated. There are insufficient data regarding the safety of resuming rituximab in patients who develop hepatitis subsequent to HBV reactivation.

The following additional serious viral infections, whether new, reactivated, or exacerbated, have been identified in clinical studies or postmarketing reports. The majority of patients received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. These viral infections included JC virus (progressive multifocal leukencephalopathy [PML]), cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C virus. In some cases, the viral infections occurred up to one year following discontinuation of rituximab and have resulted in death.

**Hypersensitivity Reactions.** Rituximab has been associated with hypersensitivity (non–IgE-mediated) reactions, which may respond to adjustments in the infusion rate and in medical management. Hypotension, bronchospasm, and angioedema have occurred in association with rituximab infusion. Infusions should be interrupted for severe hypersensitivity reactions and can be resumed at a 50% reduction in rate (e.g., from 100 mg/hour to 50 mg/hour) when symptoms have completely resolved.

Treatment of symptoms with diphenhydramine and acetaminophen is recommended; additional treatment with bronchodilators or IV saline may be indicated. In most cases, patients who have experienced non–life-threatening hypersensitivity reactions have been able to complete the full course of therapy. 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.

**Cardiovascular.** Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of rituximab. Patients with pre-existing conditions, including arrhythmias or angina, have had recurrences of these events during rituximab therapy and should be monitored throughout the infusion and the immediate post-infusion period.

**Renal.** Rituximab administration has been associated with severe renal toxicity, including acute renal failure requiring dialysis, and in some cases has led to a fatal outcome in hematologic malignancy patients. Renal toxicity has occurred in patients with high numbers of malignant cells (>25,000/mm³) or a high tumor burden who experience TLS; and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and rituximab is not an approved treatment regimen. If this combination is used in clinical trials, extreme caution should be exercised; patients should be monitored closely for signs of renal failure. Discontinuation of rituximab should be considered for those with rising serum creatinine or oliguria.

**Severe Mucocutaneous Reactions.** Mucocutaneous reactions, some with fatal outcome, have been reported in patients treated with rituximab. These reports include paraneoplastic pemphigus (an uncommon disorder that is a manifestation of the patient’s underlying malignancy), Stevens–Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of the reaction in the reported cases has varied from one to 13 weeks following rituximab exposure.

Patients experiencing a severe mucocutaneous reaction should not receive any further infusions and seek prompt medical evaluation. Skin biopsy may help to distinguish among different mucocutaneous reactions and guide subsequent treatment. The safety of re-administration of rituximab to patients with any of these mucocutaneous reactions has not been determined.

**Concomitant Use with Biologic Agents and DMARDs Other Than Methotrexate in Rheumatoid Arthritis.** Limited data are available on the safety of the use of biologic agents and disease-modifying anti-rheumatic drugs (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.

**Bowel Obstruction and Perforation.** Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, were observed in patients receiving rituximab with chemotherapy for diffuse large B-cell lymphoma (DLBCL). In postmarketing reports, which include both patients with low-grade or follicular NHL and DLBCL, the mean time to onset of symptoms was six days (range, from one to 77 days) in patients with documented gastrointestinal perforation. Complaints of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.

**Dosage and Administration.** For patients with RA, ritux-
rituximab is given as two 1,000-mg IV infusions separated by two weeks. Glucocorticoids, administered as methylprednisolone 100 mg IV or its equivalent 30 minutes before each infusion, are recommended to reduce the incidence and severity of infusion reactions. The safety and efficacy of re-treatment have not been established in controlled trials. Rituximab is given in combination with methotrexate.

The safety and efficacy of re-treatment in patients with RA 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 a non-controlled setting. In clinical trials, most patients with RA who received additional courses did so 24 weeks after the previous course. No patients were re-treated earlier than 16 weeks after the previous course.

Clinical Trials: The efficacy and safety of rituximab were evaluated in 517 patients with active disease who were receiving methotrexate and who had not responded adequately to at least one TNF inhibitor. Patients were 18 years of age or older, with a diagnosis of RA, as defined by American College of Rheumatology (ACR) criteria, and had at least eight swollen and eight tender joints.

Patients received two doses of either rituximab 1,000 mg or placebo as an IV infusion on days one and 15, in combination with continued methotrexate 10 to 25 mg weekly. Efficacy was assessed at 24 weeks. IV glucocorticoids were given as pre-medication before each rituximab infusion and orally on a tapering schedule from baseline through day 16.

Rituximab treatment resulted in statistically and clinically significant improvement in signs and symptoms of RA, including pain and disability, at 24 weeks as follows:

- 51% of patients achieved an ACR 20 response, the primary endpoint of the study, in contrast to 18% of placebo patients.
- 27% of patients attained an ACR 50 response in contrast to 5% of placebo patients.
- 12% of patients achieved an ACR 70 response, in contrast to 1% of placebo patients.

Improvement was also noted for all components of ACR responses after rituximab therapy (e.g., tender and swollen joint counts, pain, and disability index).

Commentary: A systemic, debilitating autoimmune disease, RA occurs when the immune system attacks joint tissue, causing painful inflammation and irreversible destruction of cartilage, tendons, and bones. RA often results in chronic pain, loss of function, and disability, and it can lead to cardiovascular and pulmonary complications.

Although the efficacy of rituximab was supported by two well-controlled trials in RA patients who had inadequate responses to nonbiologic DMARDs, but who had not failed TNF antagonist therapy, a favorable risk–benefit relationship has not been established in this population.

Rituximab, in combination with CHOP chemotherapy, is now the standard of care for NHL, and its novel mechanism of action should also be considered in RA treatment.

In combination with methotrexate, rituximab represents a new addition to the RA treatment armamentarium for patients who have an inadequate response to previous anti-TNF agents. It also represents a completely new targeted approach—the targeting of B cells in RA—which highlights the importance of reassessing the role of B cells in the pathophysiology of this disease.


### Alglucosidase alfa (Myozyme)

**Manufacturer:** Genzyme Corporation, Cambridge, MA

**Indication:** Alglucosidase alfa is a biologic agent indicated for patients with Pompe disease. This inherited disease is caused by a deficiency of the human enzyme acid alpha-glucosidase, which is essential for normal muscle development and function. The disease usually results in death from respiratory failure and is rapidly fatal in newborns. Alglucosidase alfa improved ventilator-free survival in patients with infantile-onset Pompe disease, compared with an untreated historical control, although its use in other forms of Pompe disease has not been adequately studied to ensure safety and efficacy.

**Drug Class:** Alglucosidase alfa, a glycoprotein, consists of the human enzyme acid alpha-glucosidase (GAA), encoded by the most predominant of nine observed haplotypes of this gene. This agent is produced by recombinant DNA technology in a Chinese hamster ovary cell line. It degrades glycogen by catalyzing the hydrolysis of alpha-1,4- and alpha-1,6-glycosidic linkages of lysosomal glycogen.

**Uniqueness of Drug:** This is the first product approved for Pompe disease and one of the first for an inherited muscle disorder.

**Boxed Warning:** The risk of hypersensitivity and life-threatening anaphylactic reactions, including anaphylactic shock, has been observed in patients during infusions of alglucosidase alfa. Because of the potential for severe infusion reactions, appropriate medical support measures should be available during the agent’s administration.

**Warnings:**

**Hypersensitivity Reactions.** In clinical trials and expanded access programs with alglucosidase alfa, 38 of 280 patients (14%) treated with this agent experienced infusion reactions involving at least two of three body systems:

- **Cardiovascular:** hypotension, cyanosis, hypertension, tachycardia, ventricular extra systoles, bradycardia, palpitations, flushing, nodal rhythm, peripheral coldness
- **Respiratory:** tachypnea, wheezing and bronchospasm, rales, throat tightness, hypoxia, dyspnea, cough, respiratory tract irritation, decreased oxygen saturation
- **Cutaneous:** angioneurotic edema, urticaria, rash, erythema, periorbital edema, pruritus, hyperhidrosis, cold sweats, livedo reticularis

Of the 38 patients, eight experienced severe or significant hypersensitivity reactions. If severe hypersensitivity or anaphylactic reactions occur, stopping alglucosidase alfa therapy should be considered, and appropriate medical treatment should be initiated. Because of the potential for severe infusion reactions, appropriate medical support measures should be available when alglucosidase alfa is administered.
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**Risk of Cardiac Arrhythmias and Sudden Cardiac Death.** Ventricular fibrillation, ventricular tachycardia, and brady-cardia have resulted in cardiac arrest or death in patients with Pompe disease. The risk of sudden death is higher for patients with cardiac hypertrophy and when the general anesthesia was used to place a central venous catheter intended for an infusion. Caution is warranted when general anesthesia is used.

**Risk of Acute Cardiorespiratory Failure.** Acute cardiorespiratory failure requiring intubation and inotropic support was observed after infusion with alglucosidase alfa in one patient with infantile-onset Pompe disease. The patient had underlying cardiac hypertrophy, possibly associated with fluid overload with IV administration of alglucosidase alfa. Clinicians should consult the instructions on reconstitution, dilution, and appropriate infusion volumes.

**Infusion Reactions.** In clinical studies, 20 of 39 treated patients (51%) experienced reactions during the infusion or during the two hours following the infusion. Most of these reactions were mild to moderate.

**Dosage and Administration:** The recommended dosage is 20 mg/kg administered every two weeks as an IV infusion. The total volume of the infusion is determined by the patient’s body weight. The infusion should be administered over four hours in a stepwise manner via an infusion pump, and the initial infusion rate should be no more than 1 mg/kg per hour. The rate may be increased by 2 mg/kg per hour every 30 minutes, after the patient’s tolerance to the infusion rate is established, until a maximum rate of 7 mg/kg per hour is reached. Vital signs should be obtained at the end of each step. If the patient is hemodynamically stable, alglucosidase alfa may be administered at the maximum rate of 7 mg/kg per hour until the infusion is completed. The infusion rate may be slowed or temporarily stopped if an infusion reaction occurs.

**Commentary:** The FDA’s approval of alglucosidase alfa is very important for the health and well-being of patients with Pompe disease, even though the disease affects only one in 40,000 to 300,000 people in the U.S. For this reason, alglucosidase alfa was granted orphan drug status. The introduction of this product should increase survival of patients with Pompe disease, and it is therefore considered a veritable lifesaver.

**Source:** www.genzyme.com/components/highlights/mz_pi.pdf

**Docetaxel (Taxotere) Injection Concentrate**

**Manufacturer:** Sanofi-Aventis, Paris, France

**Indication:** Docetaxel injection concentrate, in combination with cisplatin and fluorouracil, is used to treat patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease. Docetaxel is now approved for six indications in the U.S. and for eight in Europe.

**Drug Class:** This antineoplastic agent belongs to the taxoid family. It is prepared by semisynthesis, beginning with a precursor extracted from the renewable needle biomass of yew plants. Its chemical name is (2R,3S)-N-carboxy-3-phenylisoserine,N-tet-butyl ester, 13-ester with 5p-20-epoxy-1,2,4,7p,10p,13-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate.

**Uniqueness of Drug:** This is the first drug to be approved for advanced stomach cancer that has shown a survival advantage in more than a decade.

**Boxed Warning:** The concentrate should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are available.

**Hepatic Abnormalities.** The incidence of treatment-related mortality associated with docetaxel therapy is increased in patients with abnormal liver function, in patients receiving higher doses, and in patients with non–small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who received docetaxel as a single agent at a dose of 100 mg/m².

Docetaxel should not generally be given to patients with bilirubin levels above the upper limit of normal (ULN) or to patients with alanine and aspartate transaminases (ALT and AST) above 1.5 times the ULN along with an alkaline phosphatase level above 2.5 times the ULN. Patients with these elevated concentrations are at increased risk for grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and death from toxicity.

**Hematologic Reactions.** Docetaxel should not be given to patients with neutrophil counts below 1,500 cells/mm³. To monitor the occurrence of neutropenia, which may result in infection, frequent blood cell counts should be determined for all patients receiving docetaxel.

**Hypersensitivity Reactions.** Severe hypersensitivity reactions, characterized by hypotension, bronchospasm, rash, or erythema, occurred in two of 92 (2.2%) of patients who received the recommended three-day oral corticosteroid (e.g., dexamethasone) premedication regimen. Five patients who did not receive premedication had to discontinue the infusions because of hypersensitivity reactions. The reactions resolved after the infusion was stopped and the appropriate therapy was given. Docetaxel should not be used in patients with a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80.

**Fluid Retention.** Severe fluid retention occurred in six of 92 (6.5%) of patients despite three days of dexamethasone premedication. Patients experienced one or more of these events: peripheral edema, generalized edema, pleural effusion requiring urgent drainage, dyspnea at rest, cardiac tamponade, or pronounced abdominal distention caused by ascites.

**Dosage and Administration:** For gastric adenocarcinoma, the recommended dose of docetaxel is 75 mg/m² as a one-hour IV infusion, followed by cisplatin 75 mg/m², as a one-to-three-hour IV infusion (both on the first day only), followed by fluorouracil 750 mg/m² per day, given as a 24-hour continuous IV infusion for five days, starting at the end of the cisplatin infusion. Treatment is repeated every three weeks. Patients must receive premedication with antimietics and appropriate continued on page 341
hydration for cisplatin administration.

All patients should receive premedication with an oral corticosteroid, such as dexamethasone 16 mg/day (e.g., 8 mg twice daily), for three days starting one day before docetaxel administration to reduce the incidence and severity of fluid retention and hypersensitivity reactions.

**Clinical Trials:** The FDA based its approval on results involving 445 patients from the Tax 325 study, the largest international phase 3 trial in previously untreated advanced stomach cancer. Patients receiving docetaxel-based chemotherapy—Taxotere plus cisplatin plus 5-fluorouracil (TCF)—experienced a significant 23% reduction in the risk of death compared with patients receiving a current standard treatment of cisplatin plus 5-fluorouracil (CF). The median follow-up period was 23 months.

The median overall survival was significantly longer with the docetaxel regimen (9.2 vs. 8.6 months, \( P < .02 \)) with a hazard ratio of 1.29 (95% confidence interval [CI], 1.04–1.61). The time to disease progression was nearly two months longer for the docetaxel-containing arm (5.6 vs. 3.7 months, \( P = .0004 \)) with a hazard ratio of 1.47 (CF/TCF 95% CI, 1.19–1.83).

In total, 81.4% of the patients using the docetaxel regimen experienced at least one grade 3 and 4 (severe) adverse effect (especially neutropenia) in contrast to 75.4% in the control arm. Other common drug-related adverse effects were anemia, diarrhea, and nausea.

**Commentary:** The prognosis for patients with locally advanced or metastatic stomach cancer is poor; the long-term survival rate (two years) is only 11.5%. For many years, patients with gastric cancer had limited options. With this approval, a new standard of treatment is available for this difficult-to-treat disease.

**Sources:** [http://products.sanofi-aventis.us/Taxotere/taxotere.html#Description](http://products.sanofi-aventis.us/Taxotere/taxotere.html#Description)