RITUXAN® AND RITUXAN HYCELA®
DOSING AND ADMINISTRATION BROCHURE

Please see pages 12-15 and accompanying full Prescribing Information, including BOXED WARNINGS and Medication Guide, for RITUXAN Important Safety Information.

Please see pages 24-27 and accompanying full Prescribing Information, including BOXED WARNINGS and Medication Guide, for RITUXAN HYCELA Important Safety Information.
RITUXAN INDICATIONS

RITUXAN® (rituximab) is indicated for the treatment of adult patients with:
- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with first-line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy
- Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL, as a single agent, after first-line CVP chemotherapy
- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens
- Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC)

RITUXAN HYCELA INDICATIONS

RITUXAN HYCELA® (rituximab/hyaluronidase human) is indicated for the treatment of adult patients with:
- Relapsed or refractory, follicular lymphoma (FL) as a single agent
- Previously untreated follicular lymphoma in combination with first-line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy
- Non-progressing (including stable disease) follicular lymphoma as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy
- Previously untreated diffuse large B-cell lymphoma (DLBCL) in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens
- Previously untreated and previously treated chronic lymphocytic leukemia (CLL) in combination with fludarabine and cyclophosphamide (FC)

SELECT IMPORTANT SAFETY INFORMATION FOR RITUXAN

BOXED WARNINGS
WARNING: FATAL INFUSION-RELATED REACTIONS, SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
- Infusion-related Reactions: RITUXAN administration can result in serious, including fatal infusion-related reactions. Deaths within 24 hours of RITUXAN infusion have occurred. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. Monitor patients closely. Discontinue RITUXAN infusion for severe reactions and provide medical treatment for Grade 3 or 4 infusion-related reactions
- Severe Mucocutaneous Reactions: Severe, including fatal, mucocutaneous reactions can occur in patients receiving RITUXAN
- Hepatitis B Virus (HBV) Reactivation: HBV reactivation can occur in patients receiving rituximab-containing products, including RITUXAN HYCELA
- Progressive Multifocal Leukoencephalopathy (PML), including fatal PML, can occur in patients receiving RITUXAN

IMPORTANT SAFETY INFORMATION FOR RITUXAN HYCELA

BOXED WARNINGS: SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
- Severe Mucocutaneous Reactions: Severe, including fatal, mucocutaneous reactions can occur in patients receiving rituximab-containing products, including RITUXAN HYCELA
- Hepatitis B Virus (HBV) Reactivation: HBV reactivation can occur in patients treated with rituximab-containing products, including RITUXAN HYCELA, in some cases resulting in fulminant hepatitis, hepatic failure, and death. Screen all patients for HBV infection before treatment initiation, and monitor patients during and after treatment with RITUXAN HYCELA. Discontinue RITUXAN HYCELA and concomitant medications in the event of HBV reactivation
- Progressive Multifocal Leukoencephalopathy (PML), including fatal PML, can occur in patients receiving rituximab-containing products, including RITUXAN HYCELA

Please see pages 24-27 and accompanying full Prescribing Information, including BOXED WARNINGS and Medication Guide, for additional RITUXAN HYCELA Important Safety Information.
RITUXAN® (rituximab) AND RITUXAN HYCELA® (rituximab/hyaluronidase human) DOSING AND ADMINISTRATION GUIDE

This brochure provides dosing and administration guidelines for RITUXAN and RITUXAN HYCELA therapy. For more information, please refer to the enclosed full Prescribing Information for each product.

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Please see pages 12-15 and accompanying full Prescribing Information, including BOXED WARNINGS and Medication Guide, for RITUXAN Important Safety Information.

Please see pages 24-27 and accompanying full Prescribing Information, including BOXED WARNINGS and Medication Guide, for RITUXAN HYCELA Important Safety Information.

RITUXAN AND RITUXAN HYCELA DOSING AND ADMINISTRATION COMPARISON

<table>
<thead>
<tr>
<th>RITUXAN</th>
<th>RITUXAN HYCELA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premedications before each dose</td>
<td>✓</td>
</tr>
<tr>
<td>Dosing</td>
<td>BSA-based dosing □ Fixed dose</td>
</tr>
<tr>
<td>Preparation</td>
<td>Dilution required □ Dilution not required (ready-to-use vials)</td>
</tr>
<tr>
<td>Administration</td>
<td>Intravenous infusion □ Subcutaneous injection</td>
</tr>
</tbody>
</table>

All patients must first receive at least one full dose of RITUXAN without experiencing severe adverse reactions before starting treatment with RITUXAN HYCELA.
## RITUXAN—ESTABLISHED DOSING REGIMENS FOR TREATMENT SETTINGS IN NHL AND CLL

### RITUXAN DOSING BY TREATMENT SETTING IN NHL AND CLL²

<table>
<thead>
<tr>
<th>TREATMENT SETTING</th>
<th>INDICATED REGIMEN</th>
<th>SCHEDULE</th>
<th>RITUXAN DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line DLBCL</td>
<td>R + CHOP or other anthracycline-based chemotherapy regimens</td>
<td>Day 1 of each cycle of chemotherapy ×8</td>
<td>375 mg/m²</td>
</tr>
<tr>
<td>First-line follicular NHL</td>
<td>R + first-line chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Following a CR or PR* to first-line R + chemotherapy in follicular NHL:</td>
<td>R + first-line chemotherapy†</td>
<td>8 weeks following completion of RITUXAN in combination with chemotherapy, administer every 4 weeks for 12 doses</td>
<td></td>
</tr>
<tr>
<td>Non-progressing, low-grade NHL, after first-line CVP chemotherapy</td>
<td>CVP→R</td>
<td>Following completion of 6-8 cycles of CVP chemotherapy, administer once weekly for 4 doses at 6-month intervals to a maximum of 16 doses</td>
<td></td>
</tr>
<tr>
<td>Relapsed or refractory, low-grade or follicular NHL</td>
<td>R</td>
<td>Weekly ×4</td>
<td></td>
</tr>
<tr>
<td>R (retreatment)</td>
<td></td>
<td>Weekly ×4</td>
<td></td>
</tr>
<tr>
<td>CLL</td>
<td>R-FC</td>
<td>For 6 cycles:</td>
<td></td>
</tr>
<tr>
<td>First-line and previously treated CLL</td>
<td></td>
<td>Day prior to the first cycle of FC chemotherapy</td>
<td>375 mg/m²</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 1 of Cycles 2-6; every 28 days</td>
<td>500 mg/m²</td>
</tr>
</tbody>
</table>

*In PRIMA, patients were randomized to receive either RITUXAN or no further therapy if they achieved a CR/CRu or PR with R-CHemo induction therapy. In ECOG 1496, patients were randomized to receive either RITUXAN or no further therapy if they achieved a CR, PR, or SD with CVP induction therapy.†R-CHEMO: Approximately 71% of trial patients in both trial arms received R-CHOP, 22% received R-CVP, and 3% received R-FCM.

### SELECT IMPORTANT SAFETY INFORMATION FOR RITUXAN

#### WARNINGS AND PRECAUTIONS

**Infusion-related Reactions**
- RITUXAN can cause severe, including fatal, infusion-related reactions. Severe reactions typically occurred during the first infusion with time to onset of 30-120 minutes.
- RITUXAN-induced infusion-related reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

Please see pages 12-15 and accompanying full Prescribing Information, including BOXED WARNINGS and Medication Guide, for additional RITUXAN Important Safety Information.

### RITUXAN—ESTABLISHED DOSING REGIMENS FOR TREATMENT SETTINGS IN NHL AND CLL (CONT’D)

#### Diffuse Large B-Cell NHL (DLBCL)²
- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens.
  - **RITUXAN is not recommended for use in patients with severe, active infections.**
    - **The dose of RITUXAN is 375 mg/m² IV infusion given on Day 1 of each cycle of chemotherapy for up to 8 doses.**

#### Previously Untreated Follicular, B-Cell NHL²
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with first-line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy.
  - **RITUXAN is not recommended for use in patients with severe, active infections.**
    - **The dose of RITUXAN in combination with first-line chemotherapy is 375 mg/m² IV infusion given on Day 1 of each cycle of chemotherapy, for up to 8 doses.**
    - **The dose of RITUXAN in patients achieving a complete or partial response is 375 mg/m² IV infusion, given 8 weeks after the completion of RITUXAN in combination with chemotherapy, every 8 weeks, for up to 12 doses.**

#### Non-Progressing, Low-Grade, B-Cell NHL²
- Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL, as a single agent, after first-line CVP chemotherapy.
  - **RITUXAN is not recommended for use in patients with severe, active infections.**
    - **The dose of RITUXAN in patients who have not progressed following 6 to 8 cycles of CVP chemotherapy is 375 mg/m² IV infusion once weekly for 4 weeks, every 6 months, for up to 16 doses.**

#### Relapsed or Refractory, Low-Grade or Follicular, B-Cell NHL²
- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent.
  - **RITUXAN is not recommended for use in patients with severe, active infections.**
    - **The dose of RITUXAN is 375 mg/m² IV infusion once weekly for 4 or 8 doses.**

#### Chronic Lymphocytic Leukemia (CLL)²
- In combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive CLL.
  - **RITUXAN is not recommended for use in patients with severe, active infections.**
    - **The dose of RITUXAN is 375 mg/m² IV infusion the day prior to the initiation of FC chemotherapy, then 500 mg/m² on Day 1 of Cycles 2-6 (every 28 days).**

- **RITUXAN is not approved as monotherapy in CLL.**
RITUXAN—PREPARATION FOR ADMINISTRATION²

- Use appropriate aseptic technique. Do not use vial if particulates or discoloration is present.
- Withdraw the necessary amount of RITUXAN and dilute to a final concentration of 1 mg/mL to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP.
- Gently invert the bag to mix the solution. Do not mix or dilute with other drugs.
- Discard any unused portion left in the vial.
- RITUXAN solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for 24 hours. RITUXAN solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since RITUXAN solutions do not contain a preservative, diluted solutions should be stored refrigerated (2°C–8°C).

RITUXAN—STANDARD INFUSION²

- RITUXAN should only be administered by a healthcare professional with appropriate medical support to manage severe infusion reactions that can be fatal if they occur.
- Administer only as an intravenous (IV) infusion.
- Do not administer as an intravenous push or bolus.
- Premedicate patients with an antihistamine and acetaminophen prior to dosing.
- Pneumocystis jirovecii pneumonia (PJP) and antitherpetic viral prophylaxis is recommended for patients with CLL during treatment and for up to 12 months following treatment as appropriate.
- Depending on the severity of the infusion reaction and the required interventions, temporarily or permanently discontinue RITUXAN.
- Institute medical management (e.g., glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion reactions as needed.
- Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells (≥25,000/mm³).
- See BOXED WARNING, DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS sections of the Full Prescribing Information.

SELECT IMPORTANT SAFETY INFORMATION FOR RITUXAN

Infusion-related Reactions (cont’d)

- Premedicate patients with an antihistamine and acetaminophen prior to dosing. Institute medical management (e.g., glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion-related reactions as needed. Depending on the severity of the infusion reaction and the required interventions, temporarily or permanently discontinue RITUXAN.
- Resume infusion at a minimum 50% reduction in rate after symptoms have resolved.
- Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells (≥25,000/mm³).

RITUXAN—ADMINISTRATION FOR FIRST INFUSION²

<table>
<thead>
<tr>
<th>INFUSION</th>
<th>INFUSION RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>• Initiate infusion at 50 mg/hr</td>
</tr>
<tr>
<td></td>
<td>• In the absence of infusion toxicity, increase the rate by 50 mg/hr every 30 minutes</td>
</tr>
<tr>
<td></td>
<td>• Maximum infusion rate is 400 mg/hr</td>
</tr>
</tbody>
</table>

RITUXAN—ADMINISTRATION FOR SUBSEQUENT INFUSIONS²

<table>
<thead>
<tr>
<th>INFUSION</th>
<th>INFUSION RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subsequent standard</td>
<td>• Initiate infusion at 100 mg/hr</td>
</tr>
<tr>
<td></td>
<td>• In the absence of infusion toxicity, increase the rate by 100 mg/hr every 30 minutes</td>
</tr>
<tr>
<td></td>
<td>• Maximum infusion rate is 400 mg/hr</td>
</tr>
</tbody>
</table>

SELECT IMPORTANT SAFETY INFORMATION FOR RITUXAN

Severe Mucocutaneous Reactions

- Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with RITUXAN. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis.
- The onset of these reactions has been variable and includes reports with onset on the first day of RITUXAN exposure. Discontinue RITUXAN in patients who experience a severe mucocutaneous reaction. The safety of readministration of RITUXAN to patients with severe mucocutaneous reactions has not been determined.

Please see pages 12-15 and accompanying full Prescribing Information, including BOXEDWARNINGS and Medication Guide, for additional RITUXAN Important Safety Information.
If patients did not experience a Grade 3 or 4 infusion-related adverse event during Cycle 1, a 90-minute infusion can be administered in Cycle 2 with a glucocorticoid-containing chemotherapy regimen.

The 90-minute RITUXAN infusion can be administered to patients who:
- Have previously untreated DLBCL or FL, receiving R-CHOP or R-CVP, respectively
- Are ≥18 years of age
- Have an ECOG PS 0-2
- Have a circulating lymphocyte count ≤5,000/µL at the start of Cycle 2
- Did not experience any infusion-related serious adverse event (SAE) or Grade 3/4 infusion-related reaction (IRR) in Cycle 1
- Do not have significant cardiovascular disease*
- Patients in Stage 3 or 4 of DLBCL and FL were included in the RATE trial
- All patients were premedicated with acetaminophen and an antihistamine prior to RITUXAN administration
- Patients had a glucocorticoid component of R-CHOP or R-CVP administered prior to RITUXAN. No other glucocorticoids were allowed

SELECT IMPORTANT SAFETY INFORMATION FOR RITUXAN

Hepatitis B Virus Reactivation
- Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including RITUXAN. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation also has occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive and hepatitis B surface antibody [anti-HBs] positive)
- HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases increase in bilirubin levels, liver failure, and death can occur
- Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with RITUXAN
- For patients who show evidence of prior hepatitis B infection (HBsAg positive regardless of antibody status) or HBsAg negative but anti-HBc positive, consult with physicians with expertise in managing hepatitis B regarding monitoring for HBV antiviral therapy before and/or during RITUXAN treatment

*For the RATE trial, clinically significant cardiovascular disease is defined as uncontrolled hypertension, myocardial infarction, or unstable angina; New York Heart Association (NYHA) Classification Grade II or greater congestive heart failure; a ventricular arrhythmia requiring medication within 1 year prior to Day 1; or NYHA Grade II or greater peripheral vascular disease on Day 1.

Please see pages 12-15 and accompanying full Prescribing Information, including BOXED WARNINGS and Medication Guide, for additional RITUXAN Important Safety Information.
Severe Mucocutaneous Reactions
Infusion-related Reactions

WARNINGS AND PRECAUTIONS

WARNING: FATAL INFUSION-RELATED REACTIONS, SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Infusion-related Reactions: RITUXAN administration can result in serious, including fatal infusion-related reactions. Deaths within 24 hours of RITUXAN infusion have occurred. Approximately 80% of Fatal infusion reactions occurred in association with the first infusion. Monitor patients closely. Discontinue RITUXAN infusion for severe reactions and provide medical treatment for Grade 3 or 4 infusion-related reactions.

Severe Mucocutaneous Reactions: Severe, including Fatal, mucocutaneous reactions can occur in patients receiving RITUXAN.

Hepatitis B Virus (HBV) Reactivation: HBV reactivation can occur in patients treated with RITUXAN, in some cases resulting in fulminant hepatitis, hepatic failure, and death. Screen all patients for HBV infection before treatment initiation, and monitor patients during and after treatment with RITUXAN. Discontinue RITUXAN and concomitant medications in the event of HBV reactivation.

Progressive Multifocal Leukoencephalopathy (PML), including fatal PML, can occur in patients receiving RITUXAN.

WARNINGS AND PRECAUTIONS

Infusion-related Reactions

RITUXAN can cause severe, including fatal, infusion-related reactions. Severe reactions typically occurred during the first infusion with time to onset of 30–120 minutes.

RITUXAN-induced infusion-related reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

Premedicate patients with an antihistamine and acetaminophen prior to dosing. Institute medical management depending on the severity of the infusion reaction and the required interventions, temporarily or permanently discontinue RITUXAN. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved.

Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells (≥25,000/mm³).

Severe Mucocutaneous Reactions

Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with RITUXAN. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis.

The onset of these reactions has been variable and includes reports with onset on the first day of RITUXAN exposure. Discontinue RITUXAN in patients who experience a severe mucocutaneous reaction. The safety of readministration of RITUXAN to patients with severe mucocutaneous reactions has not been determined.

Hepatitis B Virus Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including RITUXAN. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation also has occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBC positive and hepatitis B surface antibody [anti-HBs] positive).

HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases, increase in bilirubin levels, liver failure, and death can occur.

Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with RITUXAN. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during RITUXAN treatment.

Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following RITUXAN therapy. HBV reactivation has been reported up to 24 months following completion of RITUXAN therapy.

In patients who develop reactivation of HBV while on RITUXAN, immediately discontinue RITUXAN and any concomitant chemotherapeutic agent. In patients who develop HBV reactivation, resumption of RITUXAN treatment in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing hepatitis B.

Progressive Multifocal Leukoencephalopathy

JC virus infection resulting in PML, and death can occur in RITUXAN-treated patients with hematologic malignancies or with autoimmune diseases. The majority of patients with hematologic malignancies diagnosed with PML received RITUXAN in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Most cases of PML were diagnosed within 12 months of their last infusion of RITUXAN.

Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Discontinue RITUXAN and consider discontinuation or reduction of any concomitant chemotherapeutic or immunosuppressive therapy in patients who develop PML.

Tumor Lysis Syndrome

Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, some fatal, can occur within 12–24 hours after the first infusion of RITUXAN in patients with NHL. A high number of circulating malignant cells (≥25,000/mm³) or high tumor burden, confers a greater risk of TLS.

Administer aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high risk for TLS. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.
IMPORTANT SAFETY INFORMATION FOR RITUXAN (CONT'D)

Infections
- Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of RITUXAN-based therapy. Infections have been reported in some patients with prolonged hypogammaglobulinemia (defined as hypogammaglobulinemia >11 months after rituximab exposure)
- New or reactivated viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Discontinue RITUXAN for serious infections and institute appropriate anti-infective therapy
- RITUXAN is not recommended for use in patients with severe, active infections

Cardiovascular Adverse Reactions
- Cardiac adverse reactions, including ventricular fibrillation, myocardial infarction, and cardiogenic shock may occur in patients receiving RITUXAN. Discontinue infusions for serious or life-threatening cardiac arrhythmias.
- Perform cardiac monitoring during and after all infusions of RITUXAN for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina

Renal Toxicity
- Severe, including fatal, renal toxicity can occur after RITUXAN administration in patients with NHL. Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and RITUXAN is not an approved treatment regimen. Monitor closely for signs of renal failure and discontinue RITUXAN in patients with a rising serum creatinine or oliguria

Bowel Obstruction and Perforation
- Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving RITUXAN in combination with chemotherapy. In postmarketing reports, the mean time to documented gastrointestinal perforation was 6 (range 1–77) days in patients with NHL. Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur

Immunization
- The safety of immunization with live viral vaccines following RITUXAN therapy has not been studied and vaccination with live virus vaccines is not recommended before or during treatment
- For patients treated with RITUXAN, physicians should review the patient’s vaccination status and patients should, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating RITUXAN and administer non-live vaccines at least 4 weeks prior to a course of RITUXAN

Embryo-Fetal Toxicity
- Based on human data, RITUXAN can cause fetal harm due to B-cell lymphocytopenia in infants exposed to rituximab in-utero. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception while receiving RITUXAN and for at least 12 months after the last dose

ADDITIONAL IMPORTANT SAFETY INFORMATION
- The most common Grade 3 or 4 adverse reactions in clinical trials of NHL and CLL were infusion-related reactions, neutropenia, leukopenia, anemia, thrombocytopenia, and infections. Additionally, lymphopenia and lung disorder were seen in NHL trials; and febrile neutropenia, pancytopenia, hypotension, and hepatitis B were seen in CLL trials
- The most common adverse reactions (incidence ≥25%) in clinical trials of NHL and CLL were infusion-related reactions. Additionally, fever, lymphopenia, chills, infection, and asthenia were seen in NHL trials; and neutropenia was seen in CLL trials
- Pregnancy and Nursing Mothers: Based on human data, RITUXAN can cause adverse developmental outcomes including B-cell lymphocytopenia in infants exposed to RITUXAN in-utero. Advise pregnant women of the risk to a fetus. There are no data on the presence of rituximab in human milk, the effect on the breastfed child, or the effect on milk production. Since many drugs including antibodies are present in human milk, advise a lactating woman not to breastfeed during treatment and for at least 6 months after the last dose of RITUXAN due to the potential for serious adverse reactions in breastfed infants

For additional safety information, please see the accompanying full Prescribing Information, including BOXED WARNINGS and Medication Guide.

Attention Healthcare Provider: Provide Medication Guide to patient prior to RITUXAN infusion.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.
**RITUXAN HYCELA: SAME ANTIBODY AS RITUXAN (rituximab), DELIVERED SUBCUTANEOUSLY WITH HYALURONIDASE HUMAN**

**RITUXAN HYCELA is a combination of rituximab and hyaluronidase human**

- **Rituximab**: Rituximab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab mediates B-cell lysis

- **Hyaluronidase human**: Hyaluronidase human increases the permeability of the subcutaneous tissue by temporarily depolymerizing hyaluronan, a polysaccharide found in the extracellular matrix of the subcutaneous tissue

**HOW IS RITUXAN HYCELA THOUGHT TO WORK?**

- RITUXAN HYCELA is administered by subcutaneous injection into the abdomen
- Hyaluronidase human increases permeability of the subcutaneous tissue by temporarily depolymerizing hyaluronan, based on preclinical studies
- Hyaluronidase human has been shown to increase the absorption rate of rituximab into the systemic circulation when given in the subcutaneous tissue, based on preclinical studies
- In the doses administered, hyaluronidase human in RITUXAN HYCELA acts locally
- The effects of hyaluronidase human are reversible and permeability of the subcutaneous tissue is restored within 24-48 hours

**SELECT IMPORTANT SAFETY INFORMATION FOR RITUXAN HYCELA**

**WARNINGS AND PRECAUTIONS**

**Severe Mucocutaneous Reactions**

- Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with rituximab-containing products, including RITUXAN HYCELA. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis
- Discontinue RITUXAN HYCELA in patients who experience a severe mucocutaneous reaction. The safety of re-administration of a rituximab-containing product, including RITUXAN HYCELA, to patients with severe mucocutaneous reactions has not been determined

Please see pages 24-27 and accompanying Full Prescribing Information, including BOXED WARNINGS and Medication Guide, for additional RITUXAN HYCELA Important Safety Information.
PRIOR TO RITUXAN HYCELA USE

All patients must first receive at least one full dose of RITUXAN (rituximab) without experiencing severe adverse reactions before starting treatment with RITUXAN HYCELA due to the higher risk of hypersensitivity and other acute reactions during the first infusion.

- Beginning therapy with RITUXAN allows management of hypersensitivity and other administration reactions by slowing or stopping the intravenous infusion.
- If patients are not able to receive one full dose of RITUXAN, they should continue subsequent cycles with RITUXAN and not switch to RITUXAN HYCELA until a full RITUXAN dose is successfully administered.

Hepatitis B Virus Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with CD20-directed cytolytic antibodies, including rituximab-containing products.

- HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA levels or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive.
- Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases, increase in bilirubin levels, liver failure, and death can occur.
- Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with a rituximab-containing product. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during treatment with a rituximab-containing product.
- Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following RITUXAN HYCELA. HBV reactivation has been reported up to 24 months following completion of therapy containing rituximab.

Please see pages 24-27 and accompanying full Prescribing Information, including BOXED WARNINGS and Medication Guide, for additional RITUXAN HYCELA Important Safety Information.

PRODUCT INFORMATION AND STORAGE

Packaged in single-dose vials and delivered in a fixed dose, RITUXAN HYCELA does not require dilution and BSA calculations.

- RITUXAN HYCELA should be a clear to opalescent and colorless to yellowish liquid. Do not use vial if particulates or discoloration is present.
- RITUXAN HYCELA vials must be refrigerated at 36ºF–46ºF (2ºC–8ºC); do not freeze.
- Store RITUXAN HYCELA vials in the original carton to protect from light.

Hepatitis B Virus Reactivation (cont’d)

In patients who develop reactivation of HBV while on RITUXAN HYCELA, immediately discontinue treatment and any concomitant chemotherapy, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming RITUXAN HYCELA treatment in patients who develop HBV reactivation. Resumption of RITUXAN HYCELA treatment in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing HBV.

Progressive Multifocal Leukoencephalopathy (PML)

- JC virus infection resulting in PML and death has been observed in patients receiving rituximab-containing products, including RITUXAN HYCELA.
- Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture.
- Discontinue RITUXAN HYCELA and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.
Dosing Schedules

Following completion of 6-8 cycles of CVP chemotherapy and a full RITUXAN dose at Week 1 (ie, 4 weeks in total).

§ Following a full RITUXAN dose at Week 1 (ie, 4 weeks in total).

‡ Following a full RITUXAN dose at Week 1 (ie, 4 or 8 weeks in total).

† Systemic Reactions

Hypersensitivity and Other Administration Reactions

SELECT IMPORTANT SAFETY INFORMATION FOR RITUXAN HYCELA

Hypersensitivity and Other Administration Reactions

Systemic Reactions

- Patients must receive at least one full dose of RITUXAN (rituximab) without experiencing severe adverse reactions before starting treatment with RITUXAN HYCELA.

RITUXAN HYCELA is delivered as a fixed dose, irrespective of a patient’s body surface area.

Dosing Schedules After Doce 1:

RITUXAN HYCELA is delivered as a fixed dose, irrespective of a patient’s body surface area.

<table>
<thead>
<tr>
<th>TREATMENT SETTING</th>
<th>INDICATED REGIMEN</th>
<th>SCHEDULE</th>
</tr>
</thead>
<tbody>
<tr>
<td>FL</td>
<td>RITUXAN HYCELA + chemotherapy</td>
<td>Day 1 of Cycles 2-8, every 21 days</td>
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<tr>
<td></td>
<td></td>
<td>Up to 7 cycles*</td>
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<tr>
<td>Previously untreated FL</td>
<td></td>
<td>Every 8 weeks for 12 doses</td>
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<tr>
<td>In patients with complete or partial response†</td>
<td>RITUXAN HYCELA maintenance</td>
<td>Once weekly for 3 or 7 weeks†</td>
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<tr>
<td>Relapsed or refractory FL</td>
<td>RITUXAN HYCELA</td>
<td>Once weekly for 3 weeks</td>
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<tr>
<td>Retreatment for relapsed or refractory FL</td>
<td>RITUXAN HYCELA</td>
<td>Once weekly for 3 weeks</td>
</tr>
<tr>
<td>Non-progressing FL after first-line CVP chemotherapy‡</td>
<td>RITUXAN HYCELA</td>
<td>Once weekly for 3 weeks; At 6-month intervals; To a maximum of 16 doses in total</td>
</tr>
<tr>
<td>Previously untreated DLBCL</td>
<td>RITUXAN HYCELA + CHOP</td>
<td>Day 1 of Cycles 2-8; Up to 7 cycles*</td>
</tr>
</tbody>
</table>

*Following a full RITUXAN dose on Day 1 of Cycle 1 of chemotherapy (ie, up to 8 cycles in total).

† 8 weeks following completion of RITUXAN HYCELA in combination with chemotherapy.

‡ Following a full RITUXAN dose at Week 1 (ie, 4 or 8 weeks in total).

§ Following a full RITUXAN dose at Week 1 (ie, 4 weeks in total).

¶ Following a full RITUXAN dose at Day 1 of Cycle 1 (ie, 6 or 8 cycles in total).

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|---|---|---|
| **Previously untreated FL** | RITUXAN HYCELA + chemotherapy | Day 1 of Cycles 2-8, every 21 days |
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Please see pages 24-27 and accompanying Full Prescribing Information, including BOXED WARNINGS and Medication Guide, for additional RITUXAN HYCELA Important Safety Information.
RITUXAN HYCELA PREPARATION AND STABILITY

- After the solution of RITUXAN HYCELA is withdrawn from the vial, it should be labeled with the peel-off sticker and used immediately.
  - If not used immediately, prepare in controlled and validated aseptic conditions. Once transferred from the vial into the syringe, store the solution of RITUXAN HYCELA in the refrigerator at 36°F–46°F (2°C–8°C) up to 48 hours and subsequently for 8 hours at room temperature up to 86°F (30°C) in diffuse light.
  - To avoid needle clogging, attach the hypodermic injection needle to the syringe immediately prior to administration.

RECOMMENDED PREMEDICATION AND PROPHYLACTIC MEDICATIONS

Provide prophylaxis for Pneumocystis jiroveci/pneumonia (PJP) and herpes virus infections for patients with CLL during treatment and for up to 12 months following treatment as appropriate.

RITUXAN HYCELA ADMINISTRATION

RITUXAN HYCELA is supplied in a ready-to-use vial and is administered as a fixed dose.

- FL and DLBCL Volume of 11.7 mL:
  - 1,400 mg rituximab and 23,400 Units hyaluronidase human in a single-dose vial
- CLL Volume of 13.4 mL:
  - 1,600 mg rituximab and 26,800 Units hyaluronidase human in a single-dose vial
- Dose reductions of RITUXAN HYCELA are not recommended.
- When RITUXAN HYCELA is given in combination with chemotherapy dose, reduce the chemotherapeutic drugs to manage adverse reactions.

PATIENT TYPE

- All patients
- Should also be considered

RECOMMENDED PREMEDICATIONS TO BE COMPLETED BEFORE EACH INJECTION

<table>
<thead>
<tr>
<th>Premedication</th>
<th>All patients</th>
</tr>
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<tbody>
<tr>
<td>Acetaminophen</td>
<td>All patients</td>
</tr>
<tr>
<td>Antihistamine</td>
<td>All patients</td>
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<tr>
<td>Glucocorticoid</td>
<td>Should also be considered</td>
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</tbody>
</table>

Local cutaneous reactions, including injection site reactions, have been reported in patients receiving RITUXAN HYCELA. Symptoms included pain, swelling, induration, hemorrhage, erythema, pruritus, and rash. Some local cutaneous reactions occurred more than 24 hours after RITUXAN HYCELA administration. The incidence of local cutaneous reactions following administration of RITUXAN HYCELA was 16%. Reactions were mild or moderate and resolved without any specific treatment. Local cutaneous reactions of any grade were most common during the first RITUXAN HYCELA cycle (Cycle 2: 5%), with the incidence decreasing with subsequent injections.

Please see pages 24-27 and accompanying Full Prescribing Information, including BOXED WARNINGS and Medication Guide, for additional RITUXAN HYCELA Important Safety Information.
Important Safety Information for RITUXAN HYCELA

Progressive Multifocal Leukoencephalopathy (PML)

- Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture.
- Discontinue RITUXAN HYCELA and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

Hypersensitivity and Other Administration Reactions

- Severe infusion-related reactions with fatal outcome have been reported with the use of RITUXAN, with an onset ranging within 30 minutes to 2 hours after starting the first intravenous infusion. They were characterized by pulmonary events in addition to fever, chills, rigors, hypotension, urticaria, angioedema, and other symptoms. Anaphylactic and other hypersensitivity reactions can also occur. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion.

Severe Mucocutaneous Reactions: Severe, including fatal, mucocutaneous reactions can occur in patients treated with rituximab-containing products, including RITUXAN HYCELA. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis.

- Discontinue RITUXAN HYCELA in patients who experience a severe mucocutaneous reaction. The safety of re-administration of a rituximab-containing product, including RITUXAN HYCELA, to patients with severe mucocutaneous reactions has not been determined.

Hepatitis B Virus Reactivation

- Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with CD20-directed cytolytic antibodies, including rituximab-containing products.
- HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA levels or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. Severe cases, increase in bilirubin levels, liver failure, and death can occur.
- Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with a rituximab-containing product. For patients who show evidence of prior hepatitis B infection (HBsAg positive regardless of antibody status) or HBsAg negative but anti-HBc positive, consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during treatment with a rituximab-containing product. Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following RITUXAN HYCELA. HBV reactivation has been reported up to 24 months following completion of therapy containing rituximab.
- In patients who develop reactivation of HBV while on RITUXAN HYCELA, immediately discontinue treatment and any concomitant chemotherapy, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming RITUXAN HYCELA treatment in patients who develop HBV reactivation. Resumption of RITUXAN HYCELA treatment in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing HBV.

Progressive Multifocal Leukoencephalopathy (PML)

- JC virus infection resulting in PML and death has been observed in patients receiving rituximab-containing products, including RITUXAN HYCELA.

Please see pages 24-27 and accompanying Full Prescribing Information, including BOXED WARNINGS and Medication Guide, for additional RITUXAN HYCELA Important Safety Information.
**IMPORTANT SAFETY INFORMATION FOR RITUXAN HYCELA**

(Cont’d)

**Tumor Lysis Syndrome (TLS)**
- TLS can occur within 12-24 hours after administration of a rituximab-containing product, including RITUXAN HYCELA.
- A high number of circulating malignant cells (≥25,000/mm³) or high tumor burden confers a greater risk of TLS. Administer aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high risk for TLS.
- Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis, as indicated.

**Infections**
- Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of therapy with rituximab-containing products, including RITUXAN HYCELA. The incidence of infections with RITUXAN HYCELA vs. RITUXAN was 56% and 49% respectively in patients with CLL, and 46% and 41% respectively in patients with FL/DLBCL in combination with chemotherapy. Infections have been reported in some patients with prolonged hypogammaglobulinemia (defined as hypogammaglobulinemia >11 months after rituximab exposure).
- New or reactivated viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Discontinue RITUXAN HYCELA for serious infections and institute appropriate anti-infective therapy.

**Cardiovascular Adverse Reactions**
- Cardiac adverse reactions, including ventricular fibrillation, myocardial infarction, and cardiogenic shock, may occur with rituximab-containing products, including RITUXAN HYCELA.
- Discontinue RITUXAN HYCELA for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all administrations of RITUXAN HYCELA for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina.

**Renal Toxicity**
- Severe, including fatal, renal toxicity can occur after administration of rituximab-containing products, including RITUXAN HYCELA. Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and RITUXAN HYCELA is not an approved treatment regimen. Monitor closely for signs of renal failure and discontinue RITUXAN HYCELA in patients with a rising serum creatinine or oliguria.

**Bowel Obstruction and Perforation**
- Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, can occur in patients receiving rituximab-containing products, including RITUXAN HYCELA, in combination with chemotherapy. In postmarketing reports, the mean time to documented gastrointestinal perforation was 6 (range 1-77) days. Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur.

**Immunization**
- The safety of immunization with live viral vaccines following rituximab-containing products, including RITUXAN HYCELA, has not been studied and vaccination with live virus vaccines is not recommended before or during treatment.

**Embryo-Fetal Toxicity**
- Based on human data, rituximab-containing products can cause fetal harm due to B-cell lymphocytopenia in infants exposed to rituximab in-utero. Advise pregnant women of the risk to a fetus. Females of childbearing potential should use effective contraception while receiving RITUXAN HYCELA and for 12 months following the last dose of rituximab-containing products, including RITUXAN HYCELA.

**ADVERSE REACTIONS**
- The most common adverse reactions (≥20%) of RITUXAN HYCELA observed in patients with FL in SABRINA were: infections, neutropenia, nausea, constipation, cough, and fatigue.
- The most common adverse reactions (≥20%) of RITUXAN HYCELA observed in patients with DLBCL in MABEASE were: infections, neutropenia, alopecia, nausea, and anemia.
- The most common adverse reactions (≥20%) of RITUXAN HYCELA observed in patients in part 2 of SAWYER were: infections, neutropenia, nausea, trombocytopenia, pyrexia, vomiting, and injection site erythema.

**PREGNANCY AND LACTATION**
- Based on human data, rituximab-containing products can cause adverse developmental outcomes including B-cell lymphocytopenia in infants exposed to rituximab in-utero. There are no available data on RITUXAN HYCELA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Advise pregnant women of the risk to a fetus.
- There are no data on the presence of rituximab or hyaluronidase human in human milk, the effect on the breastfed infant, or the effect on milk production. Advise lactating women not to breastfeed during treatment and for at least 6 months after the last dose of RITUXAN HYCELA due to the potential for serious adverse reactions in breastfed infants.

Please see the accompanying full Prescribing Information, including BOXED WARNINGS and Medication Guide, for additional Important Safety Information.


You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

**References:**