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®
Rituximab

RituxanHYCELA®
rituximab/hyaluronidase human
subcutaneous injection
1,400 mg/23,400 Units
1,600 mg/26,800 Units

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)

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 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**

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

Rituxan® Rituximab

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)

Limitations of Use

- Initiate treatment with RITUXAN HYCELA only after patients have received at least one full dose of a rituximab product by intravenous infusion
- RITUXAN HYCELA is not indicated for the treatment of non-malignant conditions

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.

RituxanHYCELA® rituximab/hyaluronidase human subcutaneous injection 1,400 mg/23,400 Units 1,600 mg/26,800 Units

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[1]

	RITUXAN	RITUXAN HYCELA
		All patients must first receive at least one full dose of a rituximab product by intravenous infusion without experiencing severe adverse reactions before starting treatment with RITUXAN HYCELA
1 **Premedications before each dose**	✓	✓
2 **Dosing**	BSA-based dosing	Fixed dose
3 **Preparation**	Dilution required	Dilution not required (ready-to-use vials)
4 **Administration**	Intravenous infusion	Subcutaneous injection

Rituxan® Rituximab

RituxanHYCELA® rituximab/hyaluronidase human subcutaneous injection 1,400 mg/23,400 Units 1,600 mg/26,800 Units

RITUXAN—ESTABLISHED DOSING REGIMENS FOR TREATMENT SETTINGS IN NHL AND CLL

RITUXAN DOSING BY TREATMENT SETTING IN NHL AND CLL[2]

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

*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 75% 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 NHL[2]

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 NHL[2]

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 NHL[2]

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®
Rituximab

RITUXAN—PREPARATION FOR ADMINISTRATION[2]

- 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 INFUSION[2]

- 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 antiherpetic 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
  - Resume infusion at a minimum 50% reduction in rate after symptoms have resolved
- Institute medical management (eg, 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/mm^3)
- 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/mm^3)

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

RITUXAN—ADMINISTRATION FOR FIRST INFUSION[2]

INFUSION	INFUSION RATE
First	• Initiate infusion at 50 mg/hr • In the absence of infusion toxicity, increase the rate by 50 mg/hr every 30 minutes • Maximum infusion rate is 400 mg/hr

RITUXAN—ADMINISTRATION FOR SUBSEQUENT INFUSIONS[2]

INFUSION	INFUSION RATE
Subsequent standard	• Initiate infusion at 100 mg/hr • In the absence of infusion toxicity, increase the rate by 100 mg/hr every 30 minutes • Maximum infusion rate is 400 mg/hr

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

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Rituximab

90-MINUTE RITUXAN INFUSION FOR APPROPRIATE PREVIOUSLY UNTREATED DLBCL AND FOLLICULAR NHL PATIENTS IN CYCLES 2-8[2-4]

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

*Per 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.

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 and consideration for HBV antiviral therapy before and/or during RITUXAN treatment

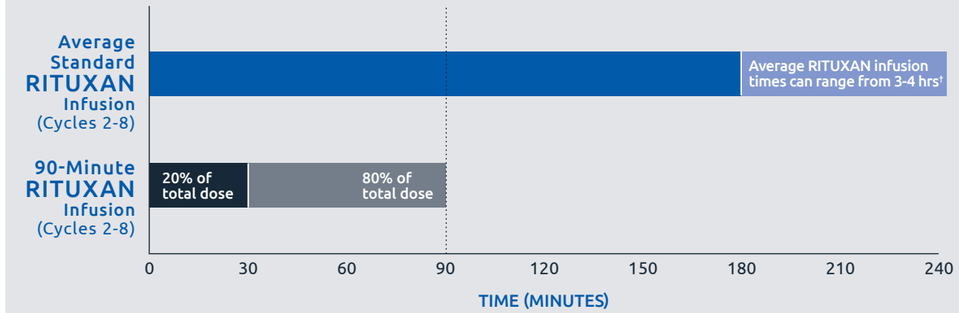
Please see pages 12-15 and accompanying full Prescribing Information, including **BOXED WARNINGS** and Medication Guide, for additional RITUXAN Important Safety Information.

90-MINUTE RITUXAN INFUSION FOR APPROPRIATE PREVIOUSLY UNTREATED DLBCL AND FOLLICULAR NHL PATIENTS IN CYCLES 2-8[2-4] (CONT'D)

The 90-minute RITUXAN infusion rate for appropriate patients is:

- 20% of the total dose over the first 30 minutes (75 mg/m^2)
- 80% of the total dose over the following 60 minutes (300 mg/m^2)
- If the 90-minute infusion is tolerated in Cycle 2, the same rate can be used when administering the remainder of the treatment regimen (through Cycle 6 or 8)

RITUXAN 375 mg/m^2 INFUSION TIME FOR APPROPRIATE PATIENTS[2,3]



†For standard infusions in Cycles 2-8, initiate at a rate of 100 mg/hr. In the absence of infusion toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.

Demonstrated safety profile with a 90-minute infusion in Cycles 2-8

- Of the 425 patients treated with RITUXAN in Cycle 1, 85% (n=363) were able to receive the 90-minute infusion of RITUXAN in Cycle 2
- Primary endpoint of the RATE trial was the incidence of Grade 3 or 4 IRRs the day of or the day after a 90-minute infusion of RITUXAN in Cycle 2‡
- Incidence of Grade 3/4 IRRs in Days 1-2 of Cycle 2 was 1.1%
- Incidence of Grade 3/4 IRRs was 2.8% cumulatively in Cycles 2-8
- No fatal IRRs or fatal AEs on Days 1-2 of any cycle

‡IRRs were categorized as Grades 1 through 5, as defined by Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

The RATE study did not enroll low-grade or follicular NHL post-induction or CLL patients. As such, there are no data in the RATE study that support using the 90-minute RITUXAN infusion in these patients

Rituxan®
Rituximab

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 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 (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/mm^3)

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 **BOXED WARNINGS** and Medication Guide, for additional RITUXAN Important Safety Information.

IMPORTANT SAFETY INFORMATION FOR RITUXAN (CONT'D)

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 chemotherapy, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming RITUXAN treatment 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 chemotherapy 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/mm^3) 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

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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

IMPORTANT SAFETY INFORMATION FOR RITUXAN (CONT'D)

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.

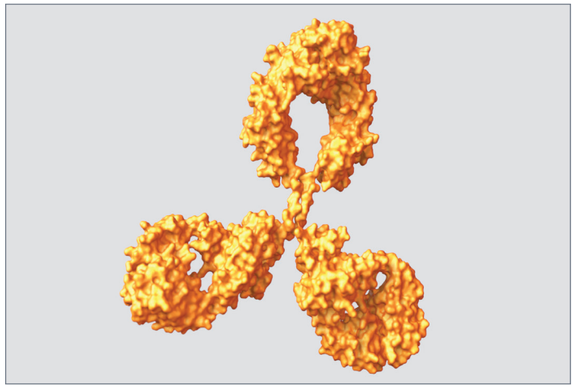
Attention Healthcare Provider: Provide Medication Guide to patient prior to RITUXAN infusion.

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.

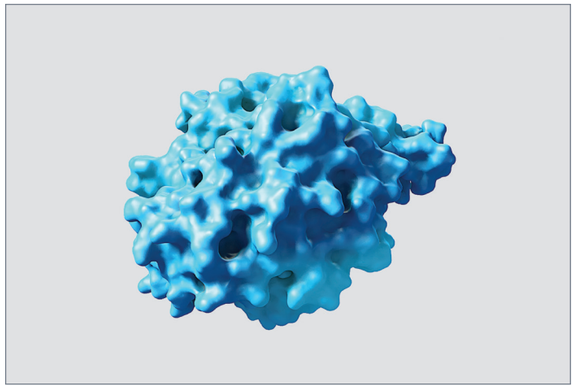
Rituxan®
Rituximab

RITUXAN HYCELA: SAME ANTIBODY AS RITUXAN (rituximab), DELIVERED SUBCUTANEOUSLY WITH HYALURONIDASE HUMAN[1]

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

SELECT IMPORTANT SAFETY INFORMATION FOR RITUXAN HYCELA

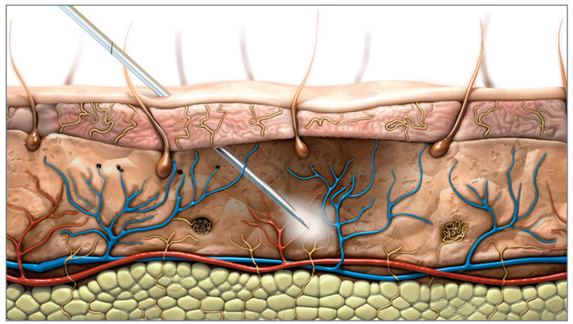
WARNINGS AND PRECAUTIONS

Severe Mucocutaneous Reactions

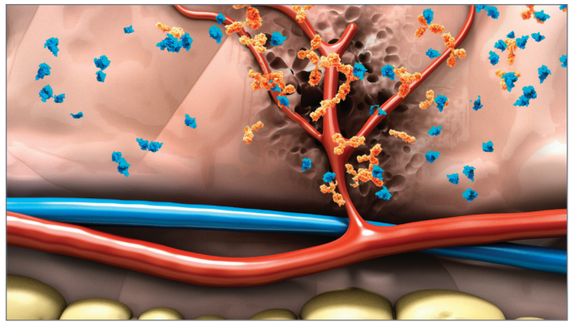
- Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with rituximab-containing products, including RITUXAN HYCELA. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis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

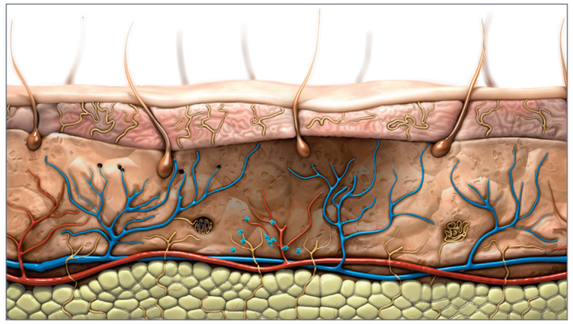
HOW IS RITUXAN HYCELA THOUGHT TO WORK?[1]



- 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

Based on preclinical studies, possible mechanisms of rituximab cell lysis include:

- Complement-dependent cytotoxicity (CDC)
- Antibody-dependent cell-mediated cytotoxicity (ADCC)

RituxanHYCELA®
rituximab/hyaluronidase human
subcutaneous injection
1,400 mg/23,400 Units
1,600 mg/26,800 Units

PRIOR TO RITUXAN HYCELA USE[1]

1st Dose Intravenous rituximab product (e.g. RITUXAN)

All patients must first receive at least one full dose of a rituximab product by intravenous infusion 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 a rituximab product 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 a rituximab product, they should continue subsequent cycles with a rituximab product and not switch to RITUXAN HYCELA until a full rituximab product dose is successfully administered

SELECT IMPORTANT SAFETY INFORMATION FOR RITUXAN HYCELA

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[1]

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

Individually packaged single-dose vials

Fixed dose

Ready-to-use vials

- 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 36°F–46°F (2°C–8°C)
- Do not freeze
- Store RITUXAN HYCELA vials in the original carton to protect from light

SELECT IMPORTANT SAFETY INFORMATION FOR RITUXAN HYCELA

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

RituxanHYCELA®
rituximab/hyaluronidase human
subcutaneous injection
1,400 mg/23,400 Units
1,600 mg/26,800 Units

FL AND DLBCL DOSING SCHEDULES AFTER DOSE 1:
11.7 mL ADMINISTERED OVER APPROXIMATELY 5 MINUTES[1]

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

All patients must first receive at least one full dose of a rituximab product by intravenous infusion without experiencing severe adverse reactions before starting treatment with RITUXAN HYCELA

TREATMENT SETTING	INDICATED REGIMEN	SCHEDULE
FL DLBCL	**Volume of 11.7 mL:** 1,400 mg rituximab and 23,400 Units hyaluronidase human **Administration Time:** Approximately 5 minutes	
Previously untreated FL	RITUXAN HYCELA + chemotherapy	▸ Day 1 of Cycles 2-8, every 21 days ▸ Up to 7 cycles*
↳ **In patients with complete or partial response**†	RITUXAN HYCELA maintenance	▸ Every 8 weeks for 12 doses
Relapsed or refractory FL	RITUXAN HYCELA	▸ Once weekly for 3 or 7 weeks‡
Retreatment for relapsed or refractory FL	RITUXAN HYCELA	▸ Once weekly for 3 weeks§
Non-progressing FL after first-line CVP chemotherapy‖	RITUXAN HYCELA	▸ Once weekly for 3 weeks ▸ At 6-month intervals ▸ To a maximum of 16 doses in total
Previously untreated DLBCL	RITUXAN HYCELA + CHOP	▸ Day 1 of Cycles 2-8 ▸ Up to 7 cycles¶

* Following a full rituximab product 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 rituximab product dose at Week 1 (ie, 4 or 8 weeks in total).
§ Following a full rituximab product dose at Week 1 (ie, 4 weeks in total).
‖ Following completion of 6-8 cycles of CVP chemotherapy and a full rituximab product dose at Week 1 (ie, 4 weeks in total).
¶ Following a full rituximab product dose at Day 1, Cycle 1 of CHOP chemotherapy (ie, up to 6-8 cycles in total).

SELECT IMPORTANT SAFETY INFORMATION FOR RITUXAN HYCELA

Hypersensitivity and Other Administration Reactions

Systemic Reactions

- Patients must receive at least one full dose of RITUXAN before receiving 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
- Rituximab-containing products, including RITUXAN HYCELA, are associated with hypersensitivity and other administration reactions, which may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be clinically indistinguishable from acute hypersensitivity reactions. This set of reactions which includes syndrome of cytokine release, tumor lysis syndrome, and anaphylactic and hypersensitivity reactions are described below. They are not specifically related to the route of administration of a rituximab-containing product

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

CLL DOSING SCHEDULES AFTER DOSE 1:
13.4 mL ADMINISTERED OVER APPROXIMATELY 7 MINUTES[1]

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

All patients must first receive at least one full dose of a rituximab product by intravenous infusion without experiencing severe adverse reactions before starting treatment with RITUXAN HYCELA

TREATMENT SETTING	INDICATED REGIMEN	SCHEDULE
CLL	**Volume of 13.4 mL:** 1,600 mg rituximab and 26,800 Units hyaluronidase human **Administration Time:** Approximately 7 minutes	
Previously untreated CLL	RITUXAN HYCELA + FC	▸ Day 1 of Cycles 2-6 ▸ Every 28 days; 5 cycles*
Previously treated CLL	RITUXAN HYCELA + FC	▸ Day 1 of Cycles 2-6 ▸ Every 28 days; 5 cycles*

* Following a full rituximab product dose at Day 1, Cycle 1 (ie, 6 cycles in total).

RITUXAN HYCELA is for subcutaneous use only

- RITUXAN HYCELA comes in a single-dose vial

SELECT IMPORTANT SAFETY INFORMATION FOR RITUXAN HYCELA

Hypersensitivity and Other Administration Reactions

Systemic Reactions (cont'd)

- 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 cytokine release syndrome is characterized by severe dyspnea, often associated by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with acute respiratory failure and death. Cytokine release syndrome may occur within 1-2 hours of initiating the infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumor infiltration may be at a greater risk of poor outcome. Rituximab product administration should be interrupted immediately and aggressive symptomatic treatment initiated

RituxanHYCELA®
rituximab/hyaluronidase human
subcutaneous injection
1,400 mg/23,400 Units
1,600 mg/26,800 Units

RITUXAN HYCELA PREPARATION AND STABILITY[1]

- 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[1]

Premedications

RECOMMENDED PREMEDICATIONS TO BE COMPLETED BEFORE EACH INJECTION	PATIENT TYPE
Acetaminophen	All patients
Antihistamine	All patients
Glucocorticoid	Should also be considered

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

SELECT IMPORTANT SAFETY INFORMATION FOR RITUXAN HYCELA

Hypersensitivity and Other Administration Reactions

Systemic Reactions (cont'd)

- During RITUXAN HYCELA administration, the injection should be interrupted immediately when observing signs of a severe reaction and aggressive symptomatic treatment should be initiated. 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/mm^3)
- Premedicate patients with an antihistamine and acetaminophen prior to each administration of RITUXAN HYCELA. Premedication with glucocorticoids should also be considered. Observe patients for at least 15 minutes following RITUXAN HYCELA. A longer period may be appropriate in patients with an increased risk of hypersensitivity reactions.

Local Cutaneous Reactions

- 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.

RITUXAN HYCELA ADMINISTRATION[1]

RITUXAN HYCELA is for subcutaneous use only

RITUXAN HYCELA Administration

5-7 MINUTES

Inject RITUXAN HYCELA into the subcutaneous tissue of the abdomen over approximately 5-7 minutes

- **RITUXAN HYCELA should only be administered by a healthcare professional with appropriate medical support to manage severe reactions that can be fatal if they occur**
- Never inject RITUXAN HYCELA into areas where the skin is red, bruised, tender, hard, or areas where there are moles or scars
- No data are available on performing the injection at other sites of the body
- If administration of RITUXAN HYCELA is interrupted, continue administering at the same site or at a different site, but restricted to the abdomen
- During treatment with RITUXAN HYCELA, do not administer other medications for subcutaneous use at the same sites as RITUXAN HYCELA
- The injection should be interrupted immediately when observing signs of a severe reaction and aggressive symptomatic treatment should be initiated

Fixed Dose

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 Observation

15+ MINUTES

Observe patients for at least 15 minutes following RITUXAN HYCELA administration

- 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/mm^3)
- A longer observation period may be appropriate in patients with an increased risk of hypersensitivity reactions

Local Cutaneous Reactions

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

RituxanHYCELA®
rituximab/hyaluronidase human
subcutaneous injection
1,400 mg/23,400 Units
1,600 mg/26,800 Units

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**

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

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
- 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)

Progressive Multifocal Leukoencephalopathy (PML) (cont'd)

- 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

Systemic Reactions

- Patients must receive at least one full dose of RITUXAN before receiving 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
- Rituximab-containing products, including RITUXAN HYCELA, are associated with hypersensitivity and other administration reactions, which may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be clinically indistinguishable from acute hypersensitivity reactions. This set of reactions which includes syndrome of cytokine release, tumor lysis syndrome, and anaphylactic and hypersensitivity reactions are described below. They are not specifically related to the route of administration of a rituximab-containing product
- 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 cytokine release syndrome is characterized by severe dyspnea, often associated by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with acute respiratory failure and death. Cytokine release syndrome may occur within 1-2 hours of initiating the infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumor infiltration may be at a greater risk of poor outcome. Rituximab product administration should be interrupted immediately and aggressive symptomatic treatment initiated
- During RITUXAN HYCELA administration, the injection should be interrupted immediately when observing signs of a severe reaction and aggressive symptomatic treatment should be initiated. 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/mm^3)
- Premedicate patients with an antihistamine and acetaminophen prior to each administration of RITUXAN HYCELA. Premedication with glucocorticoids should also be considered. Observe patients for at least 15 minutes following RITUXAN HYCELA. A longer period may be appropriate in patients with an increased risk of hypersensitivity reactions

Local Cutaneous Reactions

- 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

RituxanHYCELA®
rituximab/hyaluronidase human subcutaneous injection
1,400 mg/23,400 Units
1,600 mg/26,800 Units

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/mm^3) 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
- Verify pregnancy status in females of reproductive potential prior to initiating RITUXAN HYCELA

IMPORTANT SAFETY INFORMATION FOR RITUXAN HYCELA (CONT'D)

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 with CLL in part 2 of SAWYER were: infections, neutropenia, nausea, thrombocytopenia, pyrexia, vomiting, and injection site erythema
- With the exception of local cutaneous reactions, the incidence and profile of adverse reactions reported for RITUXAN HYCELA were comparable with those for RITUXAN. The overall incidence of adverse reactions for RITUXAN plus chemotherapy vs. RITUXAN HYCELA plus chemotherapy for FL/DLBCL was 93% vs. 95% (BSA ≤ 1.73 m^2), 89% vs. 93% (1.73 < BSA ≤ 1.92 m^2), and 94% vs. 94% (BSA > 1.92 m^2). The overall incidence of adverse reactions for RITUXAN vs. RITUXAN HYCELA in CLL was 89% vs. 100% (BSA ≤ 1.81 m^2), 97% vs. 88% (1.82 < BSA ≤ 1.99 m^2), and 88% vs. 93% (BSA > 2.00 m^2)

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 hyaluronidase human in human milk or the effect of rituximab on milk production, and there is limited data on the effect of rituximab on the breastfed child. Rituximab has also been reported to be excreted at low concentrations in human breast milk. Advise women not to breastfeed during treatment and for 6 months after the last dose of RITUXAN HYCELA due to the potential for serious adverse reactions in breastfed children.

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

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

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: 1. RITUXAN HYCELA full Prescribing Information. South San Francisco, CA: Genentech, Inc.; June 2021. **2.** RITUXAN full Prescribing Information, Genentech, Inc.; June 2021. **3.** Dakhil S, Hermann R, Schreeder MT, et al. Phase III safety study of rituximab administered as a 90-minute infusion in patients with previously untreated diffuse large B-cell and follicular lymphoma. *Leuk Lymphoma.* 2014;55(10):2335-2340. doi:10.3109/10428194.2013.877135.
4. Data on file, Genentech, Inc.

RituxanHYCELA®
rituximab/hyaluronidase human | 1,400 mg/23,400 Units
subcutaneous injection | 1,600 mg/26,800 Units

Rituxan®
Rituximab

RituxanHYCELA®
rituximab/hyaluronidase human | 1,400 mg/23,400 Units
subcutaneous injection | 1,600 mg/26,800 Units

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.

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RITUXAN HYCELA safely and effectively. See full prescribing information for RITUXAN HYCELA.

RITUXAN HYCELA® (rituximab and hyaluronidase human) injection, for subcutaneous use
Initial U.S. Approval: 2017

WARNING: SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
See full prescribing information for complete boxed warning.
- **Severe mucocutaneous reactions, some with fatal outcomes (5.1).**
- **Hepatitis B virus reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death (5.2).**
- **Progressive multifocal leukoencephalopathy resulting in death (5.3).**

----------RECENT MAJOR CHANGES----------
Dosage and Administration, Preparation and Administration (2.6) 06/2021

INDICATIONS AND USAGE
RITUXAN HYCELA is a combination of rituximab, a CD20-directed cytolytic antibody, and hyaluronidase human, an endoglycosidase, indicated for the treatment of adult patients with:
- Follicular Lymphoma (FL) (1.1)
  - Relapsed or refractory, follicular lymphoma 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
- Diffuse Large B-cell Lymphoma (DLBCL) (1.2)
  - Previously untreated diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens
- Chronic Lymphocytic Leukemia (CLL) (1.3)
  - Previously untreated and previously treated CLL in combination with fludarabine and cyclophosphamide (FC)

Limitations of Use:
- Initiate treatment with RITUXAN HYCELA only after patients have received at least one full dose of a rituximab product by intravenous infusion. (1.4, 2.1, 5.4).
- RITUXAN HYCELA is not indicated for the treatment of non-malignant conditions. (1.4)

DOSAGE AND ADMINISTRATION
- **For subcutaneous use only** (2.1)
- All patients must receive at least one full dose of a rituximab product by intravenous infusion before receiving RITUXAN HYCELA by subcutaneous injection (2.1).
- FL/DLBCL: Administer 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) subcutaneously according to recommended schedule (2.2, 2.3).
- CLL: Administer 1,600 mg/26,800 Units (1,600 mg rituximab and 26,800 Units hyaluronidase human) subcutaneously according to recommended schedule (2.4).
- Premedicate with acetaminophen and antihistamine before each dose; In addition, consider premedication with glucocorticoids (2.5, 5.4)
- Administer specified volume into subcutaneous tissue of abdomen: (2.6)
  - 11.7 mL from 1,400 mg/23,400 Units vial over approximately 5 minutes.
  - 13.4 mL from 1,600 mg/26,800 Units vial over approximately 7 minutes.
  - Observe 15 minutes following administration

DOSAGE FORMS AND STRENGTHS
Injection: (3)
- 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL (120 mg/2,000 Units per mL) solution in a single-dose vial
- 1,600 mg rituximab and 26,800 Units hyaluronidase human per 13.4 mL (120 mg/2,000 Units per mL) solution in a single-dose vial

CONTRAINDICATIONS
None. (4)

WARNINGS AND PRECAUTIONS
- Hypersensitivity and other administration reactions: Local cutaneous reactions may occur more than 24 hours after administration. Interrupt injection if severe reaction develops. Premedicate before injection. (5.4)
- Tumor lysis syndrome: Administer aggressive intravenous hydration, anti hyperuricemic agents, monitor renal function. (5.5)
- Infections: Withhold and institute appropriate anti-infective therapy. (5.6)
- Cardiac adverse reactions: Discontinue in case of serious or life-threatening events. (5.7)
- Renal toxicity: Discontinue in patients with rising serum creatinine or oliguria. (5.8)
- Bowel obstruction and perforation: Consider and evaluate for abdominal pain, vomiting, or related symptoms. (5.9)
- Immunizations: Live virus vaccinations prior to or during treatment not recommended. (5.10)
- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.11)

ADVERSE REACTIONS
Most common adverse reactions (incidence of ≥ 20%) are: (6.1)
- FL: infections, neutropenia, nausea, constipation, cough, and fatigue
- DLBCL: infections, neutropenia, alopecia, nausea, and anemia
- CLL: infections, neutropenia, nausea, thrombocytopenia, pyrexia, vomiting, and injection site erythema

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS----------
Renal toxicity when used in combination with cisplatin. (5.8)

USE IN SPECIFIC POPULATIONS
- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: 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 *[see Warnings and Precautions (5.1)]*.
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 *[see Warnings and Precautions (5.2)]*.
Progressive Multifocal Leukoencephalopathy (PML), including fatal PML, can occur in patients receiving rituximab-containing products, including RITUXAN HYCELA *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*.
1 INDICATIONS AND USAGE
1.1 Follicular Lymphoma (FL)
1.2 Diffuse Large B-Cell Lymphoma (DLBCL)
1.3 Chronic Lymphocytic Leukemia (CLL)
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5.5 Tumor Lysis Syndrome (TLS)
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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: 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 *[see Warnings and Precautions (5.1)]*.

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 *[see Warnings and Precautions (5.2)]*.

Progressive Multifocal Leukoencephalopathy (PML), including fatal PML, can occur in patients receiving rituximab-containing products, including RITUXAN HYCELA *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*.

1 INDICATIONS AND USAGE

1.1 Follicular Lymphoma (FL)

RITUXAN HYCELA is indicated for the treatment of adult patients with:

- Relapsed or refractory, follicular lymphoma 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.

1.2 Diffuse Large B-Cell Lymphoma (DLBCL)

RITUXAN HYCELA is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens.

1.3 Chronic Lymphocytic Leukemia (CLL)

RITUXAN HYCELA is indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of adult patients with previously untreated and previously treated CLL.

1.4 Limitations of Use

- Initiate treatment with RITUXAN HYCELA only after patients have received at least one full dose of a rituximab product by intravenous infusion *[see Dosage and Administration (2.1) and Warnings and Precautions (5.4)]*.
- RITUXAN HYCELA is not indicated for the treatment of non-malignant conditions.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Information

RITUXAN HYCELA is for subcutaneous use only. RITUXAN HYCELA should only be administered by a healthcare professional with appropriate medical support to manage severe reactions that can be fatal if they occur.

All patients must first receive at least one full dose of a rituximab product by intravenous infusion without experiencing severe adverse reactions before starting treatment with RITUXAN HYCELA. If patients are not

able to receive one full dose by intravenous infusion, they should continue subsequent cycles with a rituximab product by intravenous infusion and not switch to RITUXAN HYCELA until a full intravenous dose is successfully administered *[see Warnings and Precautions (5.4)]*.

Refer to the prescribing information for a rituximab product for intravenous infusion for additional information.

Premedicate before each dose of RITUXAN HYCELA *[see Dosage and Administration (2.5)]*.

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.

2.2 Recommended Dosage for Follicular Lymphoma (FL)

All patients must receive at least one full dose of a rituximab product by intravenous infusion before starting treatment with RITUXAN HYCELA *[see Dosage and Administration (2.1) and Warnings and Precautions (5.4)]*. Premedicate before each dose *[see Dosage and Administration (2.5)]*.

The recommended dose is RITUXAN HYCELA 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) subcutaneously at a fixed dose irrespective of patient's body surface area according to the following schedules:

- **Relapsed or Refractory, Follicular Lymphoma**
  Administer once weekly for 3 or 7 weeks following a full dose of a rituximab product by intravenous infusion at week 1 (i.e., 4 or 8 weeks in total).
- **Retreatment for Relapsed or Refractory, Follicular Lymphoma**
  Administer once weekly for 3 weeks following a full dose of a rituximab product by intravenous infusion at week 1 (i.e., 4 weeks in total).
- **Previously Untreated, Follicular Lymphoma**
  Administer on Day 1 of Cycles 2–8 of chemotherapy (every 21 days), for up to 7 cycles following a full dose of a rituximab product by intravenous infusion on Day 1 of Cycle 1 of chemotherapy (i.e., up to 8 cycles in total). In patients with complete or partial response, initiate RITUXAN HYCELA maintenance treatment 8 weeks following completion of RITUXAN HYCELA in combination with chemotherapy. Administer RITUXAN HYCELA as a single-agent every 8 weeks for 12 doses.
- **Non-progressing, Follicular Lymphoma after first line CVP chemotherapy**
  Following completion of 6–8 cycles of CVP chemotherapy and a full dose of a rituximab product by intravenous infusion at week 1, administer once weekly for 3 weeks (i.e., 4 weeks in total) at 6 month intervals to a maximum of 16 doses.

2.3 Recommended Dosage for Diffuse Large B-Cell Lymphoma (DLBCL)

All patients must receive at least one full dose of a rituximab product by intravenous infusion in combination with CHOP chemotherapy before starting treatment with RITUXAN HYCELA *[see Dosage and Administration (2.1) and Warnings and Precautions (5.4)]*. Premedicate before each dose *[see Dosage and Administration (2.5)]*.

The recommended dose for DLBCL is RITUXAN HYCELA 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) at a fixed dose irrespective of patient's body surface area in combination with CHOP chemotherapy. Administer RITUXAN HYCELA 1,400 mg/23,400 Units on Day 1 of Cycles 2–8 of CHOP chemotherapy for up to 7 cycles following a full dose of a rituximab product by intravenous infusion at Day 1, Cycle 1 of CHOP chemotherapy (i.e., up to 6–8 cycles in total).

2.4 Recommended Dosage for Chronic Lymphocytic Leukemia (CLL)

All patients must receive at least one full dose of a rituximab product by intravenous infusion in combination with FC chemotherapy before starting treatment with RITUXAN HYCELA *[see Dosage and Administration (2.1) and Warnings and Precautions (5.4)]*. Premedicate before each dose *[see Dosage and Administration (2.5)]*.

The recommended dose for CLL is RITUXAN HYCELA 1,600 mg/26,800 Units (1,600 mg rituximab and 26,800 Units hyaluronidase human) in combination with FC chemotherapy, at a fixed dose, irrespective of patient's body surface area. Administer RITUXAN HYCELA 1,600 mg/26,800 Units on Day 1 of Cycles 2–6 (every 28 days) for a total of 5 cycles following a full intravenous dose at Day 1, Cycle 1 (i.e., 6 cycles in total).

2.5 Recommended Premedication and Prophylactic Medications

Premedicate with acetaminophen and an antihistamine before each dose of RITUXAN HYCELA. Premedication with a glucocorticoid should also be considered *[see Dosage and Administration (2.2, 2.3, 2.4)]*.

Provide prophylaxis for Pneumocystis jiroveci pneumonia (PCP) and herpes virus infections for patients with CLL during treatment and for up to 12 months following treatment as appropriate *[see Warnings and Precautions (5.6)]*.

2.6 Preparation and Administration

To prevent medication errors, check the vial labels to ensure that the drug being prepared and administered is RITUXAN HYCELA for subcutaneous use. **Do not administer RITUXAN HYCELA intravenously**.

RITUXAN HYCELA is ready to use.

Preparation

Use a sterile needle and syringe to prepare RITUXAN HYCELA. RITUXAN HYCELA is compatible with polypropylene and polycarbonate syringe material and stainless steel transfer and injection needles.

Using a 20 mL syringe, withdraw the required volume from the vial with a narrow (e.g., 25–30 gauge) needle of any length.

Label the syringe with the provided peel-off label.

Change the needle to a 1/2" to 5/8" long, narrow gauge needle (e.g., 25–30 gauge) immediately prior to subcutaneous administration to avoid needle clogging.

Visually inspect for particulate matter and discoloration prior to administration. RITUXAN HYCELA should be a clear to opalescent and colorless to yellowish liquid. Do not use if particulates or discoloration is present.

Administration

- Inject RITUXAN HYCELA into the subcutaneous tissue of the abdomen over approximately 5–7 minutes. Never inject into areas where the skin is red, bruised, tender or hard, or areas where there are moles or scars. No data are available on performing the injection at other sites of the body.

- Inject 11.7 mL of RITUXAN HYCELA 1,400 mg/23,400 Units vial (1,400 mg rituximab and 23,400 Units hyaluronidase human) subcutaneously into the abdomen over approximately 5 minutes.

- Inject 13.4 mL of RITUXAN HYCELA 1,600 mg/26,800 Units vial (1,600 mg rituximab and 26,800 Units hyaluronidase human) subcutaneously into the abdomen over approximately 7 minutes.

If administration of RITUXAN HYCELA is interrupted, continue administering at the same site, or at a different site, but restricted to the abdomen.

Observe patients for at least 15 minutes following RITUXAN HYCELA administration *[see Warnings and Precautions (5.4)]*.

During treatment with RITUXAN HYCELA, do not administer other medications for subcutaneous use at the same sites as RITUXAN HYCELA.

Storage

Use immediately.

If not used immediately store refrigerated at 2°C to 8°C (36°F to 46°F) up to 48 hours and subsequently for 8 hours at room temperature up to 30°C (86°F) in diffuse light.

3 DOSAGE FORMS AND STRENGTHS

RITUXAN HYCELA is a colorless to yellowish, clear to opalescent solution for subcutaneous injection:

- Injection: 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL (120 mg/2,000 Units per mL) in a single-dose vial.
- Injection: 1,600 mg rituximab and 26,800 Units hyaluronidase human per 13.4 mL (120 mg/2,000 Units per mL) in a single-dose vial.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 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.

5.2 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 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.

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.

5.3 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 *[see Adverse Reactions (6.1)]*.

5.4 Hypersensitivity and other Administration Reactions

Systemic Reactions

Patients must receive at least one full dose of a rituximab product by intravenous infusion before receiving RITUXAN HYCELA due to the higher risk of hypersensitivity and other acute reactions during the first infusion *[see Dosage and Administration (2.1)]*. Beginning therapy with a rituximab product by intravenous infusion allows management of hypersensitivity and other administration reactions by slowing or stopping the intravenous infusion.

Rituximab-containing products, including RITUXAN HYCELA, are associated with hypersensitivity and other administration reactions, which may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be clinically indistinguishable from acute hypersensitivity reactions.

This set of reactions which includes syndrome of cytokine release, tumor lysis syndrome and anaphylactic and hypersensitivity reactions are described below. They are not specifically related to the route of administration of a rituximab-containing product.

Severe infusion-related reactions with fatal outcome have been reported with the use of intravenous formulations of rituximab products, 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 cytokine release syndrome is characterized by severe dyspnea, often associated by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with acute respiratory failure and death *[see Warnings and Precautions (5.5)]*. Cytokine release syndrome may occur within 1–2 hours of initiating the infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumor infiltration may be at a greater risk of poor outcome. Rituximab product administration should be interrupted immediately and aggressive symptomatic treatment initiated.

During RITUXAN HYCELA administration, the injection should be interrupted immediately when observing signs of a severe reaction and aggressive symptomatic treatment should be initiated.

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 ($\geq$ 25,000/mm^3) *[see Warnings and Precautions (5.5, 5.7)]*.

Premedicate patients with an antihistamine and acetaminophen prior to each administration of RITUXAN HYCELA *[see Dosage and Administration (2.5)]*. Premedication with glucocorticoids should also be considered. Observe patients for at least 15 minutes following RITUXAN HYCELA. A longer period may be appropriate in patients with an increased risk of hypersensitivity reactions.

Local Cutaneous Reactions

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 *[see Adverse Reactions (6.1)]*. 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.

5.5 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 ($\geq$ 25,000/mm^3) 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 *[see Warnings and Precautions (5.8)]*.

5.6 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 rituximab 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 *[see Adverse Reactions (6.1)]*.

5.7 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 *[see Adverse Reactions (6.1)]*.

5.8 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 *[see Warnings and Precautions (5.5)]*.

5.9 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.

5.10 Immunization

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

5.11 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 potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with RITUXAN HYCELA and for 12 months after the last dose of rituximab-containing products, including RITUXAN HYCELA *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Mucocutaneous reactions *[see Warnings and Precautions (5.1)]*
- Hepatitis B reactivation including fulminant hepatitis *[see Warnings and Precautions (5.2)]*
- Progressive multifocal leukoencephalopathy *[see Warnings and Precautions (5.3)]*
- Hypersensitivity and other administration reactions *[see Warnings and Precautions (5.4)]*

- Tumor lysis syndrome *[see Warnings and Precautions (5.5)]*
- Infections *[see Warnings and Precautions (5.6)]*
- Cardiac arrhythmias *[see Warnings and Precautions (5.7)]*
- Renal toxicity *[see Warnings and Precautions (5.8)]*
- Bowel obstruction and perforation *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to RITUXAN HYCELA in 892 patients in four controlled trials with exposures ranging from a single injection up to 27 months of treatment.

The population included 382 patients with follicular lymphoma (FL), 369 patients with diffuse large B-cell lymphoma (DLBCL), and 141 patients with chronic lymphocytic leukemia (CLL). The median age was 60 years (range: 18–85 years, 53% were male, and 84% were White. In the SABRINA study patients with FL received a full dose of a rituximab product by intravenous infusion, followed by RITUXAN HYCELA (1,400 mg rituximab/23,400 Units hyaluronidase human), in combination with chemotherapy for up to 7 doses (i.e., total of 8 doses in combination with chemotherapy), or as monotherapy for up to 12 doses (maintenance treatment). In the MabEase study patients with DLBCL received a full dose of a rituximab product by intravenous infusion, followed by RITUXAN HYCELA (1,400 mg rituximab/23,400 Units hyaluronidase human), given in combination with chemotherapy for up to 7 doses (i.e., up to a total of 8 doses). In the SAWYER study patients with CLL on part 2 received a full dose of a rituximab product by intravenous infusion, followed by RITUXAN HYCELA (1,600 mg rituximab/26,800 Units hyaluronidase human) for up to 5 doses, in combination with fludarabine and cyclophosphamide (i.e., total of 6 doses).

The most common adverse reactions (≥ 20%) of RITUXAN HYCELA observed in patients with FL on the SABRINA study were: infections, neutropenia, nausea, constipation, cough, and fatigue.

The most common adverse reactions (≥ 20%) of RITUXAN HYCELA observed in patients with DLBCL on the MabEase study were: infections, neutropenia, alopecia, nausea, and anemia.

The most common adverse reactions (≥ 20%) of RITUXAN HYCELA observed in patients with CLL on part 2 of the SAWYER study were: infections, neutropenia, nausea, thrombocytopenia, pyrexia, vomiting, and injection site erythema.

<u>Administration-related reactions (ARRs)</u>

Administration-related reactions (ARRs) with RITUXAN HYCELA were defined as all the adverse reactions related to the administration of RITUXAN HYCELA within the 24 hours post injection.

The incidence of ARRs with RITUXAN HYCELA was 34% in FL/DLBCL in combination with chemotherapy with injection site erythema (5%), chills (3%), dyspnea, erythema, flushing, injection site pain, nausea, pruritus, pyrexia, rash, and throat irritation (2% each) being the most common ARRs. The incidence of ARRs in FL maintenance setting was 20%. The most common ARRs were injection site erythema (7%), erythema (4%), injection site pain/edema, myalgia, and rash (2% each).

The incidence of ARRs with RITUXAN HYCELA in CLL was 44%.

With the exception of Local Cutaneous Reactions, the incidence and profile of adverse reactions reported for RITUXAN HYCELA were comparable with those for rituximab. The overall incidence of adverse reactions for intravenous rituximab versus RITUXAN HYCELA in combination with chemotherapy for FL/DLBCL was 93% versus 95% (BSA ≤ 1.73 m^2), 89% versus 93% (1.73 < BSA ≤ 1.92 m^2), and 94% versus 94% (BSA > 1.92 m^2). The overall incidence of adverse reactions for rituximab versus RITUXAN HYCELA in CLL was 89% versus 100% (BSA ≤ 1.81 m^2), 97% versus 88% (1.82 < BSA ≤ 1.99 m^2), and 88% versus 93% (BSA > 2.00 m^2).

Summary of Clinical Trial Experience in Follicular Lymphoma (FL)

The data in Table 1 were obtained in the SABRINA study, a two-stage randomized, controlled study in patients with previously untreated FL. The study compared patients receiving RITUXAN HYCELA (1,400 mg rituximab/23,400 Units hyaluronidase human; n=197) with patients receiving a rituximab product by intravenous infusion (375 mg/m^2; n=210), both in combination with CHOP or CVP followed by maintenance treatment with RITUXAN HYCELA or a rituximab product by intravenous infusion.

The majority of patients completed all 8 cycles of combination treatment with chemotherapy (91% RITUXAN HYCELA vs. 90% rituximab). In addition, 69% of patients in each of the treatment groups completed all 20 cycles of combination plus maintenance treatment. In both RITUXAN HYCELA and rituximab groups, patients experienced similar median duration of exposure (27.1 months for each arm).

Across the two stages, the overall demographics and baseline characteristics were balanced between the treatment groups. However, there were more female patients (53%) randomized in the study than male patients (47%) and a higher proportion of females were randomized to receive RITUXAN HYCELA (59% female) compared with the rituximab group (48%). The treatment groups in the combined Stage 1 and 2 population were otherwise balanced in regard to baseline demographics, characterized by a median age of 57 years (56.0 years [range 28–85 years] for RITUXAN HYCELA and 57 years [range 28–86 years] for rituximab) and median BSA of 1.83 m^2 (1.80 and 1.84 m^2 for RITUXAN HYCELA and rituximab, respectively).

The incidence of all adverse reactions was 96% for RITUXAN HYCELA vs. 95% for rituximab (Table 1). Grade 3–4 adverse reactions were reported in 55% of patients receiving RITUXAN HYCELA vs. 53% in patients receiving rituximab. Serious adverse reactions were reported in 37% of patients receiving RITUXAN HYCELA vs. 34% of patients receiving rituximab. The most common adverse reactions (occurring in ≥ 20% of patients in any arm) were infections, neutropenia, nausea, constipation, cough, and fatigue.

A total of 36 patients died, including 14/197 patients (7%) who received RITUXAN HYCELA and 22/210 patients (10%) who received rituximab. Of these 36 patients, 19 patients (7 patients RITUXAN HYCELA [4%] vs. 12 patients rituximab [6%]) died due to adverse reactions and 13 patients (6 patients RITUXAN HYCELA [3%] vs. 7 patients rituximab [3%]) died due to disease progression.

The incidence of administration-related reactions (ARRs) due to the subcutaneous route of administration associated with RITUXAN HYCELA was assessed in combination with chemotherapy and during maintenance. Thirty patients (15%) experienced an ARR during the first administration of RITUXAN HYCELA (Cycle 2). Incidence of ARRs generally decreased at subsequent cycles with 18 patients (9%) reporting ARR at Cycle 3, 13 patients (7%) at Cycle 4, 11 patients (6%) at Cycles 5 and 6, 12 patients (7%) at Cycle 7, and 8 patients (4%) at Cycle 8. During RITUXAN HYCELA monotherapy in the maintenance setting the incidence of ARRs at each cycle was ≤ 7% and was observed in 24 patients (14%) overall. Grade 1–2 ARRs constituted 96% of the overall ARRs. Grade 3 ARRs were reported during the first administration of RITUXAN HYCELA at Cycle 2 by 2 patients. Of the reported ARRs, local cutaneous reactions with RITUXAN HYCELA were reported in 32 patients. These events resolved within a median of 2 days from the onset (range 1 to 37 days). Majority of these reactions were Grade 1 and 2 and were observed in 31 patients (16%).

Table 1: Incidence of Adverse Reactions in ≥ 5% of Patients with Previously Untreated Follicular Lymphoma Receiving RITUXAN HYCELA or Rituximab in Combination with CHOP or CVP and as Monotherapy for Maintenance Treatment

Body System/Adverse Reactions	RITUXAN HYCELA (n=197)		Rituximab (n=210)	
	All Grades %	Grade 3–4 %	All Grades %	Grade 3–4 %
Gastrointestinal Disorders				
Nausea	31	0	22	0
Constipation	25	0	26	< 1
Diarrhea	18	2	16	< 1
Abdominal Pain	14	0	12	< 1
Vomiting	14	0	12	< 1
Dyspepsia	8	0	7	0
Stomatitis	6	0	5	0
Abdominal Pain Upper	5	0	5	0
General Disorders and Administration Site Conditions				
Fatigue	20	0	18	< 1
Asthenia	17	1	13	0
Pyrexia	15	< 1	16	< 1
Injection Site Erythema	13	0	0	0
Injection Site Pain	8	0	0	0
Chills	8	0	9	0
Chest Pain	6	1	3	0
Edema Peripheral	5	< 1	6	0
Mucosal Inflammation	5	1	6	< 1
Influenza Like Illness	3	0	6	0
Infections				
Upper Respiratory Tract Infection	15	< 1	10	0
Pneumonia	11	5	4	2
Nasopharyngitis	10	0	10	0
Bronchitis	8	< 1	8	< 1
Urinary Tract Infection	8	1	14	< 1
Sinusitis	7	< 1	4	0
Conjunctivitis	5	0	5	0
Influenza	4	0	6	< 1
Blood and Lymphatic System Disorders				
Neutropenia	32	26	27	21
Anemia	15	5	13	0
Febrile Neutropenia	8	7	6	6
Leukopenia	6	4	11	2
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	13	< 1	10	0
Bone Pain	10	< 1	8	0
Pain In Extremity	10	0	5	0
Back Pain	9	< 1	12	< 1
Muscle Spasms	8	0	3	0
Myalgia	8	0	5	0
Nervous System Disorders				
Paresthesia	16	0	12	0
Headache	13	0	9	0
Neuropathy Peripheral	12	2	14	< 1
Dizziness	7	0	7	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	14	< 1	10	< 1
Pruritus	10	0	12	< 1
Rash	10	0	7	0
Erythema	9	0	5	0

Body System/Adverse Reactions	RITUXAN HYCELA (n=197)		Rituximab (n=210)	
	All Grades %	Grade 3–4 %	All Grades %	Grade 3–4 %
Respiratory, Thoracic and Mediastinal Disorders				
Cough	23	0	13	< 1
Dyspnea	11	1	8	2
Oropharyngeal Pain	9	0	8	0
Psychiatric Disorders				
Insomnia	9	0	9	0
Vascular Disorders				
Hypertension	6	1	6	0

Summary of Clinical Trial Experience in Diffuse Large B-Cell Lymphoma (DLBCL)

The data in Table 2 were obtained in the MabEASE study, a comparative, randomized, parallel-group, multicenter study to investigate the efficacy of RITUXAN HYCELA (1,400 mg rituximab and 23,400 Units hyaluronidase human; n=369) versus 375 mg/m^2 a rituximab product by intravenous infusion (n=203) both in combination with CHOP (R-CHOP) in previously untreated patients with CD20-positive DLBCL.

Eighty two percent of patients receiving RITUXAN HYCELA or rituximab completed all 8 cycles of study treatment. In both RITUXAN HYCELA and rituximab treatment groups, patients experienced 4.9 months median duration of rituximab exposure in each arm.

The demographic characteristics were balanced. Most patients were White (79%) and 54% were male. The median was 64 years and median BSA was 1.83 m^2.

The incidences of adverse reactions of any grade (RITUXAN HYCELA [94%] vs. rituximab [92%]) (Table 2), Grade 3–4 adverse reactions (RITUXAN HYCELA [63%] vs. rituximab [57%]), and serious adverse reactions (RITUXAN HYCELA [42%] vs. rituximab [37%]) were generally comparable between the two treatment groups. The common adverse reactions (occurring in ≥ 20% of patients in any treatment group) were neutropenia, alopecia, nausea, and anemia.

A total of 91 patients (16%) died, including 58/369 patients (16%) in RITUXAN HYCELA and 33/203 patients (16%) in rituximab. Of these patients, 44 patients (29 patients RITUXAN HYCELA [8%] vs. 15 patients rituximab [7%]) died due to adverse reactions and 35 patients (22 patients RITUXAN HYCELA [6%] vs. 13 patients rituximab [6%]) died due to disease progression. Pneumonia (4 patients RITUXAN HYCELA vs. 1 patient rituximab), septic shock (2 patients RITUXAN HYCELA vs. 3 patients rituximab), and cardiac arrest (1 patient RITUXAN HYCELA vs. 3 patients rituximab) were the most common adverse reactions leading to death.

The incidence of administration-related reactions was balanced between the RITUXAN HYCELA and rituximab groups (28% vs. 29%). Grade 1–2 ARRs constituted 97% of the overall ARRs for the RITUXAN HYCELA arm and 80% for the rituximab arm. Of the reported ARRs, local cutaneous reactions with RITUXAN HYCELA were reported in 17 patients. These events resolved within a median of 2 days from the onset (range 1 to 32 days). Majority of these reactions were Grade 1 and 2 and were observed in 16 patients (4%).

Table 2: Incidence of Adverse Reactions in ≥ 5% of Patients with Previously Untreated DLBCL Receiving RITUXAN HYCELA or Rituximab in Combination with CHOP

Body System/Adverse Reactions	RITUXAN HYCELA + CHOP (n=369)		Rituximab + CHOP (n=203)	
	All Grades %	Grade 3–4 %	All Grades %	Grade 3–4 %
Gastrointestinal Disorders				
Nausea	22	< 1	24	< 1
Constipation	15	< 1	17	< 1
Diarrhea	14	1	10	1
Vomiting	11	< 1	8	< 1
Abdominal Pain	7	< 1	7	< 1
Stomatitis	6	< 1	5	0
Dyspepsia	5	0	7	0
General Disorders and Administration Site Conditions				
Fatigue	19	1	15	1
Pyrexia	13	< 1	13	0
Asthenia	11	< 1	12	< 1
Mucosal Inflammation	8	< 1	8	1
Edema Peripheral	8	< 1	4	0
Infections				
Pneumonia	7	3	4	2
Blood and Lymphatic System Disorders				
Neutropenia	31	25	29	19
Anemia	23	5	21	4
Febrile Neutropenia	14	14	12	11
Leukopenia	7	3	7	3
Lymphopenia	5	1	6	3
Investigations				
Neutrophil Count Decreased	14	11	14	11
White Blood Cell Count Decreased	7	4	7	5
Weight Decreased	8	< 1	4	< 1
Lymphocyte Count Decreased	5	2	3	2
Metabolism and Nutrition Disorders				
Decreased Appetite	8	< 1	9	< 1
Nervous System Disorders				
Neuropathy Peripheral	12	< 1	12	0
Paresthesia	9	< 1	6	0
Headache	6	0	7	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	24	0	24	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	11	< 1	9	0
Dyspnea	6	0	4	< 1
Psychiatric Disorders				
Insomnia	7	< 1	6	< 1

Summary of Clinical Trial Experience in Chronic Lymphocytic Leukemia

The data in Table 3 were obtained in part 2 of the SAWYER study, a two-part, comparative, randomized, parallel-group, multicenter study of RITUXAN HYCELA versus a rituximab product by intravenous infusion both in combination with fludarabine and cyclophosphamide (FC) chemotherapy in patients with previously untreated CLL.

The safety analysis population in part 2 of the study included 85 patients receiving RITUXAN HYCELA (1,600 mg rituximab/26,800 Units hyaluronidase human) and 89 patients receiving 500 mg/m^2 rituximab. In both

RITUXAN HYCELA and rituximab groups, patients had similar median duration of rituximab exposure (4.9 vs. 4.7 months). The majority of patients received all 6 cycles of study treatment (86% RITUXAN HYCELA vs. 81% rituximab).

The patient population was predominantly White (96%) and male (65%), with a median age of 60 years and median BSA of 1.9 m^2 (1.97 and 1.86 m^2 for the RITUXAN HYCELA and intravenous rituximab groups, respectively). Overall, the treatment groups were balanced with respect to demographic characteristics, with the exception of more males in the RITUXAN HYCELA arm (71% RITUXAN HYCELA vs. 60% rituximab). Baseline disease characteristics were similar between the two groups. Over half of the patients (62%) had Binet Stage B disease and the majority had typical CLL characterizations (93%), with median time from first CLL diagnosis to randomization being 18.5 months.

The incidences of adverse reactions were balanced between the two treatment groups (96% RITUXAN HYCELA vs. 91% rituximab), and the common adverse reactions (occurring in ≥ 20% of patients in any arm) were infections, neutropenia, nausea, thrombocytopenia, pyrexia, anemia, vomiting, and injection site erythema. The incidences of Grade 3–4 adverse reactions were also balanced between the two treatment groups (69% RITUXAN HYCELA vs. 71% rituximab). The incidence of serious adverse reactions was 29% for RITUXAN HYCELA and 33% for rituximab. The incidence of administration-related reactions was 44% for RITUXAN HYCELA and 45% for rituximab). Of the reported ARRs, local cutaneous reactions with RITUXAN HYCELA were reported in 15 patients. These events resolved within a median of 6 days from the onset (range 3 to 29 days). Majority of these reactions were Grade 1 and 2 and were observed in 14 patients (16%).

A total of 9 patients (5%) died, including 5 patients in the RITUXAN HYCELA group and 4 patients in the rituximab group. In the RITUXAN HYCELA group, 1 patient died due to herpes zoster infection, 1 patient died as a result of progressive multifocal leukoencephalopathy (PML) (considered by the investigator as related to rituximab), and 3 patients died due to disease progression. In the rituximab group, 2 patients died due to diarrhea and listeriosis and 2 patients died due to disease progression.

Table 3: Incidence of Adverse Reactions in ≥ 5% of Patients with Previously Untreated CLL Receiving RITUXAN HYCELA or Rituximab in Combination with FC

Body System/Adverse Reactions	RITUXAN HYCELA + FC (n=85)		Rituximab + FC (n=89)	
	All Grades %	Grade 3–4 %	All Grades %	Grade 3–4 %
Gastrointestinal Disorders				
Nausea	38	1	35	0
Vomiting	21	2	22	1
Diarrhea	12	0	11	3
Abdominal Pain	9	0	6	0
Constipation	8	0	8	0
General Disorders and Administration Site Conditions				
Pyrexia	32	5	25	1
Injection Site Erythema	26	2	0	0
Injection Site Pain	16	1	0	0
Chills	13	0	10	1
Fatigue	11	0	10	0
Asthenia	8	1	17	2
Infections				
Upper Respiratory Tract Infection	13	0	12	1
Respiratory Tract Infection	8	1	4	1
Bronchitis	7	0	6	0
Urinary Tract Infection	2	0	8	1
Pneumonia	2	2	6	2
Blood and Lymphatic System Disorders				
Neutropenia	65	56	58	52
Thrombocytopenia	24	6	26	9
Leukopenia	19	14	16	12
Anemia	13	5	24	9
Febrile Neutropenia	11	8	8	8
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	9	0	1	0
Pain In Extremity	7	1	2	0
Bone Pain	6	0	2	0
Nervous System Disorders				
Headache	7	0	9	0
Skin and Subcutaneous Tissue Disorders				
Erythema	15	0	7	0
Rash	12	0	10	1
Pruritus	8	0	4	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	13	0	11	0
Oropharyngeal Pain	6	0	3	0
Dyspnea	4	0	8	1
Psychiatric Disorders				
Insomnia	1	0	7	0
Vascular Disorders				
Hypotension	1	0	7	1
Hypertension	0	0	6	1

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to RITUXAN HYCELA and rituximab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In the SABRINA study, where previously untreated patients with follicular lymphoma were treated with RITUXAN HYCELA or rituximab in combination with CVP or CHOP, the incidence of treatment-induced/enhanced anti-rituximab antibodies in the RITUXAN HYCELA group was similar to that observed in the rituximab group (2.0% RITUXAN HYCELA vs. 1.9% rituximab). The incidence of treatment-induced/enhanced anti-recombinant human hyaluronidase antibodies was 15% in the RITUXAN HYCELA group compared with 8% in the rituximab group, and the overall proportion of patients found to have anti-recombinant human hyaluronidase antibodies remained generally constant over the follow-up period in both cohorts. All patients who tested positive for anti-recombinant human hyaluronidase antibodies at any point during the study were negative for neutralizing antibodies.

In the SAWYER study, where previously untreated patients with CLL were treated with RITUXAN HYCELA or rituximab in combination with FC, the incidence of treatment-induced/enhanced anti-rituximab antibodies was 12% in the RITUXAN HYCELA group and 15% in the rituximab group. The incidence of treatment-induced/enhanced anti- recombinant human hyaluronidase antibodies was 11% in the RITUXAN HYCELA treatment arm. None of the patients who tested positive for anti-recombinant human hyaluronidase antibodies tested positive for neutralizing antibodies.

The clinical relevance of the development of anti-rituximab or anti-recombinant human hyaluronidase antibodies after treatment with RITUXAN HYCELA is not known.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of rituximab-containing products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hematologic: prolonged pancytopenia, marrow hypoplasia, Grade 3–4 prolonged or late-onset neutropenia, hyperviscosity syndrome in Waldenstrom’s macroglobulinemia, prolonged hypogammaglobulinemia
- Cardiac: fatal cardiac failure
- Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like syndrome, serum sickness, polyarticular arthritis, and vasculitis with rash.
- Infection: viral infections, including progressive multifocal leukoencephalopathy (PML), increase in fatal infections in HIV-associated lymphoma, and a reported increased incidence of Grade 3 and 4 infections
- Neoplasia: disease progression of Kaposi’s sarcoma.
- Skin: severe mucocutaneous reactions, pyoderma gangrenosum (including genital presentation).
- Gastrointestinal: bowel obstruction and perforation.
- Pulmonary: fatal bronchiolitis obliterans and fatal interstitial lung disease.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on human data, rituximab-containing products can cause fetal harm due to B-cell lymphocytopenia in infants exposed to rituximab in-utero *(see Clinical Considerations)*. There are no available data on RITUXAN HYCELA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In

animal reproduction studies, intravenous administration of a rituximab product to pregnant cynomolgus monkeys during the period of organogenesis caused lymphoid B cell depletion in the newborn offspring at doses resulting in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Reduced fetal weight and increased fetal lethality were observed following subcutaneous administration of hyaluronidase human in mice at a dose > 2700 times higher than the human dose. Comparable systemic exposure levels could occur in a pregnant patient following accidental intravenous administration of an entire vial of RITUXAN HYCELA *(see Data)*. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk in the U.S. general population of major birth defects is 2%–4% and of miscarriage is 15%–20% of clinically recognized pregnancies.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Observe newborns and infants for signs of infection and manage accordingly.

Data

Human Data

Postmarketing data indicate that B-cell lymphocytopenia generally lasting less than 6 months can occur in infants exposed to rituximab in-utero. Rituximab was detected postnatally in the serum of infants exposed in-utero.

Animal Data

RITUXAN HYCELA for subcutaneous injection contains rituximab and hyaluronidase human *[see Description (11)]*.

Rituximab Product:

- An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received rituximab via the intravenous route during early gestation (organogenesis period; post coitum days 20 through 50). Rituximab was administered as loading doses on post coitum (PC) Days 20, 21 and 22, at 15, 37.5 or 75 mg/kg/day, and then weekly on PC Days 29, 36, 43 and 50, at 20, 50 or 100 mg/kg/week. The 100 mg/kg/week dose resulted in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Rituximab crosses the monkey placenta. Exposed offspring did not exhibit any teratogenic effects but did have decreased lymphoid tissue B cells.
- A subsequent pre-and postnatal reproductive toxicity study in cynomolgus monkeys was completed to assess developmental effects including the recovery of B cells and immune function in infants exposed to rituximab in utero. Animals were treated with a loading dose of 0, 15, or 75 mg/kg every day for 3 days, followed by weekly dosing with 0, 20, or 100 mg/kg dose. Subsets of pregnant females were treated from PC Day 20 through postpartum Day 78, PC Day 76 through PC Day 134, and from PC Day 132 through delivery and postpartum Day 28. Regardless of the timing of treatment, decreased B cells and immunosuppression were noted in the offspring of rituximab-treated pregnant animals. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months postpartum.

Hyaluronidase Human:

- In an embryo-fetal study, mice have been dosed daily by subcutaneous injection during the period of organogenesis with hyaluronidase human at dose levels up to 2,200,000 U/kg, which is > 2700 times higher than the human dose. The study found no evidence of teratogenicity. Reduced fetal weight and increased numbers of fetal resorptions were observed, with no effects found at a daily dose of 360,000 U/kg, which is > 450 times higher than the human dose.
- In a peri-and post-natal reproduction study, mice have been dosed daily by subcutaneous injection, with hyaluronidase human from implantation through lactation and weaning at dose levels up to 1,100,000

U/kg, which is > 1,300 times higher than the human dose. The study found no adverse effects on sexual maturation, learning and memory or fertility of the offspring.

8.2 Lactation

There are no data on the presence of hyaluronidase human in human milk or the effect of rituximab on milk production, and there is limited data on the effect of rituximab on the breastfed child. However, rituximab is detected in the milk of lactating cynomolgus monkeys and maternal IgG is present in human breast milk. Rituximab has also been reported to be excreted at low concentrations in human breast milk. Given that the clinical significance of this finding for children is not known, advise women not to breastfeed during treatment with RITUXAN HYCELA and for 6 months after the last dose due to the potential for serious adverse reactions in breastfed children.

8.3 Females and Males of Reproductive Potential

Rituximab-containing products can cause fetal harm *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating RITUXAN HYCELA.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with RITUXAN HYCELA and for 12 months after the last dose of rituximab-containing products, including RITUXAN HYCELA.

8.4 Pediatric Use

The safety and effectiveness of RITUXAN HYCELA in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in the SABRINA, MabEase, and SAWYER studies, 37% were 65 and over, while 10% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

11 DESCRIPTION

RITUXAN HYCELA is a combination of rituximab and hyaluronidase human. Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM. Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension.

Recombinant human hyaluronidase is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. It is produced by mammalian (Chinese Hamster Ovary) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). It is a glycosylated single-chain protein with an approximate molecular weight of 61 kD.

RITUXAN HYCELA (rituximab and hyaluronidase human) injection is a colorless to yellowish, clear to opalescent solution supplied in sterile, preservative-free, single-dose vials for subcutaneous use.

RITUXAN HYCELA is supplied as 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL in single-dose vials or 1,600 mg rituximab and 26,800 Units hyaluronidase human per 13.4 mL in single-dose vials. Each mL of solution contains rituximab (120 mg), hyaluronidase human (2,000 Units), L-histidine (0.53 mg), L-histidine hydrochloride monohydrate (3.47 mg), L-methionine (1.49 mg), polysorbate 80 (0.6 mg), α,α-trehalose dihydrate (79.45 mg), and Water for Injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC). Hyaluronan is a polysaccharide found in the extracellular matrix of the subcutaneous tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a half-life of approximately 0.5 days. Hyaluronidase human increases permeability of the subcutaneous tissue by temporarily depolymerizing hyaluronan. 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 to 48 hours.

Hyaluronidase human has been shown to increase the absorption rate of a rituximab product into the systemic circulation when given in the subcutis of Göttingen Minipigs.

12.2 Pharmacodynamics

Peripheral B-cell counts declined to levels below normal following a dose of rituximab by intravenous infusion. In patients treated with rituximab for hematological malignancies, B cell recovery began within 6 months of treatment and generally returned to normal levels within 12 months after completion of therapy, although in some patients this may take longer.

Follicular Lymphoma (FL)

Peripheral B-cell counts decline to levels below normal following the first cycle of rituximab and are maintained during treatment with RITUXAN HYCELA. After stopping RITUXAN HYCELA treatment, B-cell repletion followed similar kinetics to that of rituximab with B-cell repletion beginning after 6 months of stopping treatment, although in some patients this may take longer.

Chronic Lymphocytic Leukemia (CLL)

Following the first cycle of treatment of rituximab, B-cells begin to deplete, with 28% of patients B-cell depleted at pre-dose Cycle 2 in the SAWYER study. An increase in the proportion of B-cell depleted patients was observed with subsequent cycles of RITUXAN HYCELA and by Cycle 6, 96% of patients were depleted. Patients remained B-cell depleted until the month 9 follow-up visit, where signs of repletion were seen.

12.3 Pharmacokinetics

The geometric mean rituximab exposures are provided in Table 4. The pharmacokinetic properties of rituximab following the administration of RITUXAN HYCELA in the approved indications are provided in Table 5. The elimination of rituximab was characterized by a time-dependent process that occurred early in therapy and a time-independent process.

Table 4: Rituximab Exposure Values following Subcutaneous Administration of RITUXAN HYCELA[a]

		Study[b]	Cycle	Rituximab
FL[c]	C_{max}, mcg/mL (CV%)	SABRINA	7	237 (29.4)
			18	156 (24.7)[e]
	C_{trough}, mcg/mL (CV%)		7	122.2 (55.3)
			18	45.5 (53.6)[e]
	AUC_{TAU}, mcg•day/mL (CV%)		7	3779 (33.7)
			18	5000 (34.3)[e]
CLL[d]	C_{max}, mcg/mL (CV%)	SAWYER	6	202 (36.1)
	C_{trough}, mcg/mL (CV%)		5	97.5 (42.6)
	AUC_{TAU}, mcg•day/mL (CV%)		5	4088 (34.2)

[a] Pharmacokinetic parameters are presented as geometric mean unless otherwise specified.
[b] For study design information, see *Clinical Studies (14).*
[c] RITUXAN HYCELA 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human)
[d] RITUXAN HYCELA 1,600 mg/26,800 Units (1,600 mg rituximab and 26,800 Units hyaluronidase human)
[e] Based on predicted values

In the SABRINA study, the geometric mean C_{trough} in the RITUXAN HYCELA arm was higher than in the rituximab arm with a geometric mean ratio (C_{trough}, RITUXAN HYCELA/C_{trough}, rituximab) of 1.52 (90% CI: 1.36, 1.70) at Cycle 7 *[see Clinical Studies (14.1)]*. In the SAWYER study, the geometric mean C_{trough} in the RITUXAN HYCELA arm was higher than in the rituximab arm with an adjusted geometric mean ratio of 1.53 (90% CI: 1.27–1.85) at Cycle 5 *[see Clinical Studies (14.3)]*.

Table 5: Pharmacokinetic Parameters of Rituximab following Subcutaneous Administration of RITUXAN HYCELA[a]

	FL	CLL
Absorption		
Absolute Bioavailability[b]	0.646 (0.634–0.659[d])	0.634 (0.602–0.665[d])
Distribution		
Volume of Central compartment (L)	4.06 (26)	4.80 (18)
Apparent Volume of Distribution at steady state[c] (L)	8.09 (19)	8.52 (13)
Elimination		
Terminal Half-life (days)	34.1 (27)	32 (24)
Clearance (L/day)	0.18 (34)	0.204 (31)

[a] Parameters represented as geometric mean (%CV) unless otherwise specified
[b] Compared to a rituximab product administered intravenously
[c] Volume of central compartment and peripheral compartment
[d] 95% CI

Specific Populations

The pharmacokinetics of rituximab and hyaluronidase human in children and adolescents is unknown. The effect of either renal or hepatic impairment on the pharmacokinetics of rituximab and hyaluronidase human is unknown.

Drug Interaction Studies

The drug interaction potential of rituximab and hyaluronidase human is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long term animal studies have been performed to establish the carcinogenic or mutagenic potential of RITUXAN HYCELA or rituximab, or to determine potential effects on fertility in males or females.

RITUXAN HYCELA contains hyaluronidase human. Hyaluronidases are found in most tissues of the body. Long-term animal studies have not been performed to assess the carcinogenic or mutagenic potential of hyaluronidase human. In addition, when hyaluronidase human was administered to cynomolgus monkeys for 39 weeks at dose levels up to 220,000 U/kg, which is > 90 times higher than the human dose, no evidence of toxicity to the male or female reproductive system was found through periodic monitoring of in-life parameters, e.g., semen analyses, hormone levels, menstrual cycles, and also from gross pathology, histopathology and organ weight data.

14 CLINICAL STUDIES

14.1 Follicular Lymphoma

The SABRINA study [NCT01200758] was a randomized, two-stage, open-label, multicenter study that enrolled a total of 410 patients with previously untreated, CD20-positive follicular lymphoma of Grade 1, 2 or 3a requiring therapy. The study design is identical in stage 1 and 2. Patients were randomized (1:1) to receive either a rituximab product by intravenous infusion 375 mg/m^2 for 8 cycles or 1 cycle of a rituximab product by intravenous infusion 375 mg/m^2 followed by 7 cycles of RITUXAN HYCELA 1,400mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) both every 3 weeks in combination with a total of 6–8 cycles of CHOP or 8 cycles of CVP chemotherapy. Patients underwent interim staging after 4 cycles. Patients who received R-CHOP and achieved a CR, CRu, PR or SD at the interim assessment could receive either 4 more cycles of R-CHOP or 2 cycles of R-CHOP followed by 2 cycles of monotherapy with rituximab product or RITUXAN HYCELA depending on randomization arm (i.e., a total of 8 cycles of rituximab product or RITUXAN HYCELA). Patients with at least a PR after combination treatment with chemotherapy continued

with single agent maintenance treatment administered every 8 weeks for 24 months with rituximab product or RITUXAN HYCELA as per their randomization (i.e., total of 12 cycles of maintenance treatment).

Randomization was stratified by: underlying chemotherapy backbone (CHOP vs CVP), Follicular Lymphoma International Prognostic Index (FLIPI) (low-risk vs. intermediate-risk vs. high-risk), and region (Europe and North America vs. South and Central America vs Asia).
The main outcome measure for Stage 1 was the estimated ratio of observed rituximab serum $C_{trough\ SC}/C_{trough\ IV}$ at Cycle 7 of combination treatment with chemotherapy every 3 weeks. The main outcome measure for Stage 2 was the investigator-assessed ORR consisting of CR, CRu, and PR at the completion of combination treatment with chemotherapy. Additional outcome measures were CRR (CR and CRu) at the end of completion of combination treatment with chemotherapy, ORR and CRR at the end of completion of maintenance treatment, and time-to-event endpoints (progression-free survival (PFS), and overall survival (OS)).

Of all randomized patients, the median age was 57 years (range: 28 to 86), 53% were female, and 86% were White. The median BSA was 1.83 m^2. 45% had high risk or 34% had intermediate risk FLIPI score, and 54% had Ann Arbor Stage IV disease. Ninety percent of patients completed all 8 cycles of combination treatment with chemotherapy, and 70% of patients completed 20 cycles of both combination and maintenance treatment. Median treatment duration was 27.1 months in both groups. The median number of cycles received was 20 in both groups.

The pharmacokinetic results for the primary endpoint in Stage 1, rituximab C_{trough} at Cycle 7 (i.e., 21 days after Cycle 7 rituximab administration), demonstrated that RITUXAN HYCELA 1,400 mg/23,400 Units was non-inferior compared with rituximab at 375 mg/m^2 in patients receiving combination treatment with chemotherapy *[see Clinical Pharmacology (12.3)]*. The efficacy results are presented in Table 6.

Table 6: Efficacy in Patients with Previously Untreated Follicular Lymphoma (SABRINA Study)

	RITUXAN HYCELA N=205	Rituximab N=205
Overall Response Rate at End of combination treatment with chemotherapy[a,*]		
Number of responders (CR/CRu, PR)	173	174
Overall response (CR/CRu, PR) rate (%, [95% CI])	84% [79;89]	85% [79;90]
Difference in overall response rates[b] [95% CI]	-0.5% [-7.7;6.8]	
Number of complete responders (CR/CRu)	66	65
Complete response (CR/CRu) rate (%, [95% CI])	32% [26;39]	32% [25;39]
Difference in complete response rates[b] [95% CI]	0.0% [-9.3;9.3]	
Overall Response Rate at End of Maintenance		
Number of patients treated in maintenance (n)	172	178
Number of responders (CR/CRu, PR)	134	139
Overall response (CR/CRu, PR) rate (%, [95% CI])	78% [71;84]	78% [71;84]
Difference in overall response rates[b] [95% CI]	-0.2 [-9.2;8.8]	
Number of complete responders (CR/CRu)	87	103
Complete response (CR/CRu) rate (%, [95% CI])	51% [43;58]	58% [50;65]
Difference in complete response rates[b] [95% CI]	-7.3 [-18.0;3.5]	
Progression-free survival[c]		
Number of patients with event	65 (32%)	71 (35%)
Hazard Ratio [95% CI] (unstratified Cox model)	0.90 [0.64;1.26]	
Overall survival		
Number of patients with event	18 (8.8%)	26 (12.7%)
Hazard Ratio [95% CI] (unstratified Cox model)	0.70 [0.38;1.27]	

[a] Stage 2 main outcome measure was ORR at the end of combination treatment with chemotherapy; however pooled results which were preplanned are presented in this Table.
Response rates based on investigator assessment.
Response rates at end of maintenance based on patients who received at least one cycle of maintenance treatment (n).
[b] Difference in response rates (RITUXAN HYCELA minus rituximab).
[c] At time of final analysis (median follow-up 4.8 years).
* Investigator-assessed ORR (comprising CR, CRu and PR).

14.2 Diffuse Large B-Cell Lymphoma (DLBCL)

The MabEase study [NCT01649856] enrolled a total of 576 patients with previously untreated CD20-positive DLBCL. Patients were randomized (2:1) to receive either a rituximab product by intravenous infusion, 375 mg/m^2 for 8 cycles or 1 cycle of a rituximab product by intravenous infusion 375 mg/m^2 followed by 7 cycles of RITUXAN HYCELA 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human), both in combination with up to 6–8 cycles of CHOP chemotherapy, every 14 (CHOP-14) or 21 days (CHOP-21). Randomization was stratified by: age (< 60 years, ≥ 60 years), International Prognostic Index (IPI) risk category (low, low-intermediate, high-intermediate, high), and chemotherapy regimen (CHOP-21 or CHOP-14). The main outcome measure was investigator-assessed complete response rate (CR/CRu) at the end of combination treatment with chemotherapy. Additional outcome measures were time-to-event endpoints (PFS and OS).

Of all randomized patients, the median age was 64 years (range: 18 to 80 years); 54% were male; and 79% were White. The median BSA was 1.83 m$^{2.}$ 31% low risk or 30% low intermediate risk IPI score, 24% high intermediate risk, or 15% high risk IPI score and 42% of patients had Ann Arbor Stage IV disease. A total of 470 patients (82%) received 8 cycles of treatment. Median duration of exposure to treatment was 4.9 months in

both treatment groups. The median number of administrations/cycles (RITUXAN HYCELA or rituximab) was 8 in both groups.

The efficacy results for are presented in Table 7. The median observation time was approximately 28 months.

Table 7: Efficacy in Patients with Previously Untreated DLBCL (MabEase Study)

	RITUXAN HYCELA N=381	**Rituximab N=195**
Complete Response Rate (CR/CRu)*		
Number achieving CR/CRu[a]	179	82
Cr/CRu rate (%, [95% CI])	47% [42;52]	42% [35;49]
Difference in rates [95% CI][b]	4.9% [-3.6;13.5]	
Progression-free survival[c]		
Number of patients with event	104 (27%)	44 (23%)
Hazard Ratio [95% CI] (unstratified Cox model)	1.22 [0.85;1.73]	
Overall survival[d]		
Number of patients with event	63 (17%)	29 (15%)
Hazard Ratio [95% CI] (unstratified Cox model)	1.08 [0.70;1.68]	

[a] Four patients in the RITUXAN HYCELA group and 1 patient in the rituximab group had their response downgraded due to their bone marrow data.
[b] Difference in response rates (RITUXAN HYCELA minus rituximab).
[c] Progression-free survival is defined as the time from randomization to the first occurrence of disease progression or relapse, or death from any cause.
[d] Overall survival is defined as the time from randomization until death from any cause.
* Investigator-assessed.

14.3 Chronic Lymphocytic Leukemia (CLL)

The SAWYER study [NCT01292603] was a randomized, two-part, open-label, multicenter study that enrolled a total of 176 patients with previously untreated CLL. Patients were randomized (1:1) to receive either a rituximab product by intravenous infusion, 375 mg/m^2, in Cycle 1 followed by up to 5 cycles of rituximab, 500 mg/m^2, or rituximab, 375 mg/m^2, in Cycle 1 followed by subsequent cycles (2–6) of RITUXAN HYCELA 1,600 mg /26,800 Units (1,600 mg rituximab and 26,800 Units hyaluronidase human), both in combination with fludarabine and cyclophosphamide (FC) chemotherapy. The main outcome measure was the non-inferiority of the pharmacokinetic profile of RITUXAN HYCELA compared to rituximab. An additional outcome measure in Part 2 was investigator-assessed response rate.

The median age was 60 years (range: 25 to 78); 65% were males and 96% were White. The median BSA was 1.9 m^2, 62% had Binet Stage B disease and 93% had typical CLL characterization.

The pharmacokinetic results demonstrated that RITUXAN HYCELA 1,600mg/26,800 Units serum rituximab C_{trough} level was non-inferior compared with rituximab at 500 mg/m^2 in patients receiving combination treatment with chemotherapy *[see Clinical Pharmacology (12.3)]*.

The efficacy results for Part 2 are presented in Table 8.

Table 8: Efficacy in Patients with Previously Untreated CLL (SAWYER Study)

	Part 2

		RITUXAN HYCELA (N = 88)	Rituximab (N = 88)
ORR[a]	Point estimate	85.2% (n = 75)	80.7% (n = 71)
	95% CI	[76.1%, 91.9%]	[70.9%, 88.3%]
CRR[a]	Point estimate	27.3% (n = 24)	31.8% (n = 28)
	95% CI	[18.3%, 37.8%]	[22.3%, 42.6%]
PFS[b]	Proportion with PFS event	34.1% (n = 30)	42.0% (n = 37)
	HR 95% CI	0.76 [0.47%, 1.23%]	

ORR – Overall Response Rate
CRR – Complete Response Rate
PFS – Progression-Free Survival
[a]At 3 month follow-up visit (Part 2). Investigator-assessed.
[b]At time of final analysis (median follow-up 4.4 years). Investigator-assessed.

14.4 Patient Experience

Previously untreated adult patients outside of the United States with CD20+ diffuse large B-cell lymphoma (DLBCL) or CD20+ follicular non-Hodgkin's lymphoma (FL) Grades 1, 2, or 3a were randomized to receive a standard chemotherapy regimen (CHOP, CVP, or bendamustine) and either RITUXAN HYCELA 1,400mg/23,400 Units at Cycles 2–4 (after the first cycle with intravenous rituximab) or a rituximab product by intravenous infusion at Cycles 1–4. After the fourth cycle, patients were crossed over to the alternative route of administration for the remaining 4 cycles. After Cycle 8, 477 of 620 patients (77%) reported preferring subcutaneous administration of RITUXAN HYCELA over intravenous rituximab and the most common reason was that administration required less time in the clinic. After Cycle 8, 66 of 620 patients (11%) preferred rituximab intravenous administration and the most common reason was that it felt more comfortable during administration. Forty eight of 620 patients (7.7%) had no preference for the route of administration. Twenty nine subjects of 620 (4.7%) received Cycle 8 but did not complete the preference questionnaire.

16 HOW SUPPLIED/STORAGE AND HANDLING

RITUXAN HYCELA (rituximab and hyaluronidase human) injection, for subcutaneous use is supplied as a sterile preservative-free liquid solution in a single-dose vial. The following configurations are available:

Individually packaged single-dose vials:

- RITUXAN HYCELA 1,400 mg/23,400 Units (NDC 50242-108-01) providing 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL
- RITUXAN HYCELA 1,600 mg/26,800 Units (NDC 50242-109-01) providing 1,600 mg rituximab and 26,800 Units hyaluronidase human per 13.4 mL

Storage

Store RITUXAN HYCELA vials in the refrigerator at 2ºC to 8ºC (36ºF to 46ºF) in the original carton to protect from light. Do not freeze.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Severe Mucocutaneous Reactions

Advise patients to contact their healthcare provider immediately for symptoms of severe mucocutaneous reactions, including painful sores or ulcers on the lips or mouth, blisters, peeling skin, rash, and pustules *[see Warnings and Precautions (5.1)]*.

Hepatitis B Virus Reactivation

Advise patients to contact their healthcare provider immediately for symptoms of hepatitis including worsening fatigue or yellow discoloration of skin or eyes *[see Warnings and Precautions (5.2)]*.

Progressive Multifocal Leukoencephalopathy (PML)

Advise patients to contact their healthcare provider immediately for signs and symptoms of PML, including new or changes in neurological symptoms such as confusion, dizziness or loss of balance, difficulty talking or walking, decreased strength or weakness on one side of the body, or vision problems *[see Warnings and Precautions (5.3)]*.

Hypersensitivity and Other Administration Reactions

Inform patients about the signs and symptoms of hypersensitivity and administration-related reactions. Advise patients to contact their healthcare provider immediately to report symptoms of administration-related reactions including dizziness, nausea, chills, fever, vomiting, diarrhea, urticaria, angioedema, breathing problems, or chest pain *[see Warnings and Precautions (5.4)]*.

Tumor Lysis Syndrome (TLS)

Advise patients to contact their healthcare provider immediately for signs and symptoms of tumor lysis syndrome such as nausea, vomiting, diarrhea, and lethargy *[see Warnings and Precautions (5.5)]*.

Infections

Advise patients to contact their healthcare provider immediately for signs and symptoms of infections including fever, cold symptoms (e.g., rhinorrhea or laryngitis), flu symptoms (e.g., cough, fatigue, body aches), earache or headache, dysuria, cold sores, and painful wounds with erythema *[see Warnings and Precautions (5.6)]*

Cardiovascular Adverse Reactions

Advise patients of the risk of cardiovascular adverse reactions, including ventricular fibrillation, myocardial infarction, and cardiogenic shock. Advise patients to contact their healthcare provider immediately to report chest pain and irregular heartbeats. *[see Warnings and Precautions (5.7)]*

Renal Toxicity

Advise patients of the risk of renal toxicity. Inform patients of the need for healthcare providers to monitor kidney function *[see Warnings and Precautions (5.8)]*.

Bowel Obstruction and Perforation

Advise patients to contact their healthcare provider immediately for signs and symptoms of bowel obstruction and perforation, including severe abdominal pain or repeated vomiting *[see Warnings and Precautions (5.9)]*.

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.11), Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential to use effective contraception during treatment with RITUXAN HYCELA and for 12 months after the last dose of of rituximab-containing products, including RITUXAN HYCELA *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with RITUXAN HYCELA and for 6 months after the last dose *[see Use in Specific Populations (8.2)]*.

RITUXAN HYCELA® [rituximab and hyaluronidase human]

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
US License No.: 1048

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MEDICATION GUIDE
RITUXAN HYCELA® [rih-TUKS-an hye-SELL-uh]
(rituximab and hyaluronidase human)
injection

What is the most important information I should know about RITUXAN HYCELA?

RITUXAN HYCELA can cause serious side effects that can lead to death, including:

- **Severe skin and mouth reactions.** Tell your healthcare provider or get medical help right away if you get any of these symptoms at any time during your treatment with RITUXAN HYCELA:
  - painful sores or ulcers on your skin, lips or in your mouth
  - blisters
  - peeling skin
  - rash
  - pustules
- **Hepatitis B virus (HBV) reactivation.** Before you receive RITUXAN HYCELA, your doctor will do blood tests to check for HBV infection. If you have had hepatitis B or are a carrier of hepatitis B virus, receiving RITUXAN HYCELA could cause the virus to become an active infection again. Hepatitis B reactivation may cause serious liver problems including liver failure, and death. Your healthcare provider will monitor you for hepatitis B infection during and for several months after you stop receiving RITUXAN HYCELA.

  Tell your healthcare provider right away if you get worsening tiredness, or yellowing of your skin or white part of your eyes during treatment with RITUXAN HYCELA.
- **Progressive Multifocal Leukoencephalopathy (PML)**. PML is a rare, serious brain infection caused by a virus that can happen in people who receive RITUXAN HYCELA. People with weakened immune systems can get PML. PML can result in death or severe disability. There is no known treatment, prevention, or cure for PML.

  Tell your healthcare provider right away if you have any new or worsening symptoms or if anyone close to you notices these symptoms:
  - confusion
  - dizziness or loss of balance
  - difficulty walking or talking
  - decreased strength or weakness on one side of your body
  - vision problems, such as blurred vision or loss of vision
- **Serious allergic reactions and other severe reactions.**

  Serious allergic reactions, and reactions due to release of certain substances by your body that can lead to death, can happen with rituximab products, including RITUXAN HYCELA.

  Skin reactions at or near the injection site (local), including injection site reactions, can happen with RITUXAN HYCELA. Symptoms at or near the injection site may include: pain, swelling, hardness, redness, bleeding, itching, and rash. These reactions sometimes happen more than 24 hours after an injection of RITUXAN HYCELA.

  Tell your healthcare provider or get medical help right away if you get any of these symptoms during or after an injection of RITUXAN HYCELA:
  - hives (red itchy welts) or rash
  - itching
  - swelling of your lips, tongue, throat or face
  - sudden cough
  - shortness of breath, difficulty breathing, or wheezing
  - weakness
  - dizziness or feel faint
  - palpitations (feel like your heart is racing or fluttering)
  - chest pain
  - fever
  - chills or shaking chills

See **"What are the possible side effects of RITUXAN HYCELA?"** for more information about side effects.

What is RITUXAN HYCELA?

RITUXAN HYCELA is a prescription medicine used to treat adults with:

- **Follicular Lymphoma (FL): alone or with certain chemotherapy medicines.**
- **Diffuse Large B-Cell Lymphoma (DLBCL):** with certain other chemotherapy medicines in people who have not had previous treatment for their DLBCL.
- **Chronic Lymphocytic Leukemia (CLL):** with the chemotherapy medicines fludarabine and cyclophosphamide.

You can only receive RITUXAN HYCELA after you receive at least 1 full dose of a rituximab product by IV infusion. Read the rituximab by IV infusion Medication Guide for more information about severe infusion reactions, which usually happen during the first dose with a rituximab product given by IV infusion.

RITUXAN HYCELA is not for use to treat medical conditions other than cancers.

It is not known if RITUXAN HYCELA is safe and effective in children.

Before you receive RITUXAN HYCELA, tell your healthcare provider about all of your medical conditions, including if you:

- have had a severe reaction to a rituximab product or RITUXAN HYCELA
- have a history of heart problems, irregular heart beat or chest pain
- have lung or kidney problems
- have an infection or weakened immune system
- have or have had any severe infections including:
  - Hepatitis B virus (HBV)
  - Hepatitis C virus (HCV)
  - Cytomegalovirus (CMV)
  - Herpes simplex virus (HSV)
  - Parvovirus B19
  - Varicella zoster virus (chickenpox or shingles)
  - West Nile Virus
- have had a recent vaccination or are scheduled to receive vaccinations. You should not receive certain vaccines before or during treatment with RITUXAN HYCELA.
- are pregnant or plan to become pregnant. RITUXAN HYCELA may harm your unborn baby.

  Females who are able to become pregnant:
  - Your healthcare provider should check to see if you are pregnant before you receive RITUXAN HYCELA.
  - You should use effective birth control (contraception) during treatment with RITUXAN HYCELA and for **12 months** after the last dose of RITUXAN HYCELA. Talk to your healthcare provider about effective birth control.
  - Tell your healthcare provider if you become pregnant or think you may be pregnant during treatment with RITUXAN HYCELA.
- are breastfeeding or plan to breastfeed. RITUXAN HYCELA may pass into your breast milk. Do not breastfeed during treatment and for **6 months** after your last dose of RITUXAN HYCELA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive RITUXAN HYCELA?

- RITUXAN HYCELA is given as an injection under the skin, in the stomach-area (abdomen).
- RITUXAN HYCELA is injected over 5 or 7 minutes.
- Your healthcare provider will prescribe medicines before the injection of RITUXAN HYCELA to help reduce side effects such as fever and chills.
- Your healthcare provider should monitor you for side effects for at least 15 minutes after you receive an injection of RITUXAN HYCELA.
- If you have CLL, your healthcare provider should prescribe medicines to help prevent certain infections during treatment and for up to 12 months following treatment with RITUXAN HYCELA.

Before each injection of RITUXAN HYCELA treatment, your healthcare provider or nurse will ask you questions about your general health. Tell your healthcare provider or nurse about any new symptoms.

What are possible side effects of RITUXAN HYCELA?

RITUXAN HYCELA can cause serious side effects, including:

- See "What is the most important information I should know about RITUXAN HYCELA?"
- **Tumor Lysis Syndrome (TLS)**. TLS is caused by the fast breakdown of cancer cells. TLS can cause you to have:
  - kidney failure and the need for dialysis treatment
  - abnormal heart rhythm

  TLS can happen within 12 to 24 hours after an injection of RITUXAN HYCELA. Your healthcare provider may do blood tests to check you for TLS. Your healthcare provider may give you medicine to help prevent TLS.

  Tell your healthcare provider right away if you have any of the following signs or symptoms of TLS:
  - nausea
  - vomiting
  - diarrhea
  - lack of energy
- **Serious infections.** Serious infections can happen during and after treatment with RITUXAN HYCELA, and can lead to death. Rituximab products can increase your risk of getting infections **and** can lower the ability of your immune system to fight infections. Types of serious infections that can happen with RITUXAN HYCELA include bacterial, fungal, and viral infections. After receiving RITUXAN HYCELA, some people have developed low levels of certain antibodies in their blood for a long period of time (longer than 11 months). Some of these people with low antibody levels developed infections. Tell your healthcare provider right away if you have any symptoms of infection:
  - fever
  - cold symptoms, such as runny nose or sore throat that do not go away
  - flu symptoms, such as cough, tiredness, and body aches
  - earache or headache
  - pain during urination
  - white patches in the mouth or throat
  - cuts, scrapes or incisions that are red, warm, swollen or painful
- **Heart problems.** RITUXAN HYCELA may cause chest pain, irregular heartbeats, and heart attack. Your healthcare provider may monitor your heart during and after treatment with RITUXAN HYCELA if you have symptoms of heart problems or have a history of heart problems. Tell your healthcare provider right away if you have chest pain or irregular heartbeats during treatment with RITUXAN HYCELA.
- **Kidney problems** RITUXAN HYCELA can cause severe kidney problems that can lead to death. Your healthcare provider should do blood tests to check how well your kidneys are working.
- **Stomach and serious bowel problems that can sometimes lead to death.** Bowel problems, including blockage or tears in the bowel, can happen if you receive RITUXAN HYCELA with chemotherapy medicines. Tell your healthcare provider right away if you have severe stomach-area (abdomen) pain or repeated vomiting during treatment with RITUXAN HYCELA.

Your healthcare provider will stop treatment with RITUXAN HYCELA if you have severe, serious or life-threatening side effects.

The most common side effects of RITUXAN HYCELA in people with Follicular Lymphoma (FL) include: infections, low white blood cell count, nausea, constipation, cough, and tiredness.

The most common side effects of RITUXAN HYCELA in people with Diffuse Large B-cell Lymphoma (DLBCL) include: infections, low white blood cell count, loss of hair, nausea, and low red blood cell count.

The most common side effects of RITUXAN HYCELA in people with Chronic Lymphocytic Leukemia (CLL) include: infections, low white blood cell count, nausea, low platelet count, fever, vomiting, and injection site redness.

These are not all of the possible side effects with RITUXAN HYCELA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of RITUXAN HYCELA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about RITUXAN HYCELA that is written for health professionals.

What are the ingredients in RITUXAN HYCELA?

Active ingredient: rituximab and hyaluronidase human.

Inactive ingredients: L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, α,α-trehalose dihydrate, and Water for Injection.

Manufactured by: Genentech, Inc., A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990
U.S. License No.: 1048
Jointly marketed by: Biogen and Genentech USA, Inc.
RITUXAN HYCELA® is a registered trademark of Biogen.
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For more information, go to www.RITUXANHYCELA.com or call 1-877-436-3683.

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 6/2021

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RITUXAN HYCELA safely and effectively. See full prescribing information for RITUXAN HYCELA.

RITUXAN HYCELA® (rituximab and hyaluronidase human) injection, for subcutaneous use
Initial U.S. Approval: 2017

WARNING: SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
See full prescribing information for complete boxed warning.
- **Severe mucocutaneous reactions, some with fatal outcomes (5.1).**
- **Hepatitis B virus reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death (5.2).**
- **Progressive multifocal leukoencephalopathy resulting in death (5.3).**

----------RECENT MAJOR CHANGES----------
Dosage and Administration, Preparation and Administration (2.6) 06/2021

INDICATIONS AND USAGE
RITUXAN HYCELA is a combination of rituximab, a CD20-directed cytolytic antibody, and hyaluronidase human, an endoglycosidase, indicated for the treatment of adult patients with:
- Follicular Lymphoma (FL) (1.1)
  - Relapsed or refractory, follicular lymphoma 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
- Diffuse Large B-cell Lymphoma (DLBCL) (1.2)
  - Previously untreated diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens
- Chronic Lymphocytic Leukemia (CLL) (1.3)
  - Previously untreated and previously treated CLL in combination with fludarabine and cyclophosphamide (FC)

Limitations of Use:
- Initiate treatment with RITUXAN HYCELA only after patients have received at least one full dose of a rituximab product by intravenous infusion. (1.4, 2.1, 5.4).
- RITUXAN HYCELA is not indicated for the treatment of non-malignant conditions. (1.4)

DOSAGE AND ADMINISTRATION
- **For subcutaneous use only** (2.1)
- All patients must receive at least one full dose of a rituximab product by intravenous infusion before receiving RITUXAN HYCELA by subcutaneous injection (2.1).
- FL/DLBCL: Administer 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) subcutaneously according to recommended schedule (2.2, 2.3).
- CLL: Administer 1,600 mg/26,800 Units (1,600 mg rituximab and 26,800 Units hyaluronidase human) subcutaneously according to recommended schedule (2.4).
- Premedicate with acetaminophen and antihistamine before each dose; In addition, consider premedication with glucocorticoids (2.5, 5.4)
- Administer specified volume into subcutaneous tissue of abdomen: (2.6)
  - 11.7 mL from 1,400 mg/23,400 Units vial over approximately 5 minutes.
  - 13.4 mL from 1,600 mg/26,800 Units vial over approximately 7 minutes.
  - Observe 15 minutes following administration

DOSAGE FORMS AND STRENGTHS
Injection: (3)
- 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL (120 mg/2,000 Units per mL) solution in a single-dose vial
- 1,600 mg rituximab and 26,800 Units hyaluronidase human per 13.4 mL (120 mg/2,000 Units per mL) solution in a single-dose vial

CONTRAINDICATIONS
None. (4)

WARNINGS AND PRECAUTIONS
- Hypersensitivity and other administration reactions: Local cutaneous reactions may occur more than 24 hours after administration. Interrupt injection if severe reaction develops. Premedicate before injection. (5.4)
- Tumor lysis syndrome: Administer aggressive intravenous hydration, anti hyperuricemic agents, monitor renal function. (5.5)
- Infections: Withhold and institute appropriate anti-infective therapy. (5.6)
- Cardiac adverse reactions: Discontinue in case of serious or life-threatening events. (5.7)
- Renal toxicity: Discontinue in patients with rising serum creatinine or oliguria. (5.8)
- Bowel obstruction and perforation: Consider and evaluate for abdominal pain, vomiting, or related symptoms. (5.9)
- Immunizations: Live virus vaccinations prior to or during treatment not recommended. (5.10)
- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.11)

ADVERSE REACTIONS
Most common adverse reactions (incidence of ≥ 20%) are: (6.1)
- FL: infections, neutropenia, nausea, constipation, cough, and fatigue
- DLBCL: infections, neutropenia, alopecia, nausea, and anemia
- CLL: infections, neutropenia, nausea, thrombocytopenia, pyrexia, vomiting, and injection site erythema

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS----------
Renal toxicity when used in combination with cisplatin. (5.8)

USE IN SPECIFIC POPULATIONS
- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: 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 *[see Warnings and Precautions (5.1)]*.
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 *[see Warnings and Precautions (5.2)]*.
Progressive Multifocal Leukoencephalopathy (PML), including fatal PML, can occur in patients receiving rituximab-containing products, including RITUXAN HYCELA *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*.
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1.3 Chronic Lymphocytic Leukemia (CLL)
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FULL PRESCRIBING INFORMATION

WARNING: 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 *[see Warnings and Precautions (5.1)]*.

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 *[see Warnings and Precautions (5.2)]*.

Progressive Multifocal Leukoencephalopathy (PML), including fatal PML, can occur in patients receiving rituximab-containing products, including RITUXAN HYCELA *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*.

1 INDICATIONS AND USAGE

1.1 Follicular Lymphoma (FL)

RITUXAN HYCELA is indicated for the treatment of adult patients with:

- Relapsed or refractory, follicular lymphoma 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.

1.2 Diffuse Large B-Cell Lymphoma (DLBCL)

RITUXAN HYCELA is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens.

1.3 Chronic Lymphocytic Leukemia (CLL)

RITUXAN HYCELA is indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of adult patients with previously untreated and previously treated CLL.

1.4 Limitations of Use

- Initiate treatment with RITUXAN HYCELA only after patients have received at least one full dose of a rituximab product by intravenous infusion *[see Dosage and Administration (2.1) and Warnings and Precautions (5.4)]*.
- RITUXAN HYCELA is not indicated for the treatment of non-malignant conditions.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Information

RITUXAN HYCELA is for subcutaneous use only. RITUXAN HYCELA should only be administered by a healthcare professional with appropriate medical support to manage severe reactions that can be fatal if they occur.

All patients must first receive at least one full dose of a rituximab product by intravenous infusion without experiencing severe adverse reactions before starting treatment with RITUXAN HYCELA. If patients are not

able to receive one full dose by intravenous infusion, they should continue subsequent cycles with a rituximab product by intravenous infusion and not switch to RITUXAN HYCELA until a full intravenous dose is successfully administered *[see Warnings and Precautions (5.4)]*.

Refer to the prescribing information for a rituximab product for intravenous infusion for additional information.

Premedicate before each dose of RITUXAN HYCELA *[see Dosage and Administration (2.5)]*.

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.

2.2 Recommended Dosage for Follicular Lymphoma (FL)

All patients must receive at least one full dose of a rituximab product by intravenous infusion before starting treatment with RITUXAN HYCELA *[see Dosage and Administration (2.1) and Warnings and Precautions (5.4)]*. Premedicate before each dose *[see Dosage and Administration (2.5)]*.

The recommended dose is RITUXAN HYCELA 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) subcutaneously at a fixed dose irrespective of patient's body surface area according to the following schedules:

- **Relapsed or Refractory, Follicular Lymphoma**
  Administer once weekly for 3 or 7 weeks following a full dose of a rituximab product by intravenous infusion at week 1 (i.e., 4 or 8 weeks in total).
- **Retreatment for Relapsed or Refractory, Follicular Lymphoma**
  Administer once weekly for 3 weeks following a full dose of a rituximab product by intravenous infusion at week 1 (i.e., 4 weeks in total).
- **Previously Untreated, Follicular Lymphoma**
  Administer on Day 1 of Cycles 2–8 of chemotherapy (every 21 days), for up to 7 cycles following a full dose of a rituximab product by intravenous infusion on Day 1 of Cycle 1 of chemotherapy (i.e., up to 8 cycles in total). In patients with complete or partial response, initiate RITUXAN HYCELA maintenance treatment 8 weeks following completion of RITUXAN HYCELA in combination with chemotherapy. Administer RITUXAN HYCELA as a single-agent every 8 weeks for 12 doses.
- **Non-progressing, Follicular Lymphoma after first line CVP chemotherapy**
  Following completion of 6–8 cycles of CVP chemotherapy and a full dose of a rituximab product by intravenous infusion at week 1, administer once weekly for 3 weeks (i.e., 4 weeks in total) at 6 month intervals to a maximum of 16 doses.

2.3 Recommended Dosage for Diffuse Large B-Cell Lymphoma (DLBCL)

All patients must receive at least one full dose of a rituximab product by intravenous infusion in combination with CHOP chemotherapy before starting treatment with RITUXAN HYCELA *[see Dosage and Administration (2.1) and Warnings and Precautions (5.4)]*. Premedicate before each dose *[see Dosage and Administration (2.5)]*.

The recommended dose for DLBCL is RITUXAN HYCELA 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) at a fixed dose irrespective of patient's body surface area in combination with CHOP chemotherapy. Administer RITUXAN HYCELA 1,400 mg/23,400 Units on Day 1 of Cycles 2–8 of CHOP chemotherapy for up to 7 cycles following a full dose of a rituximab product by intravenous infusion at Day 1, Cycle 1 of CHOP chemotherapy (i.e., up to 6–8 cycles in total).

2.4 Recommended Dosage for Chronic Lymphocytic Leukemia (CLL)

All patients must receive at least one full dose of a rituximab product by intravenous infusion in combination with FC chemotherapy before starting treatment with RITUXAN HYCELA *[see Dosage and Administration (2.1) and Warnings and Precautions (5.4)]*. Premedicate before each dose *[see Dosage and Administration (2.5)]*.

The recommended dose for CLL is RITUXAN HYCELA 1,600 mg/26,800 Units (1,600 mg rituximab and 26,800 Units hyaluronidase human) in combination with FC chemotherapy, at a fixed dose, irrespective of patient's body surface area. Administer RITUXAN HYCELA 1,600 mg/26,800 Units on Day 1 of Cycles 2–6 (every 28 days) for a total of 5 cycles following a full intravenous dose at Day 1, Cycle 1 (i.e., 6 cycles in total).

2.5 Recommended Premedication and Prophylactic Medications

Premedicate with acetaminophen and an antihistamine before each dose of RITUXAN HYCELA. Premedication with a glucocorticoid should also be considered *[see Dosage and Administration (2.2, 2.3, 2.4)]*.

Provide prophylaxis for Pneumocystis jiroveci pneumonia (PCP) and herpes virus infections for patients with CLL during treatment and for up to 12 months following treatment as appropriate *[see Warnings and Precautions (5.6)]*.

2.6 Preparation and Administration

To prevent medication errors, check the vial labels to ensure that the drug being prepared and administered is RITUXAN HYCELA for subcutaneous use. **Do not administer RITUXAN HYCELA intravenously**.

RITUXAN HYCELA is ready to use.

Preparation

Use a sterile needle and syringe to prepare RITUXAN HYCELA. RITUXAN HYCELA is compatible with polypropylene and polycarbonate syringe material and stainless steel transfer and injection needles.

Using a 20 mL syringe, withdraw the required volume from the vial with a narrow (e.g., 25–30 gauge) needle of any length.

Label the syringe with the provided peel-off label.

Change the needle to a 1/2" to 5/8" long, narrow gauge needle (e.g., 25–30 gauge) immediately prior to subcutaneous administration to avoid needle clogging.

Visually inspect for particulate matter and discoloration prior to administration. RITUXAN HYCELA should be a clear to opalescent and colorless to yellowish liquid. Do not use if particulates or discoloration is present.

Administration

- Inject RITUXAN HYCELA into the subcutaneous tissue of the abdomen over approximately 5–7 minutes. Never inject into areas where the skin is red, bruised, tender or hard, or areas where there are moles or scars. No data are available on performing the injection at other sites of the body.

- Inject 11.7 mL of RITUXAN HYCELA 1,400 mg/23,400 Units vial (1,400 mg rituximab and 23,400 Units hyaluronidase human) subcutaneously into the abdomen over approximately 5 minutes.

- Inject 13.4 mL of RITUXAN HYCELA 1,600 mg/26,800 Units vial (1,600 mg rituximab and 26,800 Units hyaluronidase human) subcutaneously into the abdomen over approximately 7 minutes.

If administration of RITUXAN HYCELA is interrupted, continue administering at the same site, or at a different site, but restricted to the abdomen.

Observe patients for at least 15 minutes following RITUXAN HYCELA administration *[see Warnings and Precautions (5.4)]*.

During treatment with RITUXAN HYCELA, do not administer other medications for subcutaneous use at the same sites as RITUXAN HYCELA.

Storage

Use immediately.

If not used immediately store refrigerated at 2°C to 8°C (36°F to 46°F) up to 48 hours and subsequently for 8 hours at room temperature up to 30°C (86°F) in diffuse light.

3 DOSAGE FORMS AND STRENGTHS

RITUXAN HYCELA is a colorless to yellowish, clear to opalescent solution for subcutaneous injection:

- Injection: 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL (120 mg/2,000 Units per mL) in a single-dose vial.
- Injection: 1,600 mg rituximab and 26,800 Units hyaluronidase human per 13.4 mL (120 mg/2,000 Units per mL) in a single-dose vial.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 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.

5.2 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 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.

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.

5.3 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 *[see Adverse Reactions (6.1)]*.

5.4 Hypersensitivity and other Administration Reactions

Systemic Reactions

Patients must receive at least one full dose of a rituximab product by intravenous infusion before receiving RITUXAN HYCELA due to the higher risk of hypersensitivity and other acute reactions during the first infusion *[see Dosage and Administration (2.1)]*. Beginning therapy with a rituximab product by intravenous infusion allows management of hypersensitivity and other administration reactions by slowing or stopping the intravenous infusion.

Rituximab-containing products, including RITUXAN HYCELA, are associated with hypersensitivity and other administration reactions, which may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be clinically indistinguishable from acute hypersensitivity reactions.

This set of reactions which includes syndrome of cytokine release, tumor lysis syndrome and anaphylactic and hypersensitivity reactions are described below. They are not specifically related to the route of administration of a rituximab-containing product.

Severe infusion-related reactions with fatal outcome have been reported with the use of intravenous formulations of rituximab products, 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 cytokine release syndrome is characterized by severe dyspnea, often associated by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with acute respiratory failure and death *[see Warnings and Precautions (5.5)]*. Cytokine release syndrome may occur within 1–2 hours of initiating the infusion. Patients with a history of pulmonary insufficiency or those with pulmonary tumor infiltration may be at a greater risk of poor outcome. Rituximab product administration should be interrupted immediately and aggressive symptomatic treatment initiated.

During RITUXAN HYCELA administration, the injection should be interrupted immediately when observing signs of a severe reaction and aggressive symptomatic treatment should be initiated.

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 ($\geq$ 25,000/mm^3) *[see Warnings and Precautions (5.5, 5.7)]*.

Premedicate patients with an antihistamine and acetaminophen prior to each administration of RITUXAN HYCELA *[see Dosage and Administration (2.5)]*. Premedication with glucocorticoids should also be considered. Observe patients for at least 15 minutes following RITUXAN HYCELA. A longer period may be appropriate in patients with an increased risk of hypersensitivity reactions.

Local Cutaneous Reactions

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 *[see Adverse Reactions (6.1)]*. 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.

5.5 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 ($\geq$ 25,000/mm^3) 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 *[see Warnings and Precautions (5.8)]*.

5.6 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 rituximab 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 *[see Adverse Reactions (6.1)]*.

5.7 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 *[see Adverse Reactions (6.1)]*.

5.8 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 *[see Warnings and Precautions (5.5)]*.

5.9 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.

5.10 Immunization

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

5.11 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 potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with RITUXAN HYCELA and for 12 months after the last dose of rituximab-containing products, including RITUXAN HYCELA *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Mucocutaneous reactions *[see Warnings and Precautions (5.1)]*
- Hepatitis B reactivation including fulminant hepatitis *[see Warnings and Precautions (5.2)]*
- Progressive multifocal leukoencephalopathy *[see Warnings and Precautions (5.3)]*
- Hypersensitivity and other administration reactions *[see Warnings and Precautions (5.4)]*

- Tumor lysis syndrome *[see Warnings and Precautions (5.5)]*
- Infections *[see Warnings and Precautions (5.6)]*
- Cardiac arrhythmias *[see Warnings and Precautions (5.7)]*
- Renal toxicity *[see Warnings and Precautions (5.8)]*
- Bowel obstruction and perforation *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to RITUXAN HYCELA in 892 patients in four controlled trials with exposures ranging from a single injection up to 27 months of treatment.

The population included 382 patients with follicular lymphoma (FL), 369 patients with diffuse large B-cell lymphoma (DLBCL), and 141 patients with chronic lymphocytic leukemia (CLL). The median age was 60 years (range: 18–85 years, 53% were male, and 84% were White. In the SABRINA study patients with FL received a full dose of a rituximab product by intravenous infusion, followed by RITUXAN HYCELA (1,400 mg rituximab/23,400 Units hyaluronidase human), in combination with chemotherapy for up to 7 doses (i.e., total of 8 doses in combination with chemotherapy), or as monotherapy for up to 12 doses (maintenance treatment). In the MabEase study patients with DLBCL received a full dose of a rituximab product by intravenous infusion, followed by RITUXAN HYCELA (1,400 mg rituximab/23,400 Units hyaluronidase human), given in combination with chemotherapy for up to 7 doses (i.e., up to a total of 8 doses). In the SAWYER study patients with CLL on part 2 received a full dose of a rituximab product by intravenous infusion, followed by RITUXAN HYCELA (1,600 mg rituximab/26,800 Units hyaluronidase human) for up to 5 doses, in combination with fludarabine and cyclophosphamide (i.e., total of 6 doses).

The most common adverse reactions (≥ 20%) of RITUXAN HYCELA observed in patients with FL on the SABRINA study were: infections, neutropenia, nausea, constipation, cough, and fatigue.

The most common adverse reactions (≥ 20%) of RITUXAN HYCELA observed in patients with DLBCL on the MabEase study were: infections, neutropenia, alopecia, nausea, and anemia.

The most common adverse reactions (≥ 20%) of RITUXAN HYCELA observed in patients with CLL on part 2 of the SAWYER study were: infections, neutropenia, nausea, thrombocytopenia, pyrexia, vomiting, and injection site erythema.

<u>Administration-related reactions (ARRs)</u>

Administration-related reactions (ARRs) with RITUXAN HYCELA were defined as all the adverse reactions related to the administration of RITUXAN HYCELA within the 24 hours post injection.

The incidence of ARRs with RITUXAN HYCELA was 34% in FL/DLBCL in combination with chemotherapy with injection site erythema (5%), chills (3%), dyspnea, erythema, flushing, injection site pain, nausea, pruritus, pyrexia, rash, and throat irritation (2% each) being the most common ARRs. The incidence of ARRs in FL maintenance setting was 20%. The most common ARRs were injection site erythema (7%), erythema (4%), injection site pain/edema, myalgia, and rash (2% each).

The incidence of ARRs with RITUXAN HYCELA in CLL was 44%.

With the exception of Local Cutaneous Reactions, the incidence and profile of adverse reactions reported for RITUXAN HYCELA were comparable with those for rituximab. The overall incidence of adverse reactions for intravenous rituximab versus RITUXAN HYCELA in combination with chemotherapy for FL/DLBCL was 93% versus 95% (BSA ≤ 1.73 m^2), 89% versus 93% (1.73 < BSA ≤ 1.92 m^2), and 94% versus 94% (BSA > 1.92 m^2). The overall incidence of adverse reactions for rituximab versus RITUXAN HYCELA in CLL was 89% versus 100% (BSA ≤ 1.81 m^2), 97% versus 88% (1.82 < BSA ≤ 1.99 m^2), and 88% versus 93% (BSA > 2.00 m^2).

Summary of Clinical Trial Experience in Follicular Lymphoma (FL)

The data in Table 1 were obtained in the SABRINA study, a two-stage randomized, controlled study in patients with previously untreated FL. The study compared patients receiving RITUXAN HYCELA (1,400 mg rituximab/23,400 Units hyaluronidase human; n=197) with patients receiving a rituximab product by intravenous infusion (375 mg/m^2; n=210), both in combination with CHOP or CVP followed by maintenance treatment with RITUXAN HYCELA or a rituximab product by intravenous infusion.

The majority of patients completed all 8 cycles of combination treatment with chemotherapy (91% RITUXAN HYCELA vs. 90% rituximab). In addition, 69% of patients in each of the treatment groups completed all 20 cycles of combination plus maintenance treatment. In both RITUXAN HYCELA and rituximab groups, patients experienced similar median duration of exposure (27.1 months for each arm).

Across the two stages, the overall demographics and baseline characteristics were balanced between the treatment groups. However, there were more female patients (53%) randomized in the study than male patients (47%) and a higher proportion of females were randomized to receive RITUXAN HYCELA (59% female) compared with the rituximab group (48%). The treatment groups in the combined Stage 1 and 2 population were otherwise balanced in regard to baseline demographics, characterized by a median age of 57 years (56.0 years [range 28–85 years] for RITUXAN HYCELA and 57 years [range 28–86 years] for rituximab) and median BSA of 1.83 m^2 (1.80 and 1.84 m^2 for RITUXAN HYCELA and rituximab, respectively).

The incidence of all adverse reactions was 96% for RITUXAN HYCELA vs. 95% for rituximab (Table 1). Grade 3–4 adverse reactions were reported in 55% of patients receiving RITUXAN HYCELA vs. 53% in patients receiving rituximab. Serious adverse reactions were reported in 37% of patients receiving RITUXAN HYCELA vs. 34% of patients receiving rituximab. The most common adverse reactions (occurring in ≥ 20% of patients in any arm) were infections, neutropenia, nausea, constipation, cough, and fatigue.

A total of 36 patients died, including 14/197 patients (7%) who received RITUXAN HYCELA and 22/210 patients (10%) who received rituximab. Of these 36 patients, 19 patients (7 patients RITUXAN HYCELA [4%] vs. 12 patients rituximab [6%]) died due to adverse reactions and 13 patients (6 patients RITUXAN HYCELA [3%] vs. 7 patients rituximab [3%]) died due to disease progression.

The incidence of administration-related reactions (ARRs) due to the subcutaneous route of administration associated with RITUXAN HYCELA was assessed in combination with chemotherapy and during maintenance. Thirty patients (15%) experienced an ARR during the first administration of RITUXAN HYCELA (Cycle 2). Incidence of ARRs generally decreased at subsequent cycles with 18 patients (9%) reporting ARR at Cycle 3, 13 patients (7%) at Cycle 4, 11 patients (6%) at Cycles 5 and 6, 12 patients (7%) at Cycle 7, and 8 patients (4%) at Cycle 8. During RITUXAN HYCELA monotherapy in the maintenance setting the incidence of ARRs at each cycle was ≤ 7% and was observed in 24 patients (14%) overall. Grade 1–2 ARRs constituted 96% of the overall ARRs. Grade 3 ARRs were reported during the first administration of RITUXAN HYCELA at Cycle 2 by 2 patients. Of the reported ARRs, local cutaneous reactions with RITUXAN HYCELA were reported in 32 patients. These events resolved within a median of 2 days from the onset (range 1 to 37 days). Majority of these reactions were Grade 1 and 2 and were observed in 31 patients (16%).

Table 1: Incidence of Adverse Reactions in ≥ 5% of Patients with Previously Untreated Follicular Lymphoma Receiving RITUXAN HYCELA or Rituximab in Combination with CHOP or CVP and as Monotherapy for Maintenance Treatment

Body System/Adverse Reactions	RITUXAN HYCELA (n=197)		Rituximab (n=210)	
	All Grades %	Grade 3–4 %	All Grades %	Grade 3–4 %
Gastrointestinal Disorders				
Nausea	31	0	22	0
Constipation	25	0	26	< 1
Diarrhea	18	2	16	< 1
Abdominal Pain	14	0	12	< 1
Vomiting	14	0	12	< 1
Dyspepsia	8	0	7	0
Stomatitis	6	0	5	0
Abdominal Pain Upper	5	0	5	0
General Disorders and Administration Site Conditions				
Fatigue	20	0	18	< 1
Asthenia	17	1	13	0
Pyrexia	15	< 1	16	< 1
Injection Site Erythema	13	0	0	0
Injection Site Pain	8	0	0	0
Chills	8	0	9	0
Chest Pain	6	1	3	0
Edema Peripheral	5	< 1	6	0
Mucosal Inflammation	5	1	6	< 1
Influenza Like Illness	3	0	6	0
Infections				
Upper Respiratory Tract Infection	15	< 1	10	0
Pneumonia	11	5	4	2
Nasopharyngitis	10	0	10	0
Bronchitis	8	< 1	8	< 1
Urinary Tract Infection	8	1	14	< 1
Sinusitis	7	< 1	4	0
Conjunctivitis	5	0	5	0
Influenza	4	0	6	< 1
Blood and Lymphatic System Disorders				
Neutropenia	32	26	27	21
Anemia	15	5	13	0
Febrile Neutropenia	8	7	6	6
Leukopenia	6	4	11	2
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	13	< 1	10	0
Bone Pain	10	< 1	8	0
Pain In Extremity	10	0	5	0
Back Pain	9	< 1	12	< 1
Muscle Spasms	8	0	3	0
Myalgia	8	0	5	0
Nervous System Disorders				
Paresthesia	16	0	12	0
Headache	13	0	9	0
Neuropathy Peripheral	12	2	14	< 1
Dizziness	7	0	7	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	14	< 1	10	< 1
Pruritus	10	0	12	< 1
Rash	10	0	7	0
Erythema	9	0	5	0

Body System/Adverse Reactions	RITUXAN HYCELA (n=197)		Rituximab (n=210)	
	All Grades %	Grade 3–4 %	All Grades %	Grade 3–4 %
Respiratory, Thoracic and Mediastinal Disorders				
Cough	23	0	13	< 1
Dyspnea	11	1	8	2
Oropharyngeal Pain	9	0	8	0
Psychiatric Disorders				
Insomnia	9	0	9	0
Vascular Disorders				
Hypertension	6	1	6	0

Summary of Clinical Trial Experience in Diffuse Large B-Cell Lymphoma (DLBCL)

The data in Table 2 were obtained in the MabEASE study, a comparative, randomized, parallel-group, multicenter study to investigate the efficacy of RITUXAN HYCELA (1,400 mg rituximab and 23,400 Units hyaluronidase human; n=369) versus 375 mg/m^2 a rituximab product by intravenous infusion (n=203) both in combination with CHOP (R-CHOP) in previously untreated patients with CD20-positive DLBCL.

Eighty two percent of patients receiving RITUXAN HYCELA or rituximab completed all 8 cycles of study treatment. In both RITUXAN HYCELA and rituximab treatment groups, patients experienced 4.9 months median duration of rituximab exposure in each arm.

The demographic characteristics were balanced. Most patients were White (79%) and 54% were male. The median was 64 years and median BSA was 1.83 m^2.

The incidences of adverse reactions of any grade (RITUXAN HYCELA [94%] vs. rituximab [92%]) (Table 2), Grade 3–4 adverse reactions (RITUXAN HYCELA [63%] vs. rituximab [57%]), and serious adverse reactions (RITUXAN HYCELA [42%] vs. rituximab [37%]) were generally comparable between the two treatment groups. The common adverse reactions (occurring in ≥ 20% of patients in any treatment group) were neutropenia, alopecia, nausea, and anemia.

A total of 91 patients (16%) died, including 58/369 patients (16%) in RITUXAN HYCELA and 33/203 patients (16%) in rituximab. Of these patients, 44 patients (29 patients RITUXAN HYCELA [8%] vs. 15 patients rituximab [7%]) died due to adverse reactions and 35 patients (22 patients RITUXAN HYCELA [6%] vs. 13 patients rituximab [6%]) died due to disease progression. Pneumonia (4 patients RITUXAN HYCELA vs. 1 patient rituximab), septic shock (2 patients RITUXAN HYCELA vs. 3 patients rituximab), and cardiac arrest (1 patient RITUXAN HYCELA vs. 3 patients rituximab) were the most common adverse reactions leading to death.

The incidence of administration-related reactions was balanced between the RITUXAN HYCELA and rituximab groups (28% vs. 29%). Grade 1–2 ARRs constituted 97% of the overall ARRs for the RITUXAN HYCELA arm and 80% for the rituximab arm. Of the reported ARRs, local cutaneous reactions with RITUXAN HYCELA were reported in 17 patients. These events resolved within a median of 2 days from the onset (range 1 to 32 days). Majority of these reactions were Grade 1 and 2 and were observed in 16 patients (4%).

Table 2: Incidence of Adverse Reactions in ≥ 5% of Patients with Previously Untreated DLBCL Receiving RITUXAN HYCELA or Rituximab in Combination with CHOP

Body System/Adverse Reactions	RITUXAN HYCELA + CHOP (n=369)		Rituximab + CHOP (n=203)	
	All Grades %	Grade 3–4 %	All Grades %	Grade 3–4 %
Gastrointestinal Disorders				
Nausea	22	< 1	24	< 1
Constipation	15	< 1	17	< 1
Diarrhea	14	1	10	1
Vomiting	11	< 1	8	< 1
Abdominal Pain	7	< 1	7	< 1
Stomatitis	6	< 1	5	0
Dyspepsia	5	0	7	0
General Disorders and Administration Site Conditions				
Fatigue	19	1	15	1
Pyrexia	13	< 1	13	0
Asthenia	11	< 1	12	< 1
Mucosal Inflammation	8	< 1	8	1
Edema Peripheral	8	< 1	4	0
Infections				
Pneumonia	7	3	4	2
Blood and Lymphatic System Disorders				
Neutropenia	31	25	29	19
Anemia	23	5	21	4
Febrile Neutropenia	14	14	12	11
Leukopenia	7	3	7	3
Lymphopenia	5	1	6	3
Investigations				
Neutrophil Count Decreased	14	11	14	11
White Blood Cell Count Decreased	7	4	7	5
Weight Decreased	8	< 1	4	< 1
Lymphocyte Count Decreased	5	2	3	2
Metabolism and Nutrition Disorders				
Decreased Appetite	8	< 1	9	< 1
Nervous System Disorders				
Neuropathy Peripheral	12	< 1	12	0
Paresthesia	9	< 1	6	0
Headache	6	0	7	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	24	0	24	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	11	< 1	9	0
Dyspnea	6	0	4	< 1
Psychiatric Disorders				
Insomnia	7	< 1	6	< 1

Summary of Clinical Trial Experience in Chronic Lymphocytic Leukemia

The data in Table 3 were obtained in part 2 of the SAWYER study, a two-part, comparative, randomized, parallel-group, multicenter study of RITUXAN HYCELA versus a rituximab product by intravenous infusion both in combination with fludarabine and cyclophosphamide (FC) chemotherapy in patients with previously untreated CLL.

The safety analysis population in part 2 of the study included 85 patients receiving RITUXAN HYCELA (1,600 mg rituximab/26,800 Units hyaluronidase human) and 89 patients receiving 500 mg/m^2 rituximab. In both

RITUXAN HYCELA and rituximab groups, patients had similar median duration of rituximab exposure (4.9 vs. 4.7 months). The majority of patients received all 6 cycles of study treatment (86% RITUXAN HYCELA vs. 81% rituximab).

The patient population was predominantly White (96%) and male (65%), with a median age of 60 years and median BSA of 1.9 m^2 (1.97 and 1.86 m^2 for the RITUXAN HYCELA and intravenous rituximab groups, respectively). Overall, the treatment groups were balanced with respect to demographic characteristics, with the exception of more males in the RITUXAN HYCELA arm (71% RITUXAN HYCELA vs. 60% rituximab). Baseline disease characteristics were similar between the two groups. Over half of the patients (62%) had Binet Stage B disease and the majority had typical CLL characterizations (93%), with median time from first CLL diagnosis to randomization being 18.5 months.

The incidences of adverse reactions were balanced between the two treatment groups (96% RITUXAN HYCELA vs. 91% rituximab), and the common adverse reactions (occurring in ≥ 20% of patients in any arm) were infections, neutropenia, nausea, thrombocytopenia, pyrexia, anemia, vomiting, and injection site erythema. The incidences of Grade 3–4 adverse reactions were also balanced between the two treatment groups (69% RITUXAN HYCELA vs. 71% rituximab). The incidence of serious adverse reactions was 29% for RITUXAN HYCELA and 33% for rituximab. The incidence of administration-related reactions was 44% for RITUXAN HYCELA and 45% for rituximab). Of the reported ARRs, local cutaneous reactions with RITUXAN HYCELA were reported in 15 patients. These events resolved within a median of 6 days from the onset (range 3 to 29 days). Majority of these reactions were Grade 1 and 2 and were observed in 14 patients (16%).

A total of 9 patients (5%) died, including 5 patients in the RITUXAN HYCELA group and 4 patients in the rituximab group. In the RITUXAN HYCELA group, 1 patient died due to herpes zoster infection, 1 patient died as a result of progressive multifocal leukoencephalopathy (PML) (considered by the investigator as related to rituximab), and 3 patients died due to disease progression. In the rituximab group, 2 patients died due to diarrhea and listeriosis and 2 patients died due to disease progression.

Table 3: Incidence of Adverse Reactions in ≥ 5% of Patients with Previously Untreated CLL Receiving RITUXAN HYCELA or Rituximab in Combination with FC

Body System/Adverse Reactions	RITUXAN HYCELA + FC (n=85)		Rituximab + FC (n=89)	
	All Grades %	Grade 3–4 %	All Grades %	Grade 3–4 %
Gastrointestinal Disorders				
Nausea	38	1	35	0
Vomiting	21	2	22	1
Diarrhea	12	0	11	3
Abdominal Pain	9	0	6	0
Constipation	8	0	8	0
General Disorders and Administration Site Conditions				
Pyrexia	32	5	25	1
Injection Site Erythema	26	2	0	0
Injection Site Pain	16	1	0	0
Chills	13	0	10	1
Fatigue	11	0	10	0
Asthenia	8	1	17	2
Infections				
Upper Respiratory Tract Infection	13	0	12	1
Respiratory Tract Infection	8	1	4	1
Bronchitis	7	0	6	0
Urinary Tract Infection	2	0	8	1
Pneumonia	2	2	6	2
Blood and Lymphatic System Disorders				
Neutropenia	65	56	58	52
Thrombocytopenia	24	6	26	9
Leukopenia	19	14	16	12
Anemia	13	5	24	9
Febrile Neutropenia	11	8	8	8
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	9	0	1	0
Pain In Extremity	7	1	2	0
Bone Pain	6	0	2	0
Nervous System Disorders				
Headache	7	0	9	0
Skin and Subcutaneous Tissue Disorders				
Erythema	15	0	7	0
Rash	12	0	10	1
Pruritus	8	0	4	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	13	0	11	0
Oropharyngeal Pain	6	0	3	0
Dyspnea	4	0	8	1
Psychiatric Disorders				
Insomnia	1	0	7	0
Vascular Disorders				
Hypotension	1	0	7	1
Hypertension	0	0	6	1

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to RITUXAN HYCELA and rituximab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In the SABRINA study, where previously untreated patients with follicular lymphoma were treated with RITUXAN HYCELA or rituximab in combination with CVP or CHOP, the incidence of treatment-induced/enhanced anti-rituximab antibodies in the RITUXAN HYCELA group was similar to that observed in the rituximab group (2.0% RITUXAN HYCELA vs. 1.9% rituximab). The incidence of treatment-induced/enhanced anti-recombinant human hyaluronidase antibodies was 15% in the RITUXAN HYCELA group compared with 8% in the rituximab group, and the overall proportion of patients found to have anti-recombinant human hyaluronidase antibodies remained generally constant over the follow-up period in both cohorts. All patients who tested positive for anti-recombinant human hyaluronidase antibodies at any point during the study were negative for neutralizing antibodies.

In the SAWYER study, where previously untreated patients with CLL were treated with RITUXAN HYCELA or rituximab in combination with FC, the incidence of treatment-induced/enhanced anti-rituximab antibodies was 12% in the RITUXAN HYCELA group and 15% in the rituximab group. The incidence of treatment-induced/enhanced anti- recombinant human hyaluronidase antibodies was 11% in the RITUXAN HYCELA treatment arm. None of the patients who tested positive for anti-recombinant human hyaluronidase antibodies tested positive for neutralizing antibodies.

The clinical relevance of the development of anti-rituximab or anti-recombinant human hyaluronidase antibodies after treatment with RITUXAN HYCELA is not known.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of rituximab-containing products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hematologic: prolonged pancytopenia, marrow hypoplasia, Grade 3–4 prolonged or late-onset neutropenia, hyperviscosity syndrome in Waldenstrom’s macroglobulinemia, prolonged hypogammaglobulinemia
- Cardiac: fatal cardiac failure
- Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like syndrome, serum sickness, polyarticular arthritis, and vasculitis with rash.
- Infection: viral infections, including progressive multifocal leukoencephalopathy (PML), increase in fatal infections in HIV-associated lymphoma, and a reported increased incidence of Grade 3 and 4 infections
- Neoplasia: disease progression of Kaposi’s sarcoma.
- Skin: severe mucocutaneous reactions, pyoderma gangrenosum (including genital presentation).
- Gastrointestinal: bowel obstruction and perforation.
- Pulmonary: fatal bronchiolitis obliterans and fatal interstitial lung disease.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on human data, rituximab-containing products can cause fetal harm due to B-cell lymphocytopenia in infants exposed to rituximab in-utero *(see Clinical Considerations)*. There are no available data on RITUXAN HYCELA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In

animal reproduction studies, intravenous administration of a rituximab product to pregnant cynomolgus monkeys during the period of organogenesis caused lymphoid B cell depletion in the newborn offspring at doses resulting in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Reduced fetal weight and increased fetal lethality were observed following subcutaneous administration of hyaluronidase human in mice at a dose > 2700 times higher than the human dose. Comparable systemic exposure levels could occur in a pregnant patient following accidental intravenous administration of an entire vial of RITUXAN HYCELA *(see Data)*. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk in the U.S. general population of major birth defects is 2%–4% and of miscarriage is 15%–20% of clinically recognized pregnancies.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Observe newborns and infants for signs of infection and manage accordingly.

Data

Human Data

Postmarketing data indicate that B-cell lymphocytopenia generally lasting less than 6 months can occur in infants exposed to rituximab in-utero. Rituximab was detected postnatally in the serum of infants exposed in-utero.

Animal Data

RITUXAN HYCELA for subcutaneous injection contains rituximab and hyaluronidase human *[see Description (11)]*.

Rituximab Product:

- An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received rituximab via the intravenous route during early gestation (organogenesis period; post coitum days 20 through 50). Rituximab was administered as loading doses on post coitum (PC) Days 20, 21 and 22, at 15, 37.5 or 75 mg/kg/day, and then weekly on PC Days 29, 36, 43 and 50, at 20, 50 or 100 mg/kg/week. The 100 mg/kg/week dose resulted in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Rituximab crosses the monkey placenta. Exposed offspring did not exhibit any teratogenic effects but did have decreased lymphoid tissue B cells.
- A subsequent pre-and postnatal reproductive toxicity study in cynomolgus monkeys was completed to assess developmental effects including the recovery of B cells and immune function in infants exposed to rituximab in utero. Animals were treated with a loading dose of 0, 15, or 75 mg/kg every day for 3 days, followed by weekly dosing with 0, 20, or 100 mg/kg dose. Subsets of pregnant females were treated from PC Day 20 through postpartum Day 78, PC Day 76 through PC Day 134, and from PC Day 132 through delivery and postpartum Day 28. Regardless of the timing of treatment, decreased B cells and immunosuppression were noted in the offspring of rituximab-treated pregnant animals. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months postpartum.

Hyaluronidase Human:

- In an embryo-fetal study, mice have been dosed daily by subcutaneous injection during the period of organogenesis with hyaluronidase human at dose levels up to 2,200,000 U/kg, which is > 2700 times higher than the human dose. The study found no evidence of teratogenicity. Reduced fetal weight and increased numbers of fetal resorptions were observed, with no effects found at a daily dose of 360,000 U/kg, which is > 450 times higher than the human dose.
- In a peri-and post-natal reproduction study, mice have been dosed daily by subcutaneous injection, with hyaluronidase human from implantation through lactation and weaning at dose levels up to 1,100,000

U/kg, which is > 1,300 times higher than the human dose. The study found no adverse effects on sexual maturation, learning and memory or fertility of the offspring.

8.2 Lactation

There are no data on the presence of hyaluronidase human in human milk or the effect of rituximab on milk production, and there is limited data on the effect of rituximab on the breastfed child. However, rituximab is detected in the milk of lactating cynomolgus monkeys and maternal IgG is present in human breast milk. Rituximab has also been reported to be excreted at low concentrations in human breast milk. Given that the clinical significance of this finding for children is not known, advise women not to breastfeed during treatment with RITUXAN HYCELA and for 6 months after the last dose due to the potential for serious adverse reactions in breastfed children.

8.3 Females and Males of Reproductive Potential

Rituximab-containing products can cause fetal harm *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating RITUXAN HYCELA.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with RITUXAN HYCELA and for 12 months after the last dose of rituximab-containing products, including RITUXAN HYCELA.

8.4 Pediatric Use

The safety and effectiveness of RITUXAN HYCELA in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in the SABRINA, MabEase, and SAWYER studies, 37% were 65 and over, while 10% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

11 DESCRIPTION

RITUXAN HYCELA is a combination of rituximab and hyaluronidase human. Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM. Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension.

Recombinant human hyaluronidase is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. It is produced by mammalian (Chinese Hamster Ovary) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). It is a glycosylated single-chain protein with an approximate molecular weight of 61 kD.

RITUXAN HYCELA (rituximab and hyaluronidase human) injection is a colorless to yellowish, clear to opalescent solution supplied in sterile, preservative-free, single-dose vials for subcutaneous use.

RITUXAN HYCELA is supplied as 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL in single-dose vials or 1,600 mg rituximab and 26,800 Units hyaluronidase human per 13.4 mL in single-dose vials. Each mL of solution contains rituximab (120 mg), hyaluronidase human (2,000 Units), L-histidine (0.53 mg), L-histidine hydrochloride monohydrate (3.47 mg), L-methionine (1.49 mg), polysorbate 80 (0.6 mg), α,α-trehalose dihydrate (79.45 mg), and Water for Injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC). Hyaluronan is a polysaccharide found in the extracellular matrix of the subcutaneous tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a half-life of approximately 0.5 days. Hyaluronidase human increases permeability of the subcutaneous tissue by temporarily depolymerizing hyaluronan. 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 to 48 hours.

Hyaluronidase human has been shown to increase the absorption rate of a rituximab product into the systemic circulation when given in the subcutis of Göttingen Minipigs.

12.2 Pharmacodynamics

Peripheral B-cell counts declined to levels below normal following a dose of rituximab by intravenous infusion. In patients treated with rituximab for hematological malignancies, B cell recovery began within 6 months of treatment and generally returned to normal levels within 12 months after completion of therapy, although in some patients this may take longer.

Follicular Lymphoma (FL)

Peripheral B-cell counts decline to levels below normal following the first cycle of rituximab and are maintained during treatment with RITUXAN HYCELA. After stopping RITUXAN HYCELA treatment, B-cell repletion followed similar kinetics to that of rituximab with B-cell repletion beginning after 6 months of stopping treatment, although in some patients this may take longer.

Chronic Lymphocytic Leukemia (CLL)

Following the first cycle of treatment of rituximab, B-cells begin to deplete, with 28% of patients B-cell depleted at pre-dose Cycle 2 in the SAWYER study. An increase in the proportion of B-cell depleted patients was observed with subsequent cycles of RITUXAN HYCELA and by Cycle 6, 96% of patients were depleted. Patients remained B-cell depleted until the month 9 follow-up visit, where signs of repletion were seen.

12.3 Pharmacokinetics

The geometric mean rituximab exposures are provided in Table 4. The pharmacokinetic properties of rituximab following the administration of RITUXAN HYCELA in the approved indications are provided in Table 5. The elimination of rituximab was characterized by a time-dependent process that occurred early in therapy and a time-independent process.

Table 4: Rituximab Exposure Values following Subcutaneous Administration of RITUXAN HYCELA[a]

		Study[b]	Cycle	Rituximab
FL[c]	C_{max}, mcg/mL (CV%)	SABRINA	7	237 (29.4)
			18	156 (24.7)[e]
	C_{trough}, mcg/mL (CV%)		7	122.2 (55.3)
			18	45.5 (53.6)[e]
	AUC_{TAU}, mcg•day/mL (CV%)		7	3779 (33.7)
			18	5000 (34.3)[e]
CLL[d]	C_{max}, mcg/mL (CV%)	SAWYER	6	202 (36.1)
	C_{trough}, mcg/mL (CV%)		5	97.5 (42.6)
	AUC_{TAU}, mcg•day/mL (CV%)		5	4088 (34.2)

[a] Pharmacokinetic parameters are presented as geometric mean unless otherwise specified.
[b] For study design information, see *Clinical Studies (14).*
[c] RITUXAN HYCELA 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human)
[d] RITUXAN HYCELA 1,600 mg/26,800 Units (1,600 mg rituximab and 26,800 Units hyaluronidase human)
[e] Based on predicted values

In the SABRINA study, the geometric mean C_{trough} in the RITUXAN HYCELA arm was higher than in the rituximab arm with a geometric mean ratio (C_{trough}, RITUXAN HYCELA/C_{trough}, rituximab) of 1.52 (90% CI: 1.36, 1.70) at Cycle 7 *[see Clinical Studies (14.1)]*. In the SAWYER study, the geometric mean C_{trough} in the RITUXAN HYCELA arm was higher than in the rituximab arm with an adjusted geometric mean ratio of 1.53 (90% CI: 1.27–1.85) at Cycle 5 *[see Clinical Studies (14.3)]*.

Table 5: Pharmacokinetic Parameters of Rituximab following Subcutaneous Administration of RITUXAN HYCELA[a]

	FL	CLL
Absorption		
Absolute Bioavailability[b]	0.646 (0.634–0.659[d])	0.634 (0.602–0.665[d])
Distribution		
Volume of Central compartment (L)	4.06 (26)	4.80 (18)
Apparent Volume of Distribution at steady state[c] (L)	8.09 (19)	8.52 (13)
Elimination		
Terminal Half-life (days)	34.1 (27)	32 (24)
Clearance (L/day)	0.18 (34)	0.204 (31)

[a] Parameters represented as geometric mean (%CV) unless otherwise specified
[b] Compared to a rituximab product administered intravenously
[c] Volume of central compartment and peripheral compartment
[d] 95% CI

Specific Populations

The pharmacokinetics of rituximab and hyaluronidase human in children and adolescents is unknown. The effect of either renal or hepatic impairment on the pharmacokinetics of rituximab and hyaluronidase human is unknown.

Drug Interaction Studies

The drug interaction potential of rituximab and hyaluronidase human is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long term animal studies have been performed to establish the carcinogenic or mutagenic potential of RITUXAN HYCELA or rituximab, or to determine potential effects on fertility in males or females.

RITUXAN HYCELA contains hyaluronidase human. Hyaluronidases are found in most tissues of the body. Long-term animal studies have not been performed to assess the carcinogenic or mutagenic potential of hyaluronidase human. In addition, when hyaluronidase human was administered to cynomolgus monkeys for 39 weeks at dose levels up to 220,000 U/kg, which is > 90 times higher than the human dose, no evidence of toxicity to the male or female reproductive system was found through periodic monitoring of in-life parameters, e.g., semen analyses, hormone levels, menstrual cycles, and also from gross pathology, histopathology and organ weight data.

14 CLINICAL STUDIES

14.1 Follicular Lymphoma

The SABRINA study [NCT01200758] was a randomized, two-stage, open-label, multicenter study that enrolled a total of 410 patients with previously untreated, CD20-positive follicular lymphoma of Grade 1, 2 or 3a requiring therapy. The study design is identical in stage 1 and 2. Patients were randomized (1:1) to receive either a rituximab product by intravenous infusion 375 mg/m^2 for 8 cycles or 1 cycle of a rituximab product by intravenous infusion 375 mg/m^2 followed by 7 cycles of RITUXAN HYCELA 1,400mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) both every 3 weeks in combination with a total of 6–8 cycles of CHOP or 8 cycles of CVP chemotherapy. Patients underwent interim staging after 4 cycles. Patients who received R-CHOP and achieved a CR, CRu, PR or SD at the interim assessment could receive either 4 more cycles of R-CHOP or 2 cycles of R-CHOP followed by 2 cycles of monotherapy with rituximab product or RITUXAN HYCELA depending on randomization arm (i.e., a total of 8 cycles of rituximab product or RITUXAN HYCELA). Patients with at least a PR after combination treatment with chemotherapy continued

with single agent maintenance treatment administered every 8 weeks for 24 months with rituximab product or RITUXAN HYCELA as per their randomization (i.e., total of 12 cycles of maintenance treatment).

Randomization was stratified by: underlying chemotherapy backbone (CHOP vs CVP), Follicular Lymphoma International Prognostic Index (FLIPI) (low-risk vs. intermediate-risk vs. high-risk), and region (Europe and North America vs. South and Central America vs Asia).
The main outcome measure for Stage 1 was the estimated ratio of observed rituximab serum $C_{trough\ SC}/C_{trough\ IV}$ at Cycle 7 of combination treatment with chemotherapy every 3 weeks. The main outcome measure for Stage 2 was the investigator-assessed ORR consisting of CR, CRu, and PR at the completion of combination treatment with chemotherapy. Additional outcome measures were CRR (CR and CRu) at the end of completion of combination treatment with chemotherapy, ORR and CRR at the end of completion of maintenance treatment, and time-to-event endpoints (progression-free survival (PFS), and overall survival (OS)).

Of all randomized patients, the median age was 57 years (range: 28 to 86), 53% were female, and 86% were White. The median BSA was 1.83 m^2. 45% had high risk or 34% had intermediate risk FLIPI score, and 54% had Ann Arbor Stage IV disease. Ninety percent of patients completed all 8 cycles of combination treatment with chemotherapy, and 70% of patients completed 20 cycles of both combination and maintenance treatment. Median treatment duration was 27.1 months in both groups. The median number of cycles received was 20 in both groups.

The pharmacokinetic results for the primary endpoint in Stage 1, rituximab C_{trough} at Cycle 7 (i.e., 21 days after Cycle 7 rituximab administration), demonstrated that RITUXAN HYCELA 1,400 mg/23,400 Units was non-inferior compared with rituximab at 375 mg/m^2 in patients receiving combination treatment with chemotherapy *[see Clinical Pharmacology (12.3)]*. The efficacy results are presented in Table 6.

Table 6: Efficacy in Patients with Previously Untreated Follicular Lymphoma (SABRINA Study)

	RITUXAN HYCELA N=205	Rituximab N=205
Overall Response Rate at End of combination treatment with chemotherapy[a,*]		
Number of responders (CR/CRu, PR)	173	174
Overall response (CR/CRu, PR) rate (%, [95% CI])	84% [79;89]	85% [79;90]
Difference in overall response rates[b] [95% CI]	-0.5% [-7.7;6.8]	
Number of complete responders (CR/CRu)	66	65
Complete response (CR/CRu) rate (%, [95% CI])	32% [26;39]	32% [25;39]
Difference in complete response rates[b] [95% CI]	0.0% [-9.3;9.3]	
Overall Response Rate at End of Maintenance		
Number of patients treated in maintenance (n)	172	178
Number of responders (CR/CRu, PR)	134	139
Overall response (CR/CRu, PR) rate (%, [95% CI])	78% [71;84]	78% [71;84]
Difference in overall response rates[b] [95% CI]	-0.2 [-9.2;8.8]	
Number of complete responders (CR/CRu)	87	103
Complete response (CR/CRu) rate (%, [95% CI])	51% [43;58]	58% [50;65]
Difference in complete response rates[b] [95% CI]	-7.3 [-18.0;3.5]	
Progression-free survival[c]		
Number of patients with event	65 (32%)	71 (35%)
Hazard Ratio [95% CI] (unstratified Cox model)	0.90 [0.64;1.26]	
Overall survival		
Number of patients with event	18 (8.8%)	26 (12.7%)
Hazard Ratio [95% CI] (unstratified Cox model)	0.70 [0.38;1.27]	

[a] Stage 2 main outcome measure was ORR at the end of combination treatment with chemotherapy; however pooled results which were preplanned are presented in this Table.
Response rates based on investigator assessment.
Response rates at end of maintenance based on patients who received at least one cycle of maintenance treatment (n).
[b] Difference in response rates (RITUXAN HYCELA minus rituximab).
[c] At time of final analysis (median follow-up 4.8 years).
* Investigator-assessed ORR (comprising CR, CRu and PR).

14.2 Diffuse Large B-Cell Lymphoma (DLBCL)

The MabEase study [NCT01649856] enrolled a total of 576 patients with previously untreated CD20-positive DLBCL. Patients were randomized (2:1) to receive either a rituximab product by intravenous infusion, 375 mg/m^2 for 8 cycles or 1 cycle of a rituximab product by intravenous infusion 375 mg/m^2 followed by 7 cycles of RITUXAN HYCELA 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human), both in combination with up to 6–8 cycles of CHOP chemotherapy, every 14 (CHOP-14) or 21 days (CHOP-21). Randomization was stratified by: age (< 60 years, ≥ 60 years), International Prognostic Index (IPI) risk category (low, low-intermediate, high-intermediate, high), and chemotherapy regimen (CHOP-21 or CHOP-14). The main outcome measure was investigator-assessed complete response rate (CR/CRu) at the end of combination treatment with chemotherapy. Additional outcome measures were time-to-event endpoints (PFS and OS).

Of all randomized patients, the median age was 64 years (range: 18 to 80 years); 54% were male; and 79% were White. The median BSA was 1.83 m$^{2.}$ 31% low risk or 30% low intermediate risk IPI score, 24% high intermediate risk, or 15% high risk IPI score and 42% of patients had Ann Arbor Stage IV disease. A total of 470 patients (82%) received 8 cycles of treatment. Median duration of exposure to treatment was 4.9 months in

both treatment groups. The median number of administrations/cycles (RITUXAN HYCELA or rituximab) was 8 in both groups.

The efficacy results for are presented in Table 7. The median observation time was approximately 28 months.

Table 7: Efficacy in Patients with Previously Untreated DLBCL (MabEase Study)

	RITUXAN HYCELA N=381	**Rituximab N=195**
Complete Response Rate (CR/CRu)*		
Number achieving CR/CRu[a]	179	82
Cr/CRu rate (%, [95% CI])	47% [42;52]	42% [35;49]
Difference in rates [95% CI][b]	4.9% [-3.6;13.5]	
Progression-free survival[c]		
Number of patients with event	104 (27%)	44 (23%)
Hazard Ratio [95% CI] (unstratified Cox model)	1.22 [0.85;1.73]	
Overall survival[d]		
Number of patients with event	63 (17%)	29 (15%)
Hazard Ratio [95% CI] (unstratified Cox model)	1.08 [0.70;1.68]	

[a] Four patients in the RITUXAN HYCELA group and 1 patient in the rituximab group had their response downgraded due to their bone marrow data.
[b] Difference in response rates (RITUXAN HYCELA minus rituximab).
[c] Progression-free survival is defined as the time from randomization to the first occurrence of disease progression or relapse, or death from any cause.
[d] Overall survival is defined as the time from randomization until death from any cause.
* Investigator-assessed.

14.3 Chronic Lymphocytic Leukemia (CLL)

The SAWYER study [NCT01292603] was a randomized, two-part, open-label, multicenter study that enrolled a total of 176 patients with previously untreated CLL. Patients were randomized (1:1) to receive either a rituximab product by intravenous infusion, 375 mg/m^2, in Cycle 1 followed by up to 5 cycles of rituximab, 500 mg/m^2, or rituximab, 375 mg/m^2, in Cycle 1 followed by subsequent cycles (2–6) of RITUXAN HYCELA 1,600 mg /26,800 Units (1,600 mg rituximab and 26,800 Units hyaluronidase human), both in combination with fludarabine and cyclophosphamide (FC) chemotherapy. The main outcome measure was the non-inferiority of the pharmacokinetic profile of RITUXAN HYCELA compared to rituximab. An additional outcome measure in Part 2 was investigator-assessed response rate.

The median age was 60 years (range: 25 to 78); 65% were males and 96% were White. The median BSA was 1.9 m^2, 62% had Binet Stage B disease and 93% had typical CLL characterization.

The pharmacokinetic results demonstrated that RITUXAN HYCELA 1,600mg/26,800 Units serum rituximab C_{trough} level was non-inferior compared with rituximab at 500 mg/m^2 in patients receiving combination treatment with chemotherapy *[see Clinical Pharmacology (12.3)]*.

The efficacy results for Part 2 are presented in Table 8.

Table 8: Efficacy in Patients with Previously Untreated CLL (SAWYER Study)

	Part 2

		RITUXAN HYCELA (N = 88)	Rituximab (N = 88)
ORR[a]	Point estimate	85.2% (n = 75)	80.7% (n = 71)
	95% CI	[76.1%, 91.9%]	[70.9%, 88.3%]
CRR[a]	Point estimate	27.3% (n = 24)	31.8% (n = 28)
	95% CI	[18.3%, 37.8%]	[22.3%, 42.6%]
PFS[b]	Proportion with PFS event	34.1% (n = 30)	42.0% (n = 37)
	HR 95% CI	0.76 [0.47%, 1.23%]	

ORR – Overall Response Rate
CRR – Complete Response Rate
PFS – Progression-Free Survival
[a]At 3 month follow-up visit (Part 2). Investigator-assessed.
[b]At time of final analysis (median follow-up 4.4 years). Investigator-assessed.

14.4 Patient Experience

Previously untreated adult patients outside of the United States with CD20+ diffuse large B-cell lymphoma (DLBCL) or CD20+ follicular non-Hodgkin's lymphoma (FL) Grades 1, 2, or 3a were randomized to receive a standard chemotherapy regimen (CHOP, CVP, or bendamustine) and either RITUXAN HYCELA 1,400mg/23,400 Units at Cycles 2–4 (after the first cycle with intravenous rituximab) or a rituximab product by intravenous infusion at Cycles 1–4. After the fourth cycle, patients were crossed over to the alternative route of administration for the remaining 4 cycles. After Cycle 8, 477 of 620 patients (77%) reported preferring subcutaneous administration of RITUXAN HYCELA over intravenous rituximab and the most common reason was that administration required less time in the clinic. After Cycle 8, 66 of 620 patients (11%) preferred rituximab intravenous administration and the most common reason was that it felt more comfortable during administration. Forty eight of 620 patients (7.7%) had no preference for the route of administration. Twenty nine subjects of 620 (4.7%) received Cycle 8 but did not complete the preference questionnaire.

16 HOW SUPPLIED/STORAGE AND HANDLING

RITUXAN HYCELA (rituximab and hyaluronidase human) injection, for subcutaneous use is supplied as a sterile preservative-free liquid solution in a single-dose vial. The following configurations are available:

Individually packaged single-dose vials:

- RITUXAN HYCELA 1,400 mg/23,400 Units (NDC 50242-108-01) providing 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL
- RITUXAN HYCELA 1,600 mg/26,800 Units (NDC 50242-109-01) providing 1,600 mg rituximab and 26,800 Units hyaluronidase human per 13.4 mL

Storage

Store RITUXAN HYCELA vials in the refrigerator at 2ºC to 8ºC (36ºF to 46ºF) in the original carton to protect from light. Do not freeze.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Severe Mucocutaneous Reactions

Advise patients to contact their healthcare provider immediately for symptoms of severe mucocutaneous reactions, including painful sores or ulcers on the lips or mouth, blisters, peeling skin, rash, and pustules *[see Warnings and Precautions (5.1)]*.

Hepatitis B Virus Reactivation

Advise patients to contact their healthcare provider immediately for symptoms of hepatitis including worsening fatigue or yellow discoloration of skin or eyes *[see Warnings and Precautions (5.2)]*.

Progressive Multifocal Leukoencephalopathy (PML)

Advise patients to contact their healthcare provider immediately for signs and symptoms of PML, including new or changes in neurological symptoms such as confusion, dizziness or loss of balance, difficulty talking or walking, decreased strength or weakness on one side of the body, or vision problems *[see Warnings and Precautions (5.3)]*.

Hypersensitivity and Other Administration Reactions

Inform patients about the signs and symptoms of hypersensitivity and administration-related reactions. Advise patients to contact their healthcare provider immediately to report symptoms of administration-related reactions including dizziness, nausea, chills, fever, vomiting, diarrhea, urticaria, angioedema, breathing problems, or chest pain *[see Warnings and Precautions (5.4)]*.

Tumor Lysis Syndrome (TLS)

Advise patients to contact their healthcare provider immediately for signs and symptoms of tumor lysis syndrome such as nausea, vomiting, diarrhea, and lethargy *[see Warnings and Precautions (5.5)]*.

Infections

Advise patients to contact their healthcare provider immediately for signs and symptoms of infections including fever, cold symptoms (e.g., rhinorrhea or laryngitis), flu symptoms (e.g., cough, fatigue, body aches), earache or headache, dysuria, cold sores, and painful wounds with erythema *[see Warnings and Precautions (5.6)]*

Cardiovascular Adverse Reactions

Advise patients of the risk of cardiovascular adverse reactions, including ventricular fibrillation, myocardial infarction, and cardiogenic shock. Advise patients to contact their healthcare provider immediately to report chest pain and irregular heartbeats. *[see Warnings and Precautions (5.7)]*

Renal Toxicity

Advise patients of the risk of renal toxicity. Inform patients of the need for healthcare providers to monitor kidney function *[see Warnings and Precautions (5.8)]*.

Bowel Obstruction and Perforation

Advise patients to contact their healthcare provider immediately for signs and symptoms of bowel obstruction and perforation, including severe abdominal pain or repeated vomiting *[see Warnings and Precautions (5.9)]*.

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.11), Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential to use effective contraception during treatment with RITUXAN HYCELA and for 12 months after the last dose of of rituximab-containing products, including RITUXAN HYCELA *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with RITUXAN HYCELA and for 6 months after the last dose *[see Use in Specific Populations (8.2)]*.

RITUXAN HYCELA® [rituximab and hyaluronidase human]

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
US License No.: 1048

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MEDICATION GUIDE
RITUXAN HYCELA® [rih-TUKS-an hye-SELL-uh]
(rituximab and hyaluronidase human)
injection

What is the most important information I should know about RITUXAN HYCELA?

RITUXAN HYCELA can cause serious side effects that can lead to death, including:

- **Severe skin and mouth reactions.** Tell your healthcare provider or get medical help right away if you get any of these symptoms at any time during your treatment with RITUXAN HYCELA:
  - painful sores or ulcers on your skin, lips or in your mouth
  - blisters
  - peeling skin
  - rash
  - pustules
- **Hepatitis B virus (HBV) reactivation.** Before you receive RITUXAN HYCELA, your doctor will do blood tests to check for HBV infection. If you have had hepatitis B or are a carrier of hepatitis B virus, receiving RITUXAN HYCELA could cause the virus to become an active infection again. Hepatitis B reactivation may cause serious liver problems including liver failure, and death. Your healthcare provider will monitor you for hepatitis B infection during and for several months after you stop receiving RITUXAN HYCELA.

  Tell your healthcare provider right away if you get worsening tiredness, or yellowing of your skin or white part of your eyes during treatment with RITUXAN HYCELA.
- **Progressive Multifocal Leukoencephalopathy (PML)**. PML is a rare, serious brain infection caused by a virus that can happen in people who receive RITUXAN HYCELA. People with weakened immune systems can get PML. PML can result in death or severe disability. There is no known treatment, prevention, or cure for PML.

  Tell your healthcare provider right away if you have any new or worsening symptoms or if anyone close to you notices these symptoms:
  - confusion
  - dizziness or loss of balance
  - difficulty walking or talking
  - decreased strength or weakness on one side of your body
  - vision problems, such as blurred vision or loss of vision
- **Serious allergic reactions and other severe reactions.**

  Serious allergic reactions, and reactions due to release of certain substances by your body that can lead to death, can happen with rituximab products, including RITUXAN HYCELA.

  Skin reactions at or near the injection site (local), including injection site reactions, can happen with RITUXAN HYCELA. Symptoms at or near the injection site may include: pain, swelling, hardness, redness, bleeding, itching, and rash. These reactions sometimes happen more than 24 hours after an injection of RITUXAN HYCELA.

  Tell your healthcare provider or get medical help right away if you get any of these symptoms during or after an injection of RITUXAN HYCELA:
  - hives (red itchy welts) or rash
  - itching
  - swelling of your lips, tongue, throat or face
  - sudden cough
  - shortness of breath, difficulty breathing, or wheezing
  - weakness
  - dizziness or feel faint
  - palpitations (feel like your heart is racing or fluttering)
  - chest pain
  - fever
  - chills or shaking chills

See **"What are the possible side effects of RITUXAN HYCELA?"** for more information about side effects.

What is RITUXAN HYCELA?

RITUXAN HYCELA is a prescription medicine used to treat adults with:

- **Follicular Lymphoma (FL): alone or with certain chemotherapy medicines.**
- **Diffuse Large B-Cell Lymphoma (DLBCL):** with certain other chemotherapy medicines in people who have not had previous treatment for their DLBCL.
- **Chronic Lymphocytic Leukemia (CLL):** with the chemotherapy medicines fludarabine and cyclophosphamide.

You can only receive RITUXAN HYCELA after you receive at least 1 full dose of a rituximab product by IV infusion. Read the rituximab by IV infusion Medication Guide for more information about severe infusion reactions, which usually happen during the first dose with a rituximab product given by IV infusion.

RITUXAN HYCELA is not for use to treat medical conditions other than cancers.

It is not known if RITUXAN HYCELA is safe and effective in children.

Before you receive RITUXAN HYCELA, tell your healthcare provider about all of your medical conditions, including if you:

- have had a severe reaction to a rituximab product or RITUXAN HYCELA
- have a history of heart problems, irregular heart beat or chest pain
- have lung or kidney problems
- have an infection or weakened immune system
- have or have had any severe infections including:
  - Hepatitis B virus (HBV)
  - Hepatitis C virus (HCV)
  - Cytomegalovirus (CMV)
  - Herpes simplex virus (HSV)
  - Parvovirus B19
  - Varicella zoster virus (chickenpox or shingles)
  - West Nile Virus
- have had a recent vaccination or are scheduled to receive vaccinations. You should not receive certain vaccines before or during treatment with RITUXAN HYCELA.
- are pregnant or plan to become pregnant. RITUXAN HYCELA may harm your unborn baby.

  Females who are able to become pregnant:
  - Your healthcare provider should check to see if you are pregnant before you receive RITUXAN HYCELA.
  - You should use effective birth control (contraception) during treatment with RITUXAN HYCELA and for **12 months** after the last dose of RITUXAN HYCELA. Talk to your healthcare provider about effective birth control.
  - Tell your healthcare provider if you become pregnant or think you may be pregnant during treatment with RITUXAN HYCELA.
- are breastfeeding or plan to breastfeed. RITUXAN HYCELA may pass into your breast milk. Do not breastfeed during treatment and for **6 months** after your last dose of RITUXAN HYCELA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive RITUXAN HYCELA?

- RITUXAN HYCELA is given as an injection under the skin, in the stomach-area (abdomen).
- RITUXAN HYCELA is injected over 5 or 7 minutes.
- Your healthcare provider will prescribe medicines before the injection of RITUXAN HYCELA to help reduce side effects such as fever and chills.
- Your healthcare provider should monitor you for side effects for at least 15 minutes after you receive an injection of RITUXAN HYCELA.
- If you have CLL, your healthcare provider should prescribe medicines to help prevent certain infections during treatment and for up to 12 months following treatment with RITUXAN HYCELA.

Before each injection of RITUXAN HYCELA treatment, your healthcare provider or nurse will ask you questions about your general health. Tell your healthcare provider or nurse about any new symptoms.

What are possible side effects of RITUXAN HYCELA?

RITUXAN HYCELA can cause serious side effects, including:

- See "What is the most important information I should know about RITUXAN HYCELA?"
- **Tumor Lysis Syndrome (TLS)**. TLS is caused by the fast breakdown of cancer cells. TLS can cause you to have:
  - kidney failure and the need for dialysis treatment
  - abnormal heart rhythm

  TLS can happen within 12 to 24 hours after an injection of RITUXAN HYCELA. Your healthcare provider may do blood tests to check you for TLS. Your healthcare provider may give you medicine to help prevent TLS.

  Tell your healthcare provider right away if you have any of the following signs or symptoms of TLS:
  - nausea
  - vomiting
  - diarrhea
  - lack of energy
- **Serious infections.** Serious infections can happen during and after treatment with RITUXAN HYCELA, and can lead to death. Rituximab products can increase your risk of getting infections **and** can lower the ability of your immune system to fight infections. Types of serious infections that can happen with RITUXAN HYCELA include bacterial, fungal, and viral infections. After receiving RITUXAN HYCELA, some people have developed low levels of certain antibodies in their blood for a long period of time (longer than 11 months). Some of these people with low antibody levels developed infections. Tell your healthcare provider right away if you have any symptoms of infection:
  - fever
  - cold symptoms, such as runny nose or sore throat that do not go away
  - flu symptoms, such as cough, tiredness, and body aches
  - earache or headache
  - pain during urination
  - white patches in the mouth or throat
  - cuts, scrapes or incisions that are red, warm, swollen or painful
- **Heart problems.** RITUXAN HYCELA may cause chest pain, irregular heartbeats, and heart attack. Your healthcare provider may monitor your heart during and after treatment with RITUXAN HYCELA if you have symptoms of heart problems or have a history of heart problems. Tell your healthcare provider right away if you have chest pain or irregular heartbeats during treatment with RITUXAN HYCELA.
- **Kidney problems** RITUXAN HYCELA can cause severe kidney problems that can lead to death. Your healthcare provider should do blood tests to check how well your kidneys are working.
- **Stomach and serious bowel problems that can sometimes lead to death.** Bowel problems, including blockage or tears in the bowel, can happen if you receive RITUXAN HYCELA with chemotherapy medicines. Tell your healthcare provider right away if you have severe stomach-area (abdomen) pain or repeated vomiting during treatment with RITUXAN HYCELA.

Your healthcare provider will stop treatment with RITUXAN HYCELA if you have severe, serious or life-threatening side effects.

The most common side effects of RITUXAN HYCELA in people with Follicular Lymphoma (FL) include: infections, low white blood cell count, nausea, constipation, cough, and tiredness.

The most common side effects of RITUXAN HYCELA in people with Diffuse Large B-cell Lymphoma (DLBCL) include: infections, low white blood cell count, loss of hair, nausea, and low red blood cell count.

The most common side effects of RITUXAN HYCELA in people with Chronic Lymphocytic Leukemia (CLL) include: infections, low white blood cell count, nausea, low platelet count, fever, vomiting, and injection site redness.

These are not all of the possible side effects with RITUXAN HYCELA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of RITUXAN HYCELA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about RITUXAN HYCELA that is written for health professionals.

What are the ingredients in RITUXAN HYCELA?

Active ingredient: rituximab and hyaluronidase human.

Inactive ingredients: L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, α,α-trehalose dihydrate, and Water for Injection.

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For more information, go to www.RITUXANHYCELA.com or call 1-877-436-3683.

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