Pfizer Oncology together™

INJECTION
Ruxience®
rituximab-pvvr
Pfizer

RUXIENCE® (rituximab-pvvr) Billing and Coding Guide

Please see Important Safety Information and Indications on pages 13-18 and full Prescribing Information for RUXIENCE, including BOXED WARNINGS and Medication Guide.

Introduction

Pfizer Inc. has developed this reference guide to assist healthcare providers (HCPs) with understanding coding for RUXIENCE®* (rituximab-pvvr), a rituximab biosimilar approved for use in the United States for intravenous use.

The information provided in this document is intended for informational purposes only and is not a comprehensive description of potential coding requirements for RUXIENCE. Coding and coverage policies change periodically and often without notice. The HCP is solely responsible for determining coverage and reimbursement parameters and appropriate coding for treatment of their patients. The information provided should not be considered a guarantee of coverage or reimbursement for RUXIENCE.

*Pfizer Oncology Together™ supports patients prescribed RUXIENCE for oncology indications. Pfizer enCompass® is available to support patients prescribed RUXIENCE for its FDA-approved non-oncology indication. For more information, visit www.pfizerencompass.com.

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Making your patients' support needs a priority. Together.

At Pfizer Oncology Together, patient support is at the core of everything we do. We've gathered resources and developed tools to help patients and their loved ones throughout RUXIENCE treatment. From helping to identify financial assistance options to connecting patients to resources for emotional support, your patients' needs are our priority.*

Benefits Verification

We can help determine a patient's coverage and out-of-pocket costs.

Prior Authorization (PA) Assistance

We can coordinate with a patient's insurer to determine PA requirements. After a PA request is submitted, we can follow up with the payer until a final outcome is determined.

Appeals Assistance

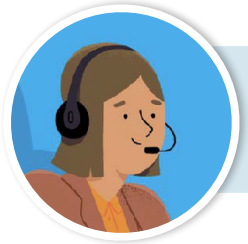
We can review the reasons for a denied claim and provide information on payer requirements. After an appeal is submitted, we can follow up with the payer until a final outcome is determined.

Billing and Coding Assistance for Injectable Products

For your patient claim submissions, we provide easy access to sample forms and template letters, along with billing and coding information for physician office and hospital outpatient settings of care.

Patient Financial Assistance

We can help patients understand their benefits and connect them with financial assistance resources.



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Call **1-877-744-5675** (Monday–Friday 8 AM–8 PM ET)

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PfizerOncologyTogether.com

*Some services are provided through third-party organizations that operate independently and are not controlled by Pfizer. Availability of services and eligibility requirements are determined solely by these organizations.

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Coding for RUXIENCE

In the physician office and hospital outpatient department sites of care, Medicare, Medicaid, and private commercial payers typically recognize the following codes for reporting RUXIENCE and its administration on claim forms. The following Healthcare Common Procedure Coding System (HCPCS) code for RUXIENCE is available for dates on service on or after July 1, 2020*:

HCPCS Code[1]	Descriptor	Relevant Sites of Service
Q5119	Injection, rituximab-pvvr, biosimilar, (RUXIENCE), 10 mg	Physician office and hospital outpatient department

Modifiers may be included on claims to provide additional information. Some payers may require modifier JA to be reported, indicating the route of administration. The JW modifier is used to report the amount of the drug that is unused after administration to a patient. For Medicare and some payers, the unused amount should be reported on a separate line of the claim form, and the claim should include the drug code, modifier, and number of units discarded.[2] Additional modifiers may also be considered appropriate when submitting claims.

HCPCS Modifier[2,3]	Descriptor
JA	Intravenous administration
JW[a]	Drug amount discarded/not administered to any patient
JZ[a]	Zero drug amount discarded/not administered to any patient

*Medicare made the effective payment date retroactive to February 3, 2020. Please confirm with your patient's payer for guidance regarding coding for RUXIENCE prior to submitting a claim.
[a]Use of the JZ modifier (in situations where it applies) is required on Medicare claims with a date of service on or after 7/1/2023. An applicable claim without modifier JW or JZ may be rejected beginning on 10/1/2023.

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RUXIENCE National Drug Codes

National Drug Codes (NDCs) are unique 10-digit, 3-segment numbers used to identify drugs.[4]

Strength[5]	*Vial Size*	*10-Digit NDC*
100 mg/10 mL	Single-dose vial	0069-0238-01
500 mg/50 mL	Single-dose vial	0069-0249-01

NDC Conversion Example

For reimbursement purposes, some payers may require the HCP to include NDCs on the claim form. For claims-reporting purposes, some payers may also require HCPs to convert the 10-digit NDC to an 11-digit NDC by adding a "0" (zero) where appropriate to create a 5-4-2 configuration. The zero is added in front of the first segment of numbers when the 10-digit format is the 4-4-2 configuration. See placement of the red zero in the example below.

Strength	*Vial Size*	*10-Digit NDC*	*11-Digit NDC*
100 mg/10 mL	Single-dose vial	0069-0238-01	00069-0238-01
500 mg/50 mL	Single-dose vial	0069-0249-01	00069-0249-01

Coding for RUXIENCE Administration Services

Current Procedural Terminology (CPT®) codes define specific medical procedures performed by physicians.[6]
The following codes may be used to report the administration of RUXIENCE:

Type of Code	*Code/Descriptor*	*Relevant Sites of Service*
Administration: CPT® codes[6]	**96413:** Chemotherapy administration, IV infusion technique; up to 1 hour, single or initial substance/drug	Physician office and hospital outpatient department
	96415: Chemotherapy administration, IV infusion technique; each additional hour (List separately in addition to code for primary procedure)	
	96417: Chemotherapy administration, IV infusion technique; each additional sequential infusion (different substance/drug), up to 1 hour (List separately in addition to code for primary procedure)	
	96365: Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour	
	96366: Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)	
	96367: Intravenous infusion, for therapy, prophylaxis or diagnosis (specify substance or drug); additional sequential infusion of a new drug/substance, up to 1 hour (List separately in addition to code for primary procedure)	

Key: IV – intravenous
Current Procedural Terminology (CPT®) is a registered trademark of the American Medical Association.

Hospital outpatient departments use revenue codes to report specific accommodations and/or ancillary charges.[7]

Type of Code	*Code/Descriptor*	*Relevant Sites of Service*
Revenue codes[8]	**0636:** Drugs requiring specific identification – detailed coding	Hospital outpatient department
	0500: Outpatient services – general classification	
	0510: Clinic – general classification	

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Diagnosis Coding for RUXIENCE

RUXIENCE (rituximab-pvvr) is a Food and Drug Administration (FDA)-approved biosimilar.

The International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code set should be used, as appropriate, to report the patient-specific diagnosis.

Reporting the medical necessity for RUXIENCE may require a primary and secondary diagnosis, in some cases. HCPs should verify payer-specific coding requirements before submitting a claim and the order of required codes (eg, primary, secondary), as these may vary by payer. ICD-10-CM codes may include, but are not limited to, the codes listed below:

ICD-10-CM Code[9]	*Descriptor*
C82.00–C82.99	Follicular lymphoma, Grades I–IIIb, diffuse follicle center lymphoma, cutaneous follicle center lymphoma, other types and unspecified follicular lymphoma
C83.00–C83.09	Small cell B-cell lymphoma
C83.30–C83.39	Diffuse large B-cell lymphoma, lymph nodes of various sites
C83.80–C83.89	Other non-follicular lymphoma, lymph nodes of specific sites
C85.10–C85.19	Unspecified B-cell lymphoma
C85.80–C85.89	Other specified types of non-Hodgkin lymphoma
C85.90–C85.99	Non-Hodgkin lymphoma, unspecified
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
M31.7	Microscopic polyangiitis
M31.30	Wegener's granulomatosis without renal involvement
M31.31	Wegener's granulomatosis with renal involvement

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RUXIENCE Billing Units

The RUXIENCE HCPCS code Q5119 is described as "Injection, rituximab-pvvr, biosimilar, (Ruxience), 10 mg." Each dose increment of 10 milligrams equals 1 billing unit. For example, a 100 mg vial of RUXIENCE represents 10 billing units of Q5119. See the chart below correlating a vial of RUXIENCE administered with the number of billing units based on the description of Q5119.

Strength	*Vial Size*	*Number of Q5119 Billing Units (10 mg rituximab-pvvr) Equivalent to the Milligrams of RUXIENCE in Each Vial*
100 mg/10 mL	Single-dose vial	10 units
500 mg/50 mL	Single-dose vial	50 units

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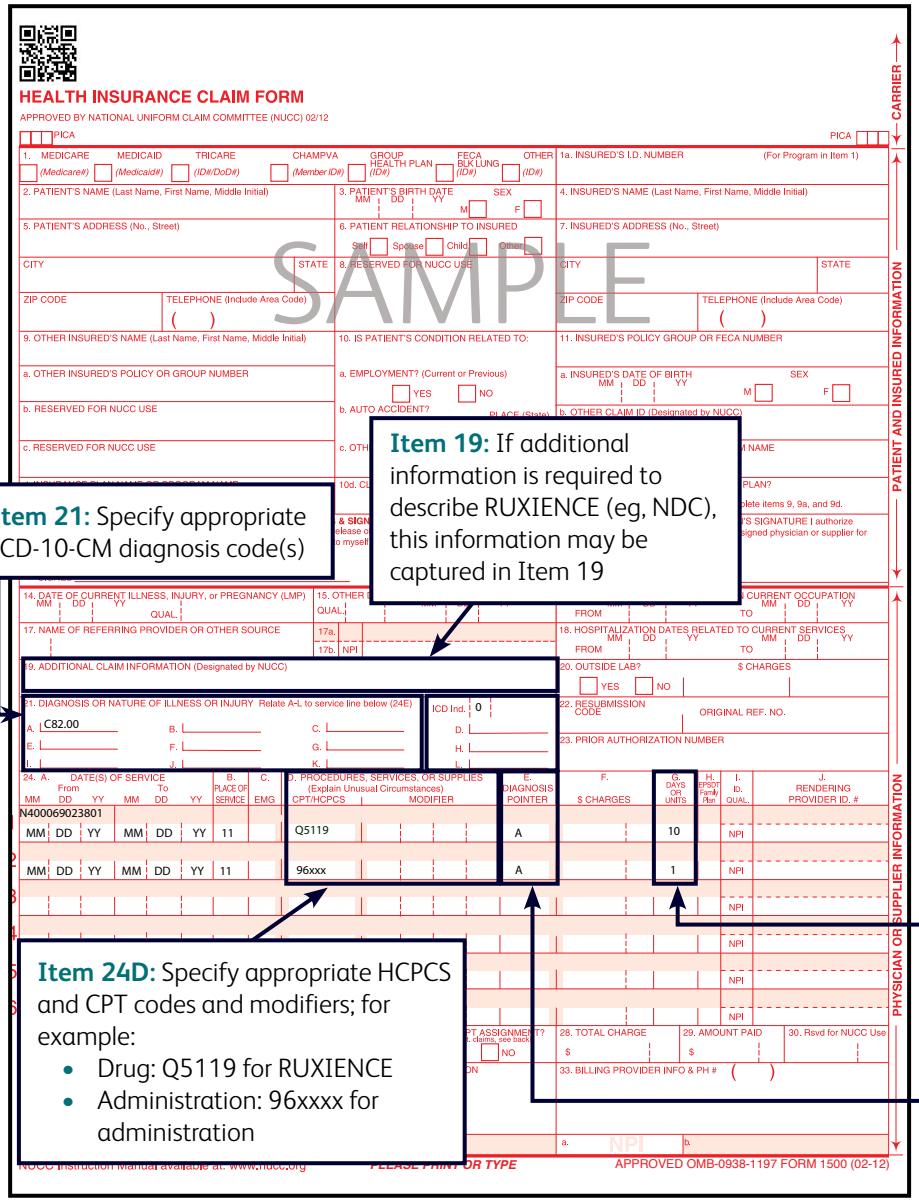
Sample Claim Form: CMS-1500, Physician Office Site of Service



Item 21: Specify appropriate ICD-10-CM diagnosis code(s)

Item 19: If additional information is required to describe RUXIENCE (eg, NDC), this information may be captured in Item 19

Item 24G: Specify the billing units. For example, 1 billing unit = **10** mg of rituximab-pvvr biosimilar (RUXIENCE). To bill 100 mg of RUXIENCE, enter 10 units

Item 24D: Specify appropriate HCPCS and CPT codes and modifiers; for example:

- Drug: Q5119 for RUXIENCE
- Administration: 96xxxx for administration

Item 24E: Enter reference to the diagnosis for the CPT and HCPCS codes from Item 21

This sample form is intended as a reference for the coding and billing of RUXIENCE. This form is not intended to be directive, and the use of the recommended codes does not guarantee reimbursement. HCPs may deem other codes or policies more appropriate and should select the coding options that most accurately reflect their internal guidelines, payer requirements, practice patients, and services rendered.

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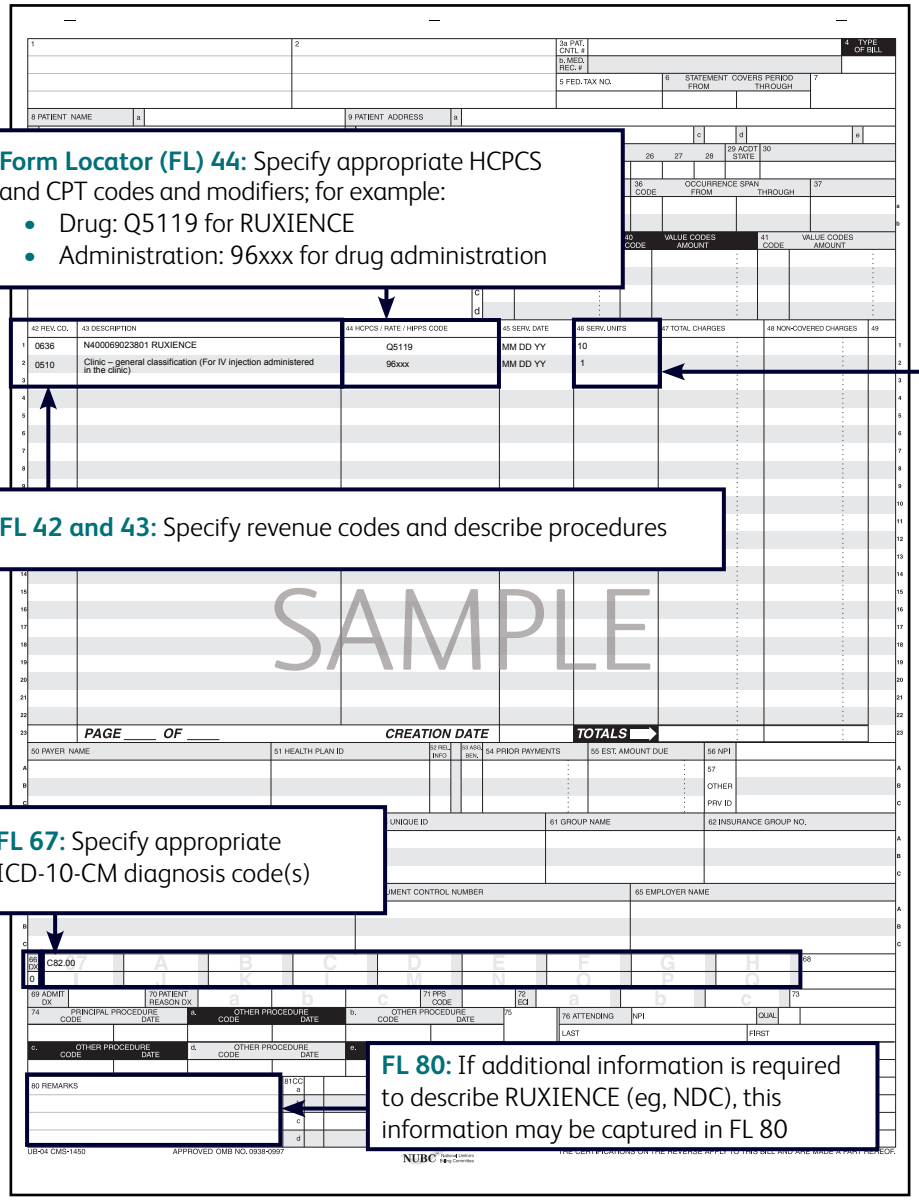
Sample Claim Form: UB-04, Hospital Outpatient Site of Service



This sample form is intended as a reference for the coding and billing of RUXIENCE. This form is not intended to be directive, and the use of the recommended codes does not guarantee reimbursement. HCPs may deem other codes or policies more appropriate and should select the coding options that most accurately reflect their internal guidelines, payer requirements, practice patients, and services rendered.

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Claims Submission Checklist

The following may be considered to assist with submitting claims completely and accurately, which is important for timely claims processing, for appropriate payment, and to avoid denied claims.

- ☑ **Provide the patient name, address, and insurance identification number, and review these for accuracy**
- ☑ **Include the HCP's name, National Provider Identifier (NPI), and payer-specific provider ID (if applicable)**
- ☑ **Indicate the appropriate place of service code (2-digit code) for where the treatment was provided**
- ☑ **Check to ensure that ICD-10-CM diagnosis codes, CPT procedure codes, and modifiers (if applicable) are consistent with information included in the patient's medical record**
- ☑ **Review the RUXIENCE-specific information (eg, name of drug, HCPCS code, NDC, number of units, route, and frequency of administration)**

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References

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2. Centers for Medicare & Medicaid Services (CMS). Medicare Program Discarded Drugs and Biologicals – JW Modifier and JZ Modifier Policy Frequently Asked Questions. Accessed July 9, 2023. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalOutpatientPPS/Downloads/JW-Modifier-FAQs.pdf
3. Centers for Medicare & Medicaid Services (CMS). July 2023 Alpha-Numeric HCPCS File. Accessed June 29, 2023. https://www.cms.gov/files/zip/july-2023-alpha-numeric-hcpcs-file.zip
4. FDA. National Drug Code Database Background Information. Accessed November 17, 2021. https://www.fda.gov/drugs/development-approval-process-drugs/national-drug-code-database-background-information
5. Ruxience prescribing information. Pfizer Inc.; 2021.
6. American Medical Association. 2021 CPT Professional Edition. Current Procedural Terminology (CPT®) is copyright 2020 by the American Medical Association. All rights reserved. Chicago, IL: AMA; 2020.
7. Centers for Medicare & Medicaid Services (CMS). Transmittal 167. Accessed November 17, 2021. https://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/downloads/R167CP.pdf
8. Research Data Assistance Center (ResDAC). Revenue center code. Accessed November 17, 2021. https://resdac.org/sites/datadocumentation.resdac.org/files/Revenue%20Center%20Code%20Table_2.txt
9. Centers for Medicare & Medicaid Services (CMS). 2022 ICD-10-CM Tabular list of disease and injuries. Accessed November 17, 2021. https://www.cms.gov/medicare/icd-10/2022-icd-10-cm

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IMPORTANT SAFETY INFORMATION

BOXED WARNINGS

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

Infusion-Related Reactions: Rituximab product administration can result in serious, including fatal, infusion-related reactions. Deaths within 24 hours of rituximab infusion have occurred. Approximately 80% of fatal infusion-related reactions occurred in association with the first infusion. Monitor patients closely. Discontinue RUXIENCE 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 rituximab products. Discontinue RUXIENCE in patients who experience a severe mucocutaneous reaction. The safety of readministration of RUXIENCE to patients with severe mucocutaneous reactions has not been determined

Hepatitis B Virus (HBV) Reactivation: HBV reactivation can occur in patients treated with rituximab products, 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 RUXIENCE. Discontinue RUXIENCE and concomitant medications in the event of HBV reactivation

Progressive Multifocal Leukoencephalopathy (PML), including fatal PML, can occur in patients receiving rituximab products. Discontinue RUXIENCE and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML

Infusion-Related Reactions (IRR)

- Rituximab products can cause severe, including fatal, infusion-related reactions. Severe reactions typically occurred during the first infusion with time to onset of 30–120 minutes
- Rituximab product–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. For patients with rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis), and microscopic polyangiitis (MPA), methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion. Institute medical management (eg, glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion-related reactions as needed. Depending on the severity of the infusion-related reaction and the required interventions, temporarily or permanently discontinue RUXIENCE. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved
- Closely monitor the following patients: those with preexisting 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)

Severe Mucocutaneous Reactions

- Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with rituximab products. 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 rituximab exposure. Discontinue RUXIENCE in patients who experience a severe mucocutaneous reaction. The safety of readministration of rituximab products to patients with severe mucocutaneous reactions has not been determined

Hepatitis B Virus (HBV) Reactivation

- 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 products. 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 has also occurred in patients who appear to have resolved hepatitis B infection (ie, 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, ie, increase in transaminase levels. In severe cases, increase in bilirubin levels, liver failure, and death can occur

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IMPORTANT SAFETY INFORMATION (Continued)

Hepatitis B Virus (HBV) Reactivation (Continued)

- Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with RUXIENCE. 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 RUXIENCE 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 RUXIENCE therapy. HBV reactivation has been reported up to 24 months following completion of rituximab therapy
- In patients who develop reactivation of HBV while on RUXIENCE, immediately discontinue RUXIENCE and any concomitant chemotherapy, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming rituximab product treatment in patients who develop HBV reactivation. Resumption of RUXIENCE 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 progressive multifocal leukoencephalopathy (PML) and death can occur in rituximab product-treated patients with hematologic malignancies or with autoimmune diseases. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. The patients with autoimmune diseases had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab
- 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 RUXIENCE and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML

Tumor Lysis Syndrome (TLS)

- Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, some fatal, can occur within 12–24 hours after the first infusion of RUXIENCE in patients with non-Hodgkin's lymphoma (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 antihyperuricemic 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 rituximab product-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 RUXIENCE for serious infections and institute appropriate anti-infective therapy
- RUXIENCE 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 rituximab products. Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all infusions of RUXIENCE 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 rituximab product administration in patients with NHL. Renal toxicity has occurred in patients who experience TLS and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and RUXIENCE is not an approved treatment regimen. Monitor closely for signs of renal failure and discontinue RUXIENCE in patients with a rising serum creatinine or oliguria

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Please see full Prescribing Information for RUXIENCE, including BOXED WARNINGS and Medication Guide.

IMPORTANT SAFETY INFORMATION (Continued)

Bowel Obstruction and Perforation

- Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, can occur in patients receiving rituximab products 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 rituximab product therapy has not been studied, and vaccination with live virus vaccines is not recommended before or during treatment
- For patients treated with RUXIENCE, 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 RUXIENCE; administer nonlive vaccines at least 4 weeks prior to a course of RUXIENCE
- The effect of rituximab on immune responses was assessed in a randomized, controlled study in patients with RA treated with rituximab and methotrexate (MTX) compared to patients treated with MTX alone
- A response to pneumococcal vaccination (a T-cell–independent antigen) as measured by an increase in antibody titers to at least 6 of 12 serotypes was lower in patients treated with rituximab plus MTX as compared to patients treated with MTX alone (19% vs 61%). A lower proportion of patients in the rituximab plus MTX group developed detectable levels of anti-keyhole limpet hemocyanin antibodies (a novel protein antigen) after vaccination compared to patients on MTX alone (47% vs 93%)
- A positive response to tetanus toxoid vaccine (a T-cell–dependent antigen with existing immunity) was similar in patients treated with rituximab plus MTX compared to patients on MTX alone (39% vs 42%). The proportion of patients maintaining a positive Candida skin test (to evaluate delayed type hypersensitivity) was also similar (77% of patients on rituximab plus MTX vs 70% of patients on MTX alone)
- Most patients in the rituximab-treated group had B-cell counts below the lower limit of normal at the time of immunization. The clinical implications of these findings are not known

Embryo-Fetal Toxicity

- Based on human data, rituximab products can cause fetal harm due to B-cell lymphocytopenia in infants exposed in utero. Advise pregnant women of the potential risk to a fetus. Verify pregnancy status in females of reproductive potential prior to initiating RUXIENCE. Advise females of reproductive potential to use effective contraception during treatment with RUXIENCE and for 12 months after the last dose

Concomitant Use With Other Biologic Agents and Disease Modifying Antirheumatic Drugs (DMARDs), Other Than MTX, in RA, GPA, and MPA

- Limited data are available on the safety of the use of biologic agents or DMARDs, other than MTX, in RA patients exhibiting peripheral B-cell depletion following treatment with rituximab products. Observe patients closely for signs of infection if biologic agents and/or DMARDs are used concomitantly. Use of concomitant immunosuppressants other than corticosteroids has not been studied in GPA or MPA patients exhibiting peripheral B-cell depletion following treatment with rituximab products

Use in RA Patients Who Have Not Had Prior Inadequate Response to Tumor Necrosis Factor (TNF) Antagonists

- While the efficacy of rituximab was supported in 4 controlled trials in patients with RA with prior inadequate responses to non-biologic DMARDs, and in a controlled trial in MTX-naïve patients, a favorable risk-benefit relationship has not been established in these populations. The use of RUXIENCE in patients with RA who have not had prior inadequate response to one or more TNF antagonists is not recommended

Lactation

- Rituximab has 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 RUXIENCE and for 6 months after the last dose due to the potential for serious adverse reactions in breastfed children

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IMPORTANT SAFETY INFORMATION (Continued)

Adverse Reactions

- The most common grade 3 or 4 adverse reactions in clinical trials of NHL and chronic lymphocytic leukemia (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
- In RA clinical trials, among all exposed patients, adverse reactions reported in greater than 10% of patients include infusion-related reactions, upper respiratory tract infection, nasopharyngitis, urinary tract infection, and bronchitis
- In RA placebo-controlled studies, adverse reactions reported in ≥5% of patients were hypertension (8% vs 5%), nausea (8% vs 5%), upper respiratory tract infection (7% vs 6%), arthralgia (6% vs 4%), pyrexia (5% vs 2%), and pruritus (5% vs 1%), rituximab-treated vs placebo, respectively

Clinical Trials Experience in RA Infusion-Related Reactions

- In the rituximab RA pooled placebo-controlled studies, 32% of rituximab-treated patients experienced an adverse reaction during or within 24 hours following their first infusion, compared to 23% of placebo-treated patients receiving their first infusion. The incidence of adverse reactions during the 24-hour period following the second infusion, rituximab or placebo, decreased to 11% and 13%, respectively. Acute infusion-related reactions (manifested by fever, chills, rigors, pruritus, urticaria/rash, angioedema, sneezing, throat irritation, cough, and/or bronchospasm, with or without associated hypotension or hypertension) were experienced by 27% of rituximab-treated patients following their first infusion, compared to 19% of placebo-treated patients receiving their first placebo infusion. The incidence of these acute infusion-related reactions following the second infusion of rituximab or placebo decreased to 9% and 11%, respectively. Serious acute infusion-related reactions were experienced by <1% of patients in either treatment group. Acute infusion-related reactions required dose modification (stopping, slowing, or interruption of the infusion) in 10% and 2% of patients receiving rituximab or placebo, respectively, after the first course

Infections

- In the pooled, placebo-controlled studies, 39% of patients in the rituximab group experienced an infection of any type compared to 34% of patients in the placebo group. The most common infections were nasopharyngitis, upper respiratory tract infections, urinary tract infections, bronchitis, and sinusitis
- The incidence of serious infections was 2% in the rituximab-treated patients and 1% in the placebo group
- In the experience with rituximab in 2578 RA patients, the rate of serious infections was 4.31 per 100 patient-years. The most common serious infections (≥ 0.5%) were pneumonia or lower respiratory tract infections, cellulitis, and urinary tract infections. Fatal serious infections included pneumonia, sepsis, and colitis. Rates of serious infection remained stable in patients receiving subsequent courses. In 185 rituximab-treated RA patients with active disease, subsequent treatment with a biologic DMARD, the majority of which were TNF antagonists, did not appear to increase the rate of serious infection

Cardiovascular Adverse Reactions

- In the pooled, placebo-controlled studies, the proportion of patients with serious cardiovascular reactions was 1.7% and 1.3% in the rituximab and placebo treatment groups, respectively. Three cardiovascular deaths occurred during the double-blind period of the RA studies including all rituximab regimens (3/769=0.4%) as compared to none in the placebo treatment group (0/389)
- In the experience with rituximab in 2578 RA patients, the rate of serious cardiac reactions was 1.93 per 100 patient-years. The rate of myocardial infarction (MI) was 0.56 per 100 patient-years (28 events in 26 patients), which is consistent with MI rates in the general RA population. These rates did not increase over 3 courses of rituximab
- Since patients with RA are at increased risk for cardiovascular events compared with the general population, patients with RA should be monitored throughout the infusion and RUXIENCE should be discontinued in the event of a serious or life-threatening cardiac event

Please see full Prescribing Information for RUXIENCE, including BOXED WARNINGS and Medication Guide.

IMPORTANT SAFETY INFORMATION (Continued)

Hypophosphatemia and Hyperuricemia

- In the pooled, placebo-controlled studies, newly occurring hypophosphatemia (<2.0 mg/dL) was observed in 12% (67/540) of patients on rituximab vs 10% (39/398) of patients on placebo. Hypophosphatemia was more common in patients who received corticosteroids. Newly occurring hyperuricemia (>10 mg/dL) was observed in 1.5% (8/540) of patients on rituximab vs 0.3% (1/398) of patients on placebo

Retreatment in Patients With RA

- In the experience with rituximab in RA patients, 2578 patients have been exposed to rituximab and have received up to 10 courses of rituximab in RA clinical trials, with 1890, 1043, and 425 patients having received at least 2, 3, and 4 courses, respectively. Most of the patients who received additional courses did so 24 weeks or more after the previous course and none were retreated sooner than 16 weeks. The rates and types of adverse reactions reported for subsequent courses of rituximab were similar to rates and types seen for a single course of rituximab
- In RA Study 2, where all patients initially received rituximab, the safety profile of patients who were retreated with rituximab was similar to those who were retreated with placebo

Immunogenicity

- A total of 273/2578 (11%) patients with RA tested positive for antirituximab antibodies at any time after receiving rituximab. Antirituximab antibody positivity was not associated with increased rates of infusion-related reactions or other adverse events. Upon further treatment, the proportions of patients with infusion-related reactions were similar between antirituximab antibody–positive and –negative patients, and most reactions were mild to moderate. Four antirituximab antibody–positive patients had serious infusion-related reactions, and the temporal relationship between antirituximab antibody positivity and infusion-related reaction was variable

Clinical Trials Experience in GPA and MPA

- Adverse reactions reported in ≥15% of rituximab-treated patients were infections, nausea, diarrhea, headache, muscle spasms, anemia, and peripheral edema (other important adverse reactions include infusion-related reactions)

Induction Treatment of Patients With Active GPA/MPA (GPA/MPA Study 1)

Infusion-Related Reactions

- In GPA/MPA Study 1, 12% vs 11% (rituximab-treated vs cyclophosphamide-treated, respectively) of patients experienced at least one infusion-related reaction. Infusion-related reactions included cytokine release syndrome, flushing, throat irritation, and tremor. In the rituximab group, the proportion of patients experiencing an infusion reaction was 12%, 5%, 4%, and 1% following the first, second, third, and fourth infusions, respectively. Patients were premedicated with antihistamine and acetaminophen before each rituximab infusion and were on background oral corticosteroids, which may have mitigated or masked an infusion-related reaction; however, there is insufficient evidence to determine whether premedication diminishes the frequency or severity of infusion-related reactions

Infections

- In GPA/MPA Study 1, 62% vs 47% (rituximab-treated vs cyclophosphamide-treated, respectively) of patients experienced an infection by month 6. The most common infections in the rituximab group were upper respiratory tract infections, urinary tract infections, and herpes zoster. The incidence of serious infections was 11% vs 10% (rituximab-treated vs cyclophosphamide-treated, respectively), with rates of approximately 25 and 28 per 100 patient-years, respectively. The most common serious infection was pneumonia

Hypogammaglobulinemia

- Hypogammaglobulinemia (IgA, IgG, or IgM below the lower limit of normal) has been observed in patients with GPA and MPA treated with rituximab in GPA/MPA Study 1. At 6 months, in the rituximab group, 27%, 58%, and 51% of patients with normal immunoglobulin levels at baseline had low IgA, IgG, and IgM levels, respectively, compared to 25%, 50%, and 46% in the cyclophosphamide group

Immunogenicity

- A total of 23/99 (23%) rituximab-treated adult patients with GPA or MPA tested positive for antirituximab antibodies by 18 months in GPA/MPA Study 1. The clinical relevance of antirituximab antibody formation in rituximab-treated adult patients is unclear

Continued on the next page

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IMPORTANT SAFETY INFORMATION (Continued)

Treatment of Patients With GPA/MPA Who Have Achieved Disease Control With Induction Treatment (GPA/MPA Study 2)

- In GPA/MPA Study 2, the safety profile was consistent with the known safety profile of rituximab in immunologic indications

Infusion-Related Reactions (IRR)

- In GPA/MPA Study 2, 7/57 (12%) patients in the non-US-licensed approved rituximab arm reported infusion-related reactions. The incidence of IRR symptoms was highest during or after the first infusion (9%) and decreased with subsequent infusions (<4%). One patient had 2 serious IRRs; 2 IRRs led to a dose modification; and no IRRs were severe, fatal, or led to withdrawal from the study

Infections

- In GPA/MPA Study 2, 30/57 (53%) patients in the non-US-licensed approved rituximab arm and 33/58 (57%) in the azathioprine arm reported infections. The incidence of all-grade infections was similar between the arms. The incidence of serious infections was similar in both arms (12%). The most commonly reported serious infection in the group was mild or moderate bronchitis

INDICATIONS

- Non-Hodgkin's Lymphoma (NHL)
  RUXIENCE® (rituximab-pvvr) 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 cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy
  - Previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens
- Chronic Lymphocytic Leukemia (CLL)
  - In combination with fludarabine and cyclophosphamide (FC), for the treatment of adult patients with previously untreated and previously treated CD20-positive CLL
- Rheumatoid Arthritis (RA)
  - In combination with methotrexate (MTX), for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies
- Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids

Attention Healthcare Provider: Provide Medication Guide to patients prior to RUXIENCE infusion and advise patients to read guide.

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/MedWatch.

Please see full Prescribing Information for RUXIENCE, including BOXED WARNINGS and Medication Guide.