FDA-approved biosimilars such as rituximab-pvvr (RUXIENCE®) are recommended as appropriate substitutes for rituximab in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[1,2*†]

INJECTION
Ruxience®
rituximab-pvvr
Pfizer

RUXIENCE® (rituximab-pvvr)

Product Monograph

BUILDING ONTO THE CLINICAL EXPERIENCE OF RITUXIMAB

*Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar and the reference product.

†NCCN Guidelines® recommend the use of an FDA-approved biosimilar as an appropriate substitute for rituximab. See the NCCN Guidelines for detailed recommendations, including specific treatment regimens. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

SELECTED 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

(continued on next page)

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Please see Important Safety Information and Indications on pages 31-42 and full Prescribing Information, including BOXED WARNINGS and Medication Guide, also available at RuxienceHCP.com.

Next

Indications

RUXIENCE® (rituximab-pvvr) is FDA approved for the following listed indications of Rituxan® (rituximab)[3]

INDICATIONS

Non-Hodgkin's Lymphoma (NHL)

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, and 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

Please see Important Safety Information and Indications on pages 31-42 and full Prescribing Information, including BOXED WARNINGS and Medication Guide, also available at RuxienceHCP.com.

SELECTED SAFETY INFORMATION

BOXED WARNINGS (CONTINUED)

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

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

(continued on next page)

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Indications

RUXIENCE® (rituximab-pvvr) is FDA approved for the following listed indications of Rituxan® (rituximab)[3]

INDICATIONS

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

Please see Important Safety Information and Indications on pages 31-42 and full Prescribing Information, including BOXED WARNINGS and Medication Guide, also available at RuxienceHCP.com.

SELECTED SAFETY INFORMATION

BOXED WARNINGS (CONTINUED)

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

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

(continued on next page)

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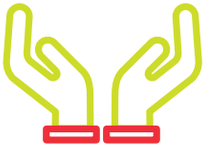
With the largest portfolio of biosimilars—including RUXIENCE® (rituximab-pvvr)—Pfizer is committed to expanding options for patient care[4]

Favorable coverage[5]

Potential savings[5]



Support for you and your patients

Pfizer has over 30 years of biologic experience, and more than a decade in the global biosimilars market.[5,6]

Please see Important Safety Information and Indications on pages 31-42 and full Prescribing Information, including BOXED WARNINGS and Medication Guide, also available at RuxienceHCP.com.

SELECTED SAFETY INFORMATION

BOXED WARNINGS (CONTINUED)

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

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

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RUXIENCE® (rituximab-pvvr) coverage for oncology patients

Learn about access in your area

Coverage for RUXIENCE varies by location. Your Pfizer Sales Representative can share plan-specific commercial and Medicare coverage rates in your region.

Please see Important Safety Information and Indications on pages 31-42 and full Prescribing Information, including BOXED WARNINGS and Medication Guide, also available at RuxienceHCP.com.

SELECTED SAFETY INFORMATION

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

(continued on next page)

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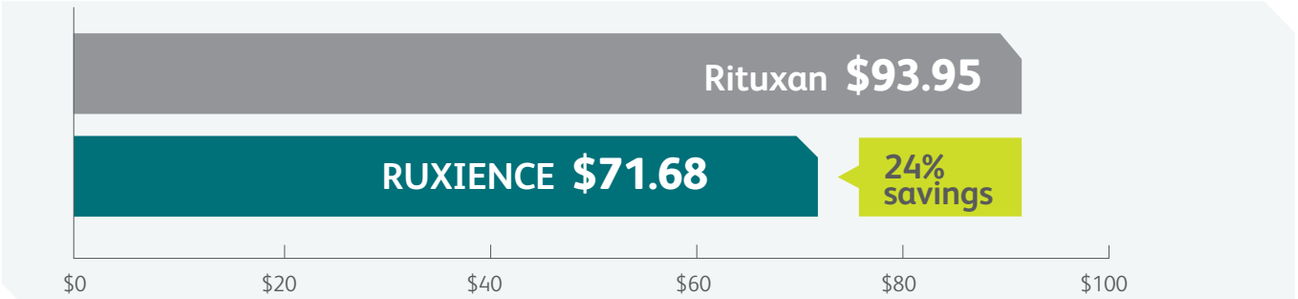
Potential cost savings with RUXIENCE® (rituximab-pvvr)

Wholesale acquisition cost (WAC) represents a 24% discount vs Rituxan® (rituximab) per 10 mg[5*]



An estimated cumulative maximum potential savings over 10 years from implementation of all available biosimilars could reach as much as $150 billion.[7†]

*WAC is a manufacturer's undiscounted or list price to wholesalers/direct purchasers and, therefore, is not inclusive of discounts to payers, providers, distributors, and other purchasing organizations. Data as of October 2022.

†Estimated reduction in direct spending on biologic drugs between 2017 and 2026 (RAND Corporation). Based on an assumption of a biosimilar market share of 50% and biosimilar prices at 50% of the reference product.

Please see Important Safety Information and Indications on pages 31-42 and full Prescribing Information, including BOXED WARNINGS and Medication Guide, also available at RuxienceHCP.com.

SELECTED SAFETY INFORMATION

Infusion-Related Reactions (IRR) (continued)

- 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 (≥25,000/mm^3)

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Pfizer Oncology Together™ Co-Pay Savings Program for Injectables

Eligible patients may pay as little as **$0** per Tx

Eligible,* commercially insured patients† may pay as little as $0 per RUXIENCE treatment.‡ Limits, terms, and conditions apply.

- This program covers up to **$25,000 per calendar year**§
- There are **no income requirements** for patients to qualify
- Patients enrolled in state- or federally funded prescription insurance programs are not eligible for this program
- For information on enrollment, claims submissions, and reimbursement, visit **PfizerOncologyTogether.com** to download the Co-Pay Savings Program Brochure

***Terms and Conditions:** By using this program, you acknowledge that you currently meet the eligibility criteria and will comply with the terms and conditions described below:

- The Pfizer Oncology Together Co-Pay Savings Program for Injectables for RUXIENCE is not valid for patients who are enrolled in a state or federally funded insurance program, including but not limited to Medicare, Medicaid, TRICARE, Veterans Affairs health care, a state prescription drug assistance program, or the Government Health Insurance Plan available in Puerto Rico (formerly known as "La Reforma de Salud").
- Program offer is not valid for cash-paying patients.
- Patients prescribed RUXIENCE for pemphigus vulgaris are not eligible for this co-pay savings program.

Click to view full Terms

†For patients to be eligible for the Injectables Co-Pay Program for RUXIENCE, they must have commercial insurance that covers RUXIENCE and they cannot be enrolled in a state or federally funded insurance program. Whether a co-pay expense is eligible for the Injectables Co-Pay Program for RUXIENCE benefit will be determined at the time the benefit is paid. Co-pay expenses must be in connection with a separately paid claim for RUXIENCE administered in the outpatient setting.

‡The Injectables Co-Pay Program for RUXIENCE will pay the co-pay for RUXIENCE up to the annual assistance limit of $25,000 per calendar year per patient.

§The Injectables Co-Pay Program for RUXIENCE provides assistance for eligible, commercially insured patients prescribed RUXIENCE for co-pays or coinsurance incurred for RUXIENCE up to $25,000 per calendar year. It does not cover or provide support for supplies, services, procedures, or any other physician-related services associated with RUXIENCE treatment.

Please see Important Safety Information and Indications on pages 31-42 and full Prescribing Information, including BOXED WARNINGS and Medication Guide, also available at RuxienceHCP.com.

SELECTED SAFETY INFORMATION

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

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*__Terms and Conditions:__ By using this program, you acknowledge that you currently meet the eligibility criteria and will comply with the terms and conditions described below:

- The Pfizer Oncology Together Co-Pay Savings Program for Injectables for RUXIENCE is not valid for patients who are enrolled in a state or federally funded insurance program, including but not limited to Medicare, Medicaid, TRICARE, Veterans Affairs health care, a state prescription drug assistance program, or the Government Health Insurance Plan available in Puerto Rico (formerly known as "La Reforma de Salud").
- Program offer is not valid for cash-paying patients.
- Patients prescribed RUXIENCE for pemphigus vulgaris are not eligible for this co-pay savings program.
- With this program, eligible patients may pay as little as $0 co-pay per RUXIENCE treatment, subject to a maximum benefit of $25,000 per calendar year for out-of-pocket expenses for RUXIENCE including co-pays or coinsurances.
- The amount of any benefit is the difference between your co-pay and $0. After the maximum of $25,000 you will be responsible for the remaining monthly out-of-pocket costs.
- Patient must have private insurance with coverage of RUXIENCE.
- This offer is not valid when the entire cost of your prescription drug is eligible to be reimbursed by your private insurance plans or other private health or pharmacy benefit programs.
- You must deduct the value of this assistance from any reimbursement request submitted to your private insurance plan, either directly by you or on your behalf.
- You are responsible for reporting use of the program to any private insurer, health plan, or other third party who pays for or reimburses any part of the prescription filled using the program, as may be required.
- You should not use the program if your insurer or health plan prohibits use of manufacturer co-pay assistance programs.
- This program is not valid where prohibited by law.
- This program cannot be combined with any other savings, free trial or similar offer for the specified prescription.
- **Co-pay card will be accepted only at participating pharmacies.**
- **This program is not health insurance.**
- This program is good only in the U.S. and Puerto Rico.
- This program is limited to 1 per person during this offering period and is not transferable.
- No other purchase is necessary.
- Data related to your redemption of the program assistance may be collected, analyzed, and shared with Pfizer, for market research and other purposes related to assessing Pfizer's programs. Data shared with Pfizer will be aggregated and de-identified; it will be combined with data related to other assistance redemptions and will not identify you.
- Pfizer reserves the right to rescind, revoke or amend this program without notice.
- This program may not be available to patients in all states.
- For more information about Pfizer, visit www.pfizer.com.
- For more information about the Pfizer Oncology Together Co-Pay Savings Program for Injectables, visit pfizeroncologytogether.com, call 1-877-744-5675, or write to
  Pfizer Oncology Together Co-Pay Savings Program for Injectables
  P.O. Box 220366
  Charlotte, NC 28222
- Program terms and offer will expire at the end of each calendar year. Before the calendar year ends, you will receive information and eligibility requirements for continued participation.

CLOSE

Navigating access and reimbursement. Together.

Pfizer Oncology together™

Patient Support. Financial Assistance. Together.

If patients need access or reimbursement support, Pfizer Oncology Together is here to help.

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 the PA requirements. After a PA request is submitted, we can follow up with the payer until a final outcome is determined.

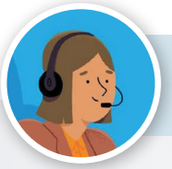
Appeals Assistance
We can review the reasons for a denied claim and provide information on payer requirements. After an appeal is submitted, we can follow up with the payer until a final outcome is determined.

Product Distribution
RUXIENCE is available through most major wholesalers.

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

Dedicated Local Support
A Pfizer Oncology Account Specialist can provide detailed information on Pfizer Oncology medications and access resources. In addition, they can help you and your office staff contact a Pfizer Field Reimbursement Manager (FRM) in your area.

FRMs are trained to help address specific access issues—in person or over the phone. They can help educate your staff on our access and reimbursement resources and help address challenging or urgent Pfizer Oncology patient cases you have sent to Pfizer Oncology Together.



FOR LIVE, PERSONALIZED SUPPORT
Call **1-877-744-5675** (Monday–Friday 8 AM–8 PM ET)

VISIT
PfizerOncologyTogether.com

Please see Important Safety Information and Indications on pages 31-42 and full Prescribing Information, including BOXED WARNINGS and Medication Guide, also available at RuxienceHCP.com.

SELECTED SAFETY INFORMATION

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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Pfizer is committed to supporting you and your patients

For commercially insured patients

Co-Pay Savings Program for Injectables

Finding financial support options. Together.

Limits, terms, and conditions apply.
Please see page 7 for terms and conditions.

Eligible patients may pay as little as **$0** per Tx

Pfizer Oncology together™

FOR LIVE, PERSONALIZED SUPPORT
Call **1-877-744-5675** (Monday–Friday 8 AM–8 PM ET) or
Visit **PfizerOncologyTogether.com**

PfizerBiosimilarsResource.com

Downloadable tools are available to help support you when implementing Pfizer biosimilars into your practice.

ThisIsLivingWithCancer.com

A free app designed to help manage life with cancer

Help your patients and their caregivers stay connected and get organized by telling them about **LivingWith™**.

The **LivingWith** app is available to anyone living with cancer and their loved ones, and is not specific to RUXIENCE.

Pfizer enCompass®

Patients treated for RA with RUXIENCE can receive support through Pfizer enCompass®. For assistance, call Pfizer enCompass at 1-844-722-6672, Monday–Friday, 8 AM–8 PM ET.

Please see Important Safety Information and Indications on pages 31-42 and full Prescribing Information, including BOXED WARNINGS and Medication Guide, also available at RuxienceHCP.com.

SELECTED SAFETY INFORMATION

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

(continued on next page)

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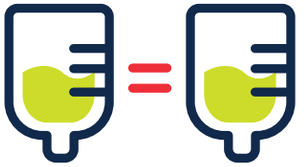
Introduction

Dosing and Administration

Ordering and Product Information

RUXIENCE® (rituximab-pvvr) is a biosimilar to Rituxan® (rituximab)[3]

Approved for 4 indications of Rituxan[3]



Same dosing and administration schedule as Rituxan[3]

Useful ordering and coding information

Please see Important Safety Information and Indications on pages 31-42 and full Prescribing Information, including BOXED WARNINGS and Medication Guide, also available at RuxienceHCP.com.

SELECTED SAFETY INFORMATION

Hepatitis B Virus (HBV) Reactivation (continued)

- 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

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Introduction >

Dosing and Administration >

Ordering and Product Information >

RUXIENCE® (rituximab-pvvr) has the same dosing and administration schedule as Rituxan® (rituximab)[3]

INDICATIONS AND USAGE	DOSING*
Non-Hodgkin's Lymphoma (NHL)†	
• Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL	• 375 mg/m^2 once weekly for 4 or 8 doses
• Retreatment for relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL	• 375 mg/m^2 once weekly for 4 doses
• Previously untreated follicular, CD20-positive, B-cell NHL	• 375 mg/m^2 on day 1 of each chemotherapy cycle for up to 8 doses. In patients with complete or partial response, initiate RUXIENCE maintenance 8 weeks after rituximab product + chemotherapy completion. Administer RUXIENCE as a single agent every 8 weeks for 12 doses
• Non-progressing, low-grade, CD20-positive, B-cell NHL, after first-line CVP chemotherapy	• 375 mg/m^2 once weekly for 4 doses at 6-month intervals (on completion of 6-8 cycles of CVP chemotherapy) for a maximum of 16 doses
• Diffuse large B-cell NHL	• 375 mg/m^2 on day 1 of each chemotherapy cycle for up to 8 infusions

CVP=cyclophosphamide, vincristine, and prednisone.
*Please see the Dosage and Administration section in the full Prescribing Information for additional details, including important dosing information, premedication and prophylactic medications, and administration and storage instructions.
†For administration of Zevalin® (ibritumomab tiuxetan) for the treatment for NHL, please see the full Prescribing Information.

Please see the full Prescribing Information for Important Dosing Considerations.

Please see Important Safety Information and Indications on pages 31-42 and full Prescribing Information, including BOXED WARNINGS and Medication Guide, also available at RuxienceHCP.com.

SELECTED SAFETY INFORMATION

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

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Introduction
Dosing and Administration
Ordering and Product Information

RUXIENCE® (rituximab-pvvr) has the same dosing and administration schedule as Rituxan® (rituximab)[3]

INDICATIONS AND USAGE	DOSING*
Chronic Lymphocytic Leukemia (CLL)	• 375 mg/m^2 on the day prior to the initiation of FC chemotherapy • Then 500 mg/m^2 on day 1 of cycles 2-6 (every 28 days)
Rheumatoid Arthritis (RA)	• Two 1000-mg intravenous infusions separated by 2 weeks • Subsequent courses should be administered every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks • RUXIENCE is given in combination with MTX
Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)	• Induction dose: 375 mg/m^2 once weekly for 4 weeks for active GPA or MPA† • Follow-up dose‡: Two 500-mg infusions separated by 2 weeks, followed by 500 mg every 6 months

FC=fludarabine and cyclophosphamide; MTX=methotrexate.
*Please see the Dosage and Administration section in the full Prescribing Information for additional details, including important dosing information, premedication and prophylactic medications, and administration and storage instructions.
†Please see the Dosage and Administration section in the full Prescribing Information for additional details, including recommended glucocorticoid administration and other dosing considerations.
‡Follow-up dosing for patients who have achieved disease control with induction treatment.

Please see the full Prescribing Information for Important Dosing Considerations.

Please see Important Safety Information and Indications on pages 31-42 and full Prescribing Information, including BOXED WARNINGS and Medication Guide, also available at RuxienceHCP.com.

SELECTED SAFETY INFORMATION

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

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Introduction

Dosing and Administration

Ordering and Product Information

RUXIENCE® (rituximab-pvvr) is available in single-dose vials for intravenous infusion[3]

Ordering RUXIENCE—What you need to know[3,8]

Unit of Sale	100 mg/10 mL SDV	500 mg/50 mL SDV
Unit of Sale NDC	0069-0238-01	0069-0249-01
Unit of Sale Quantity	1 vial per carton	1 vial per carton
Unit of Sale List Price*	$716.80	$3,584.00
HCPCS Code	Q5119	
OPPS Status	G: Pass-through payment	

OPPS=Outpatient Prospective Payment System; SDV=single-dose vial.
*As of October 2022.

Please see Important Safety Information and Indications on pages 31-42 and full Prescribing Information, including BOXED WARNINGS and Medication Guide, also available at RuxienceHCP.com.

SELECTED SAFETY INFORMATION

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

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Introduction

Dosing and Administration

Ordering and Product Information

RUXIENCE® (rituximab-pvvr) is available in single-dose vials for intravenous infusion[3]

Storage and handling

Available in **100 mg/10 mL SDVs** and **500 mg/50 mL SDVs**

Store in the refrigerator at 2 to 8 °C (36 to 46 °F)*

Keep in original carton and protect from light. Do not freeze or shake the vial or carton

*Diluted RUXIENCE solutions for infusion may be stored refrigerated at 2 to 8 °C (36 to 46 °F) for 24 hours. Complete administration within 8 hours from removal from refrigeration. No incompatibilities between RUXIENCE and polyvinylchloride bags have been observed.

Please see the full RUXIENCE Prescribing Information for additional details.

Please see Important Safety Information and Indications on pages 31-42 and full Prescribing Information, including BOXED WARNINGS and Medication Guide, also available at RuxienceHCP.com.

SELECTED SAFETY INFORMATION

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

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A totality of evidence supports biosimilarity to Rituxan® (rituximab)[3,9]

Biosimilarity established based on a totality of evidence[3,9]

Extrapolation allows potential approval for nonstudied indications[9]

No clinically meaningful differences in terms of efficacy or safety[5]

FDA-approved biosimilars such as rituximab-pvvr (RUXIENCE®) are recommended as appropriate substitutes for rituximab in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®).[1,2*]

*NCCN Guidelines® recommend the use of an FDA-approved biosimilar as an appropriate substitute for rituximab. See the NCCN Guidelines for detailed recommendations, including specific treatment regimens. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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SELECTED SAFETY INFORMATION

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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RUXIENCE® (rituximab-pvvr) was approved by the FDA based on the totality of evidence demonstrating it is highly similar to Rituxan® (rituximab)[3,9]

CLINICAL STUDY	RUXIENCE showed no clinically meaningful difference compared with Rituximab-EU[5*†]
CLINICAL PHARMACOLOGY (PK/PD)	RUXIENCE demonstrated PK similarity to Rituxan[5]
NONCLINICAL	RUXIENCE demonstrated similarity to Rituximab-EU based on TK and tolerability properties[5]
ANALYTICAL	Rigorous and comprehensive side-by-side analytical characterization was the cornerstone of the biosimilar development program and supports that RUXIENCE is highly similar to Rituxan in terms of structure and function[5]

PD=pharmacodynamic; PK=pharmacokinetic; TK=toxicokinetic.
*Product sourced from the EU is often used as a comparator in trials to demonstrate biosimilarity.
†MabThera is the brand name of rituximab outside of the United States.

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SELECTED SAFETY INFORMATION

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

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CLINICAL STUDY

RUXIENCE showed no clinically meaningful difference compared with Rituximab-EU[5*†]

- In a study of patients with CD20-positive, low–tumor burden follicular lymphoma,[‡] RUXIENCE demonstrated statistical equivalence to Rituximab-EU
  - ORR was 75.5% vs 70.7% for RUXIENCE and Rituximab-EU, respectively (95% CI: -4.16%, 13.47%)

CLINICAL PHARMACOLOGY (PK/PD)

RUXIENCE demonstrated PK similarity to Rituxan[5]

- In a phase 1/2 study, the 90% CIs for the test-to-reference ratios of C_{max} and $AUC_{0-\infty}$ were within the bioequivalence window of 80% to 125% for pairwise comparisons of RUXIENCE to Rituximab-EU, RUXIENCE to Rituximab-US, and Rituximab-EU to Rituximab-US

NONCLINICAL

RUXIENCE demonstrated similarity to Rituximab-EU based on TK and tolerability properties[5]

- Findings from the 2 comparative GLP-compliant toxicity studies with the incorporation of PD, PK/TK, and immunogenicity assessments demonstrated that RUXIENCE and licensed rituximab product produced similar effects to Rituxan in study animals

ANALYTICAL

Rigorous and comprehensive side-by-side analytical characterization was the cornerstone of the biosimilar development program and supports that RUXIENCE is highly similar to Rituxan in terms of structure and function[5]

Comparative characterization of physiochemical attributes included:

- Primary structure, post-translational modifications, molecular mass, protein concentration, purity, charge heterogeneity, higher-order structure, drug product stability (comparative forced degradation)

Comparative functional assessment included:

- In vitro biological activity (CDC, ADCC, apoptosis) and in vitro receptor binding and kinetics

ADCC=antibody-dependent cellular cytotoxicity; $AUC_{0-\infty}$=area under the serum concentration-time profile from time 0 extrapolated to infinite time; CDC=complement-dependent cytotoxicity; CI=confidence interval; C_{max}=maximum serum concentration; GLP=good laboratory practice; ORR=overall response rate; PD=pharmacodynamic; PK=pharmacokinetic; TK=toxicokinetic.

*Product sourced from the EU is often used as a comparator in trials to demonstrate biosimilarity.

†MabThera is the brand name of rituximab outside of the United States.

‡Based upon guidance from key health authorities, including FDA, this study was conducted to support biosimilarity. Neither Rituxan nor RUXIENCE is indicated for use as first-line monotherapy in this specific patient population.

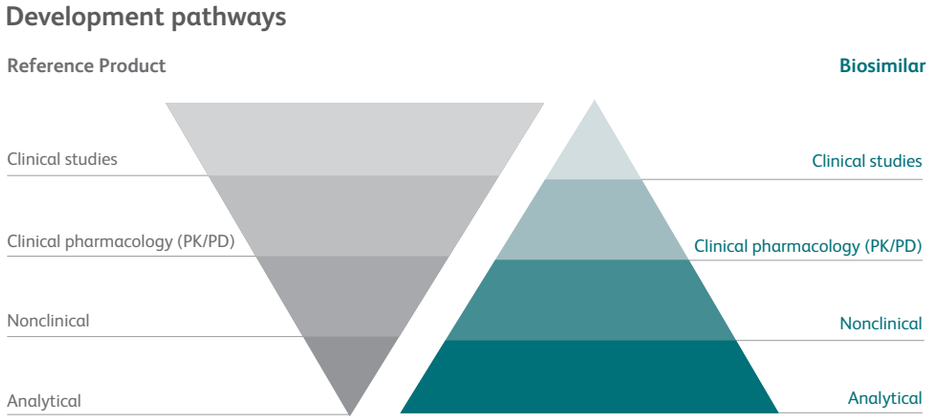
CLOSE

Please see Important Safety Information and Indications on pages 31-42 and full Prescribing Information, including BOXED WARNINGS and Medication Guide, also available at RuxienceHCP.com.

Biosimilars: Highly similar versions of existing biologic medicines[9]

- According to the FDA, a biosimilar is a medicine highly similar to another biological medicine or reference product already marketed in the United States
  - Biosimilars have no clinically meaningful differences in terms of safety, purity, and potency from their reference products

The FDA evaluates biosimilars based on a totality of evidence approach[9,10]



- The goal of biosimilar development is to demonstrate that there are no clinically meaningful differences based on the totality of evidence[9,10]
- Analytical studies are the foundation of biosimilar development and provide the greatest sensitivity for detecting differences between a biosimilar and its reference product[9,10]

Click to enlarge

SELECTED SAFETY INFORMATION

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

(continued on next page)

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- According to the FDA, a biosimilar is a medicine highly similar to another biological medicine or reference product already marketed in the United States
  - Biosimilars have no clinically meaningful differences in terms of safety, purity, and potency from their reference products

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CLOSE

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- 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

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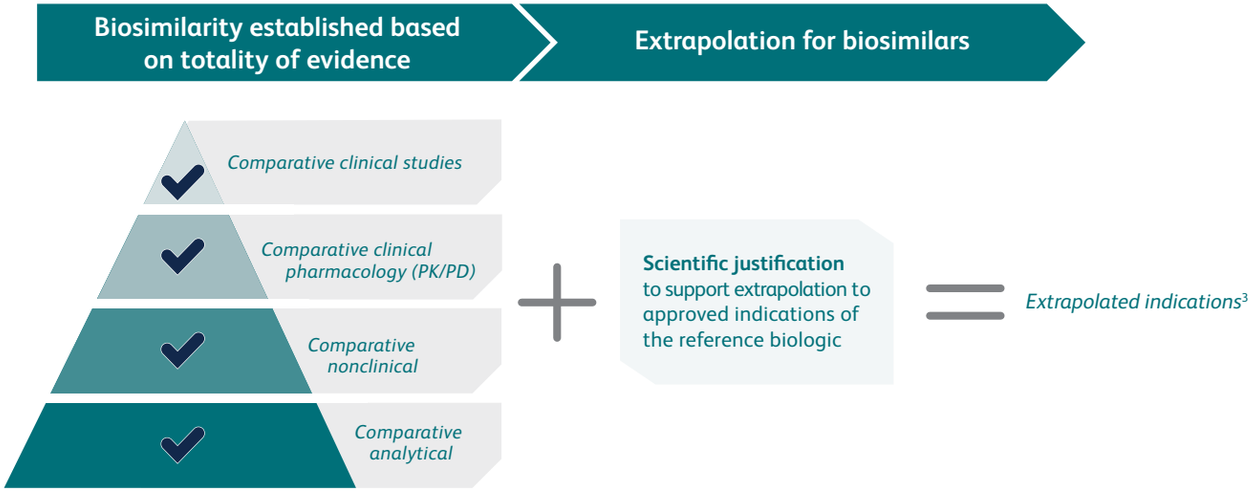
Extrapolation: After biosimilarity is established, allows potential approval for nonstudied indications[9]



Extrapolation builds on the thorough analysis of similarity between the biosimilar and reference biologic supported by the scientific evidence generated in robust analytical, nonclinical, and clinical comparability studies. Together with the well-known understanding of the reference biologic, this evidence is carefully analyzed to support scientific justification of extrapolated indications.[9]

Please see Important Safety Information and Indications on pages 31-42 and full Prescribing Information, including BOXED WARNINGS and Medication Guide, also available at RuxienceHCP.com.

SELECTED SAFETY INFORMATION

Immunization (continued)

- 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

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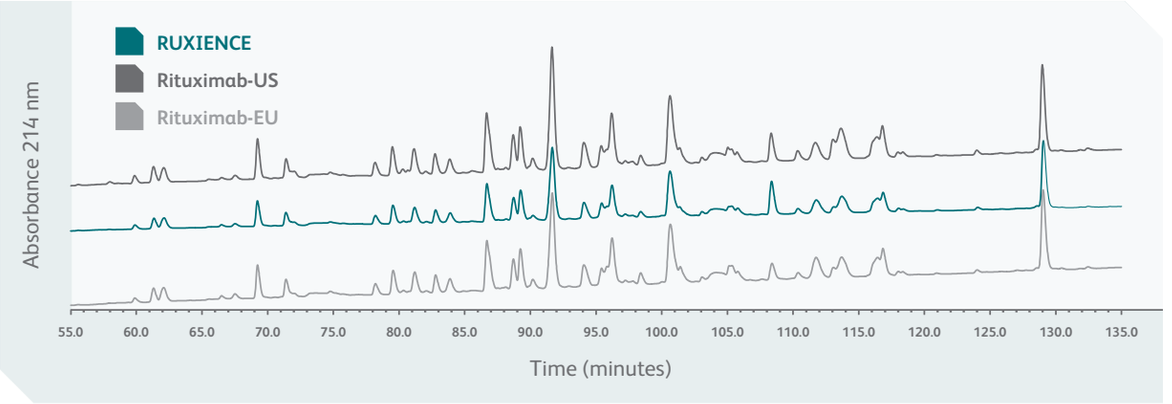
RUXIENCE® (rituximab-pvvr) is highly similar in structure and function to Rituxan® (rituximab)[5]

Structural similarity: Identical primary amino acid sequence†

Peptide mapping data supported identical primary amino acid sequence for RUXIENCE and Rituxan[5]



*RUXIENCE was highly similar to Rituxan in structure and function, as determined by using a comprehensive set of state-of-the-art analytical methods. There was little residual uncertainty after analytical and biological characterization.

†This is one of multiple tests conducted to demonstrate high similarity. In addition, primary structure, post-translational modifications, molecular mass, protein concentration, purity, charge heterogeneity, higher-order structure, and drug product stability (comparative forced degradation) all supported high similarity (not shown here).

SELECTED SAFETY INFORMATION

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

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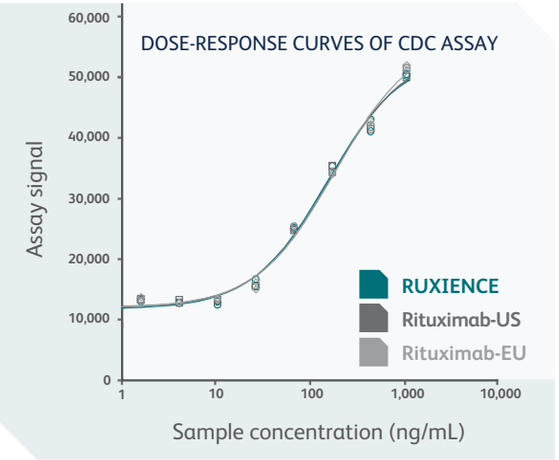
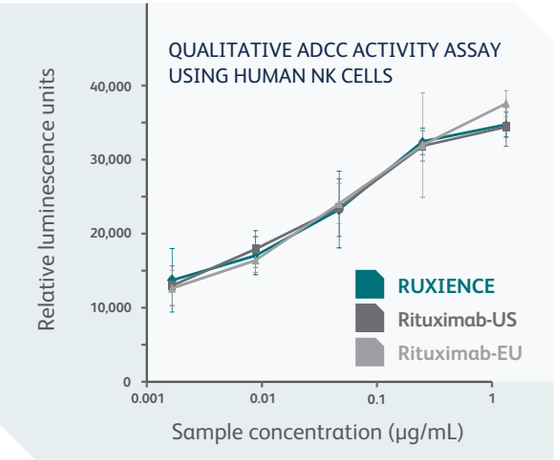
RUXIENCE® (rituximab-pvvr) is highly similar in structure and function to Rituxan® (rituximab)[5]

Functional similarity: Representative examples of dose-response curves from the development program that supported highly similar CDC and ADCC activity[5]





*RUXIENCE was highly similar to Rituxan in structure and function, as determined by using a comprehensive set of state-of-the-art analytical methods. There was little residual uncertainty after analytical and biological characterization.

SELECTED SAFETY INFORMATION

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

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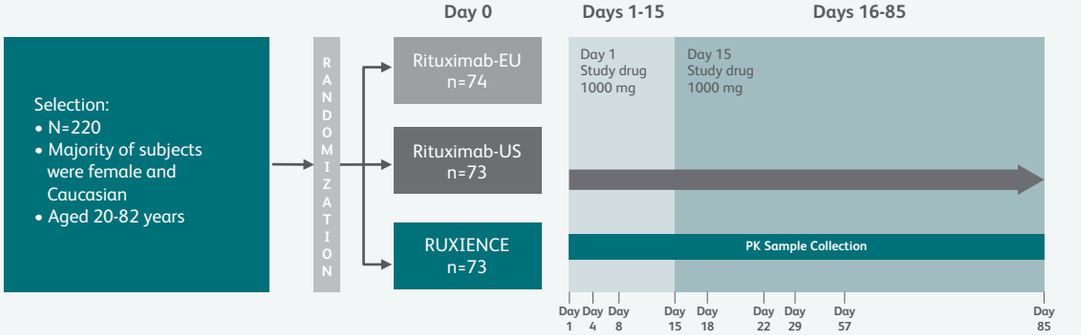
Double-blind, comparative clinical pharmacology study[5]



- Patients with active RA on a background of MTX who have had an inadequate response to 1 or more TNF antagonist therapies
- Dose: 1000 mg on study days 1 and 15
- Primary goal—to establish PK similarity
- Additional goals—to evaluate PD, safety, and immunogenicity similarity

This study was conducted to support biosimilarity.

Study Design
PK Profile
Adverse Events

Please see Important Safety Information and Indications on pages 31-42 and full Prescribing Information, including BOXED WARNINGS and Medication Guide, also available at RuxienceHCP.com.

SELECTED SAFETY INFORMATION

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

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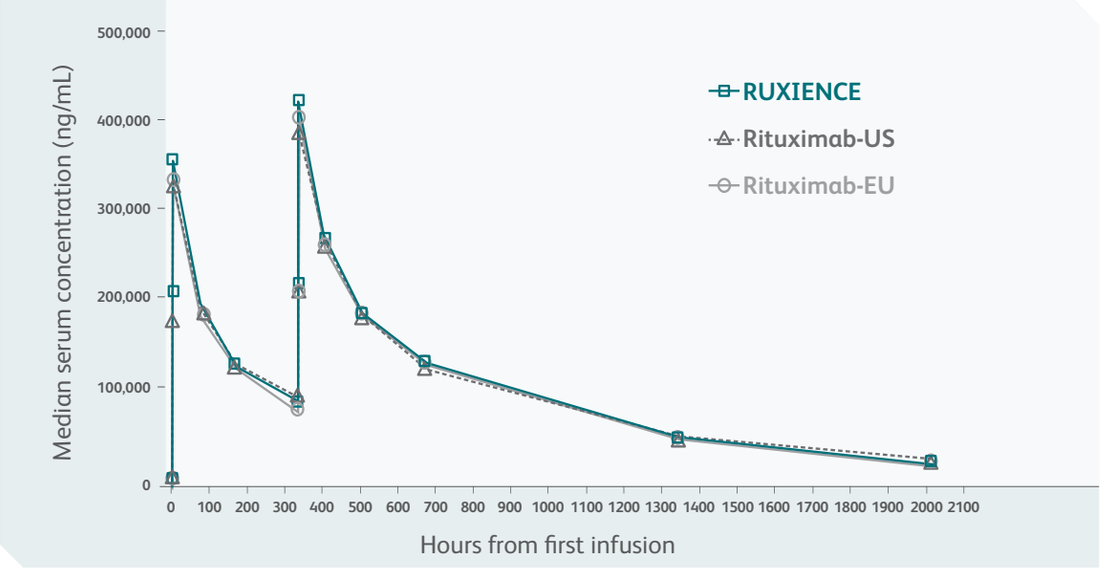
Similar PK profile to Rituximab-US and Rituximab-EU in a 3-arm study[5]

Median serum concentration-time profiles of RUXIENCE, Rituximab-US, and Rituximab-EU in 198 RA patients receiving 2 intravenous doses of 1000 mg on day 1 and day 15



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SELECTED SAFETY INFORMATION

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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Similar PK profile to rituximab across treatment groups[5]

Similarity to rituximab was determined in subjects with active RA on MTX with inadequate response to 1 or more TNF antagonist therapies

Summary of statistical comparisons of PK exposure parameters between test and reference products

Parameter (units)		Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means*	90% CI for Ratio
		Test	Reference		
RUXIENCE (Test) vs Rituximab-EU (Reference)	C_{max} (µg/mL)	432	409	105.67	(96.91, 115.21)
	$AUC_{0\text{-}T}$ (µg.hr/mL)	184,000	178,000	103.36	(92.81, 115.12)
	$AUC_{0\text{-}\infty}$ (µg.hr/mL)	196,000	188,000	104.19	(92.75, 117.06)
	$AUC_{0\text{-}2wk}$ (µg.hr/mL)	49,500	47,700	103.74	(95.10, 113.15)
RUXIENCE (Test) vs Rituximab-US (Reference)	C_{max} (µg/mL)	432	405	106.62	(97.65, 116.41)
	$AUC_{0\text{-}T}$ (µg.hr/mL)	184,000	181,000	101.33	(90.82, 113.04)
	$AUC_{0\text{-}\infty}$ (µg.hr/mL)	196,000	195,000	100.45	(89.20, 113.11)
	$AUC_{0\text{-}2wk}$ (µg.hr/mL)	49,500	46,900	105.56	(96.64, 115.30)
Rituximab-EU (Test) vs Rituximab-US (Reference)	C_{max} (µg/mL)	409	405	100.90	(92.38, 110.20)
	$AUC_{0\text{-}T}$ (µg.hr/mL)	178,000	181,000	98.03	(87.83, 109.40)
	$AUC_{0\text{-}\infty}$ (µg.hr/mL)	188,000	195,000	96.40	(85.57, 108.60)
	$AUC_{0\text{-}2wk}$ (µg.hr/mL)	47,700	46,900	101.76	(93.13, 111.18)

$AUC_{0\text{-}T}$=area under the serum concentration-time profile from time 0 to the last measured concentration at time T; $AUC_{0\text{-}2wk}$=area under the serum concentration-time profile from time 0 to 2 weeks.

*The ratios (and 90% CIs) are expressed as percentages.

This study was conducted to support biosimilarity.

Study Design
PK Profile
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SELECTED SAFETY INFORMATION

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

(continued on next page)

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Overall, there were no clinically meaningful differences among treatment groups in the incidence or severity of AEs[5]

Treatment-emergent AEs—all causalities (mITT population)[5]

n (%)	RUXIENCE n=73	Rituximab-EU n=74	Rituximab-US n=73
Patients with AEs	50 (68.5)	41 (55.4)	45 (61.6)
Patients with serious AEs	5 (6.8)	1 (1.4)	4 (5.5)
Patients withdrawn from treatment due to AEs	2 (2.7)	1 (1.4)	1 (1.4)
Patients with treatment-related AEs	22 (30.1)	17 (23.0)	18 (24.7)
Patients with AEs grade ≥3	10 (13.7)	1 (1.4)	10 (13.7)

AE=adverse event; mITT=modified intent to treat.

This study was conducted to support biosimilarity.

Study Design
PK Profile
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SELECTED SAFETY INFORMATION

Adverse Reactions (continued)

- 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

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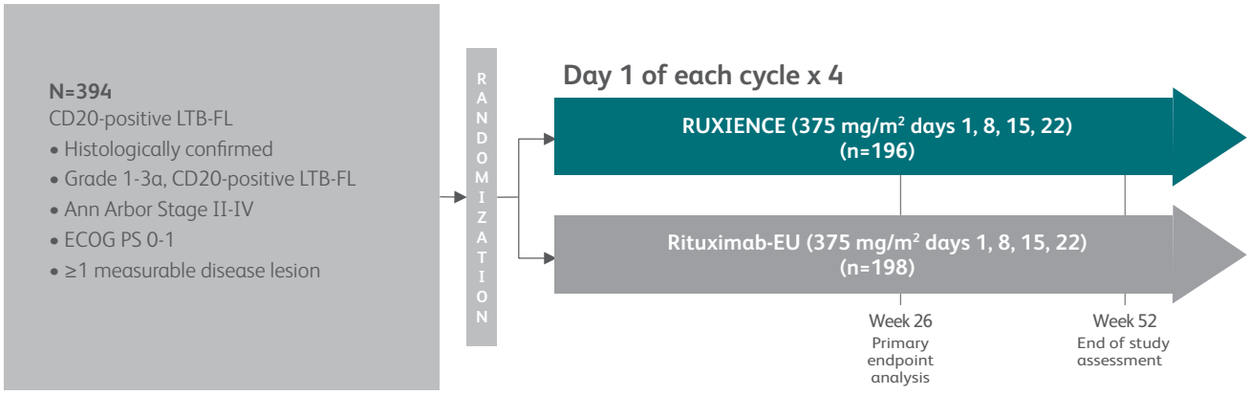
Primary comparative efficacy data in patients with low–tumor burden follicular lymphoma (LTB-FL)[5]

The primary objective of Study B3281006 was to compare the efficacy of RUXIENCE to rituximab when administered to patients with CD20-positive LTB-FL



ECOG PS=Eastern Cooperative Oncology Group performance status.
*Based on week 26 data.

Based upon guidance from key health authorities, including FDA, this study was conducted to support biosimilarity. Neither Rituxan® (rituximab) nor RUXIENCE® (rituximab-pvvr) is indicated for use as first-line monotherapy in this specific patient population.

Study Design
Primary Endpoint
Secondary Endpoints

SELECTED SAFETY INFORMATION
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

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*Primary comparative efficacy data in patients with low–tumor burden follicular lymphoma (LTB-FL)[5]**

Primary endpoint

- ORR at week 26 based on central review of radiographic assessment and clinical data for the ITT population (B-cell depletion and bone marrow biopsy results). Criteria based on Cheson et al, 2007
- The ORR was defined as the proportion of subjects who achieved either CR or partial response. Terminology based on Lugano Classification

The secondary objectives of Study B3281006 included:

- Evaluating the safety of RUXIENCE and Rituximab-EU
- Evaluating the population pharmacokinetics of RUXIENCE and Rituximab-EU
- Evaluating the immunogenicity of RUXIENCE and Rituximab-EU
- Characterizing CD19-positive B-cell depletion and recovery in subjects receiving RUXIENCE and Rituximab-EU

Secondary endpoints

- PFS, OS, TTF, DOR, and CR at week 26

CR=complete response; DOR=duration of response; ITT=intent to treat; OS=overall survival; PFS=progression-free survival; TTF=time-to-treatment failure.
*Based on week 26 data.

Based upon guidance from key health authorities, including FDA, this study was conducted to support biosimilarity. Neither Rituxan® (rituximab) nor RUXIENCE® (rituximab-pvvr) is indicated for use as first-line monotherapy in this specific patient population.

SELECTED SAFETY INFORMATION

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

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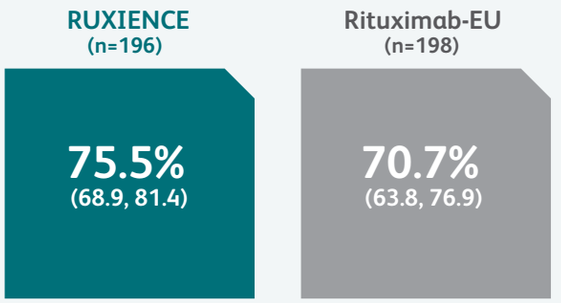
ORRs between the RUXIENCE® (rituximab-pvvr) and rituximab treatment groups at week 26 were equivalent[5]

Primary endpoint: ORR at week 26—central review assessment—ITT population[5]



4.66% difference RUXIENCE minus Rituximab-EU (-4.16, 13.47)

- The analysis of ORR showed an estimated difference of 4.66% (95% CI: -4.16, 13.47), which fell entirely within the prespecified equivalence margin agreed to by the FDA (±16%)

Based upon guidance from key health authorities, including FDA, this study was conducted to support biosimilarity. Neither Rituxan® (rituximab) nor RUXIENCE® (rituximab-pvvr) is indicated for use as first-line monotherapy in this specific patient population.

Study Design
Primary Endpoint
Secondary Endpoints

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SELECTED SAFETY INFORMATION

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

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Secondary endpoints involving RUXIENCE® (rituximab-pvvr) and Rituximab-EU evaluated:

- PFS, OS, TTF, DOR, and CR at week 26[5]
- The study was not designed to demonstrate equivalence in secondary endpoints[11]
- Review of immunogenicity data and cross-analyses with clinical data showed no notable differences between RUXIENCE and Rituximab-EU. At week 52, ADA formation was 21.5% in the RUXIENCE group and 20.4% in the Rituximab-EU group[11]

ADA=antidrug antibody.

Based upon guidance from key health authorities, including FDA, this study was conducted to support biosimilarity. Neither Rituxan® (rituximab) nor RUXIENCE® (rituximab-pvvr) is indicated for use as first-line monotherapy in this specific patient population.

Study Design
Primary Endpoint
Secondary Endpoints

Please see Important Safety Information and Indications on pages 31-42 and full Prescribing Information, including BOXED WARNINGS and Medication Guide, also available at RuxienceHCP.com.

SELECTED SAFETY INFORMATION

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

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RUXIENCE® (rituximab-pvvr) demonstrated a similar safety profile in the comparative clinical trial through week 26[5]

Summary of tier 1 treatment-emergent AEs for ≥2% of subjects in either treatment group (all causalities)—safety population

System Organ Class Preferred Term	Rituximab-EU n (%)	RUXIENCE n (%)	Risk Difference %	Lower Limit 95% CI %	Upper Limit 95% CI %
Injury, poisoning, and procedural complications					
Infusion-related reaction*	59 (29.9)	50 (25.5)	-4.4	-13.4	4.5
General disorders and administration site conditions					
Pyrexia	0	5 (2.6)	2.6	0.4	5.9
Infections and infestations					
Upper respiratory tract infection	5 (2.5)	9 (4.6)	2.1	-1.8	6.3
Sinusitis	2 (1.0)	5 (2.6)	1.5	-1.4	4.9
Urinary tract infection	5 (2.5)	5 (2.6)	0	-3.6	3.6
Pharyngitis	4 (2.0)	4 (2.0)	0	-3.3	3.4
Bronchitis	5 (2.5)	3 (1.5)	-1.0	-4.5	2.2
Nasopharyngitis	8 (4.1)	5 (2.6)	-1.5	-5.6	2.3
Investigations					
Neutrophil count decreased	0	5 (2.6)	2.6	0.4	5.9

Risk difference and 95% CI were obtained from Proc Binomial Asymptotic approach. The 95% CI was provided to help gauge the precision of the estimates for risk difference. CIs were not adjusted for multiplicity and were used for screening purposes only. Risk difference was computed as RUXIENCE vs Rituximab-EU. MedDRA (v20.1) coding dictionary applied.

MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term.
*Infusion-related reactions may or may not include other PTs within this table.

SELECTED SAFETY INFORMATION

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

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RUXIENCE® (rituximab-pvvr) demonstrated a similar safety profile in the comparative clinical trial through week 26[5]

Summary of tier 1 treatment-emergent AEs for ≥2% of subjects in either treatment group (all causalities)—safety population

System Organ Class Preferred Term	Rituximab-EU n (%)	RUXIENCE n (%)	Risk Difference %	Lower Limit 95% CI %	Upper Limit 95% CI %
Respiratory, thoracic, and mediastinal disorders					
Throat irritation	9 (4.6)	14 (7.1)	2.6	-2.2	7.6
Cough	11 (5.6)	11 (5.6)	0	-4.8	4.9
Dyspnea	9 (4.6)	6 (3.1)	-1.5	-5.8	2.6
Oropharyngeal pain	9 (4.6)	1 (0.5)	-4.1	-8.0	-1.0
Skin and subcutaneous tissue disorders					
Erythema	2 (1.0)	7 (3.6)	2.6	-0.5	6.3
Rash	8 (4.1)	10 (5.1)	1.0	-3.4	5.6
Urticaria	6 (3.0)	3 (1.5)	-1.5	-5.1	1.7
Pruritus	22 (11.2)	13 (6.6)	-4.5	-10.5	1.2
Vascular disorders					
Flushing	4 (2.0)	1 (0.5)	-1.5	-4.6	1.0

Risk difference and 95% CI were obtained from Proc Binomial Asymptotic approach. The 95% CI was provided to help gauge the precision of the estimates for risk difference. CIs were not adjusted for multiplicity and were used for screening purposes only. Risk difference was computed as RUXIENCE vs Rituximab-EU. MedDRA (v20.1) coding dictionary applied.

MedDRA=Medical Dictionary for Regulatory Activities.

SELECTED SAFETY INFORMATION

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

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Important Safety Information and Indications

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

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SELECTED SAFETY INFORMATION

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)

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Important Safety Information and Indications

- 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 (≥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)

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SELECTED SAFETY INFORMATION

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

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Important Safety Information and Indications

- 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
- 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

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SELECTED SAFETY INFORMATION

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

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Important Safety Information and Indications

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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SELECTED SAFETY INFORMATION

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

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Important Safety Information and Indications

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

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SELECTED SAFETY INFORMATION

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

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

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Important Safety Information and Indications

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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SELECTED SAFETY INFORMATION

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

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Important Safety Information and Indications

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

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SELECTED SAFETY INFORMATION

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

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Important Safety Information and Indications

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

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SELECTED 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

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Important Safety Information and Indications

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)

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SELECTED SAFETY INFORMATION

BOXED WARNINGS (CONTINUED)

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

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

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Important Safety Information and Indications

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

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SELECTED SAFETY INFORMATION

BOXED WARNINGS (CONTINUED)

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

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

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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

Please see Important Safety Information and Indications on pages 31-42 and full Prescribing Information, including BOXED WARNINGS and Medication Guide, also available at RuxienceHCP.com.

SELECTED SAFETY INFORMATION

BOXED WARNINGS (CONTINUED)

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

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

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Important Safety Information and Indications

- 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 Important Safety Information and Indications on pages 31-42 and full Prescribing Information, including BOXED WARNINGS and Medication Guide, also available at RuxienceHCP.com.

SELECTED SAFETY INFORMATION

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

(continued on next page)

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Summary

References

RUXIENCE® (rituximab-pvvr): Pfizer Oncology's commitment to building onto the clinical experience of rituximab

With the largest portfolio of biosimilars—including RUXIENCE—Pfizer is committed to expanding options for patient care[4]

Favorable coverage[5]

Potential savings[5]

Support for you and your patients

Approved for certain indications of Rituxan® (rituximab), with an identical dosing and administration schedule[3]

Realize the full potential of biosimilars. Ask about the Pfizer Oncology Biosimilars Portfolio

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SELECTED SAFETY INFORMATION

Infusion-Related Reactions (IRR) (continued)

- 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 (≥25,000/mm^3)

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Summary

References

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma V.1.2022. © 2021 National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the guideline, go online to NCCN.org.
2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas V.5.2021. © 2021 National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the guideline, go online to NCCN.org.
3. RUXIENCE [prescribing information]. New York, NY: Pfizer Inc.; November 2021.
4. Biehn B, Nell C. U.S. Biosimilar Report. AmerisourceBergen. October 17, 2022. Accessed November 10, 2022. https://www.amerisourcebergen.com/-/media/assets/amerisourcebergen/biosimilars-page/sgs-biosimilars-usmarketlandscape-101722-v1.pdf.
5. Data on file. Pfizer Inc.; New York, NY.
6. Generics and Biosimilar Initiative Online. Biosimilars approved in Europe. Updated July 1, 2022. Accessed October 12, 2022. https://gabionline.net/biosimilars/general/biosimilars-approved-in-europe.
7. Mulcahy AW, Hlavka JP, Case SR. Biosimilar cost savings in the United States: initial experience and future potential. *RAND Health Quarterly*. 2018;7(4):3.
8. Centers for Medicare & Medicaid Services. July 2020 Update of the Hospital Outpatient Prospective Payment System (OPPS). Updated July 1, 2020.
9. US Food and Drug Administration. Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Silver Spring, MD: FDA, US Dept of Health and Human Services; April 2015. Accessed October 12, 2022. https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf.
10. Melosky B, Reardon DA, Nixon AB, Subramanian J, Bair AH, Jacobs I. Bevacizumab biosimilars: scientific justification for extrapolation of indications. *Future Oncol*. 2018;14(24):2507-2520.
11. US Food and Drug Administration. Center for Drug Evaluation and Research. Application Number: 761103Orig1s000 Ruxience Summary Review. July 25, 2019. Accessed October 12, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761103Orig1s000SumR.pdf.

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SELECTED SAFETY INFORMATION

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

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