INJECTION
Inflectra®
infliximab-dyyb

INJECTION
Ruxience®
rituximab-pvvr

Pfizer enCompass® Patient Support Program Guide

Pfizer enCompass®

Please see full Prescribing Information for INFLECTRA, including BOXED WARNING and Medication Guide, on last pages or at INFLECTRApi.com.
Please see full Prescribing Information for RUXIENCE, including BOXED WARNING and Medication Guide, on last pages or at RUXIENCEhcp.com.

Pfizer is committed to offering reimbursement and patient support for eligible patients who have been prescribed INFLECTRA and RUXIENCE*. As part of this commitment, we have developed Pfizer enCompass (the Program). Pfizer enCompass provides access and reimbursement resources, support, and educational materials for patients prescribed INFLECTRA and RUXIENCE. Various free resources are available to help patients understand and navigate their treatment journey.

Reimbursement and patient support information is available at **www.pfizerencompass.com**.

For questions about how the Program may be able to help patients access INFLECTRA or RUXIENCE, please contact an Access Counselor at 1-844-722-6672, Monday through Friday, 8 AM to 8 PM ET.

*For more information on INFLECTRA, visit **www.inflectrahcp.com**.*
*For more information on RUXIENCE, visit **www.ruxiencehcp.com**.*

The Pfizer enCompass Provider Portal

The Program has a provider portal for healthcare providers (HCPs) and their staff. The portal allows the convenience of online, real-time access to Program support and resources, including patient insurance benefit investigations (BIs), prior authorizations (PAs), and patient support such as co-pay assistance for eligible patients. BIs may also be completed through the portal using electronic features such as electronic benefit investigation (eBI). To get started, select one of the following options:

Visit **www.pfizerencompassonline.com**, fill out the required information, and click "SIGN UP"

Call the Program at 1-844-722-6672 to speak to an Access Counselor about getting started with the provider portal.

Once registered, HCPs can request support for patients prescribed INFLECTRA and RUXIENCE, complete a BI and a PA, view progress on patient requests, and access HCP and patient brochures and resources.

*Pfizer enCompass supports eligible patients prescribed INFLECTRA and RUXIENCE for select FDA-approved indications. For more information, visit **www.pfizerencompass.com**. Additional FDA-approved indications for RUXIENCE may be supported by Pfizer Oncology Together. For more information, visit **www.pfizeroncologytogether.com**.

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Pfizer enCompass Patient Support

Verifying Patient Insurance Benefits

Verifying a patient's insurance coverage for INFLECTRA or RUXIENCE is the first step toward potential access and reimbursement for eligible patients.

- HCPs may request a BI on behalf of their patient in 1 of 4 ways:

A Enroll your patient through the provider portal and request a BI within the provider portal

B For HCPs who prefer a more self-service approach, an eBI may be initiated directly within the provider portal, even if you have not enrolled a patient

C Download a fillable PDF of the Pfizer enCompass Enrollment Form for INFLECTRA and RUXIENCE from **www.pfizerencompass.com** or from the provider portal and fax or mail the completed form to the Program

D Call the Program at 1-844-722-6672, Monday through Friday, 8 AM to 8 PM ET

After the Program completes a BI, it will provide a Summary of Patient Insurance Benefits that may include complete insurance information, such as:

Determination of payer-mandated specialty pharmacy	**Coverage limitations and restrictions**	**Patient out-of-pocket requirements**
PA and/or predetermination requirements	**Determination of specific insurance benefit that provides coverage for INFLECTRA or RUXIENCE**	

This information is not a guarantee of insurance coverage or reimbursement. All benefit information is subject to the insured patient's plan at the time support is provided.

The Program will fax the Summary of Patient Insurance Benefits approximately 2 business days after a BI request is submitted.

PA Assistance

The Program is available to assist eligible patients and their HCPs through the PA process by:

- Researching and identifying PA requirements and required submission forms
- Prepopulating the payer's PA form with the patient's demographic information and sending it to the HCP for completion and submission
- Monitoring and following up on the PA request after the HCP has submitted it to the patient's insurance until a final determination is made

Pfizer enCompass Follow-up With Claims Submission

General Coding and Billing Assistance

Program Access Counselors may provide general billing and coding guidance based on a payer's published policies. Additional coding and billing information may be available at the Pfizer enCompass website or the provider portal.†

Claims Assistance

Program Access Counselors are available to assist with:

- Status review for pending claims
- Research of underpaid and denied claims

Appeals Assistance*

If the claim is denied, the Program can provide support with the appeal process, where appropriate, by:

- Investigating the plan's reason(s) for denying a claim or PA request and determining if and how it may be appealed
- Providing a letter of appeal template
- Monitoring and following up on the status of an appeal until a final outcome is received

Pfizer enCompass Co-Pay Assistance Program

The Pfizer enCompass Co-Pay Assistance Program for INFLECTRA and RUXIENCE provides eligible, commercially insured patients assistance of up to $10,000 to $20,000 for INFLECTRA and $25,000 for RUXIENCE per calendar year for claims received by the Program. Eligible enrolled patients may pay as little as $0 for each INFLECTRA or RUXIENCE treatment. Federal and state healthcare beneficiaries are not eligible. The co-pay program is for patients with private insurance only and covers only drug costs, not procedures, administration fees, or office visits. See full Terms and Conditions at **www.PfizerCopay.com**.

*Appeals assistance is provided only for patients with FDA-approved indications.
†The HCP is solely responsible for determining coverage and reimbursement parameters and appropriate coding for treatment of their patients.

The Pfizer enCompass Co-Pay Portal

You can find the Pfizer enCompass Co-Pay Program at **www.PfizerCopay.com**.

- The co-pay portal allows HCPs to:
  - Register their practice
  - Select preferences, including payment method and payment address
    - Get paid by check or use electronic funds transfer (EFT)
      - Set up and maintain the payment within the portal
  - View a patient's status in the co-pay program
  - Submit claims
  - View claim and payment status history
  - Enroll eligible patients directly into the co-pay program if no other patient support is needed
- Enroll eligible patients directly into the co-pay program if no other support is needed
  - The co-pay portal will also allow eligible patients to register and self-enroll, if preferred
  - For patients needing additional support, HCPs may continue to enroll eligible patients into the Program where additional patient support, including BIs and financial assistance, may be identified

There are 2 ways to enroll your eligible patients in the Pfizer enCompass Co-Pay Assistance Program after you register your site on www.PfizerCopay.com.

1 Enroll your eligible patients into the co-pay program using the co-pay portal

- This is intended for eligible patients who do not require other patient support
- The co-pay card is activated in real time during enrollment

2 Enroll eligible patients requiring additional support into the Pfizer enCompass program

- Either fax or mail the completed enrollment form to Pfizer enCompass or complete the enrollment form on the provider portal at **www.pfizerencompassonline.com**
- Pfizer enCompass will determine eligibility for the co-pay program. If approved, you and your patient will receive an approval letter containing co-pay card numbers
- If you prefer a more self-service approach, log on to the provider portal to complete an eBI

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Meet the SmartCard!

The Pfizer enCompass Co-Pay Assistance Program includes a SmartCard option for HCPs to receive payment.

The SmartCard may be used as both a debit and co-pay card. Your patients use this card to pay their co-pays to HCPs using the debit card feature.

A co-pay claim must be submitted and approved prior to funds being loaded onto the SmartCard.

If you are receiving payment via EFT or paper check, you can still receive payment that way.

Claim Submission

You have 2 ways to submit your co-pay claims:

1. Submit claims directly at **www.PfizerCopay.com**
2. Fax claims to **1-877-847-FAX1** (1-877-847-3291)

- Claims must be submitted within 180 days of each treatment date
- Complete claims require a copy of the Explanation of Benefits (EOB) document for the treatment date, available from your patient's insurance company

Payment

- HCPs can receive payment via EFT or check
- Eligible patients who did not assign benefits to their HCP can get payment in the following ways:
  - **Check:** If the patient has already paid the co-pay, a check will be mailed to them
  - **Funds loaded onto the SmartCard:** The patient can provide the SmartCard to the HCP for payment processing

Getting Started With INFLECTRA or RUXIENCE

Process to Enroll Patients to Obtain Pfizer enCompass Support

1 Patient is prescribed treatment with INFLECTRA or RUXIENCE

2 HCP initiates enrollment into the Program by completing the Pfizer enCompass Enrollment Form

3

Option 1
Access Counselor performs a BI based on patient's information and faxes the Summary of Patient Insurance Benefits within 2 business days

Option 2
If the HCP prefers a more self-service approach, log on to the provider portal at **www.pfizerencompass.com** to complete an eBI

Option 3
HCP or eligible patient can enroll directly into the co-pay assistance program through **www.PfizerCopay.com**

4 If a BI is performed, an Access Counselor will refer eligible patients in need of assistance with out-of-pocket expenses to appropriate patient support options

5 HCP and patient schedule treatment

6 HCP administers treatment

7 HCP prepares and submits the claim to the patient's insurance

8 If participating in the Pfizer enCompass Co-Pay Assistance Program, the HCP, eligible patient, or specialty pharmacy will submit the claim either using the co-pay portal or the Pfizer Co-Pay Claim Form by following the instructions on the form and providing the EOB

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Pfizer enCompass®

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

INFLECTRA® (infliximab-dyyb) for injection, for intravenous use
Initial U.S. Approval: 2016
INFLECTRA (infliximab-dyyb) is biosimilar* to REMICADE (infliximab)

WARNING: SERIOUS INFECTIONS and MALIGNANCY

See full prescribing information for complete boxed warning

- **Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis) and infections due to other opportunistic pathogens. (5.1)**
- **Discontinue INFLECTRA if a patient develops a serious infection.**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting INFLECTRA. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)**
- **Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor (TNF) blockers, including infliximab products. (5.2)**
- **Postmarketing cases of fatal hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF blockers, including infliximab products. Almost all had received azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. The majority of cases were reported in patients with Crohn's disease or ulcerative colitis, most of whom were adolescent or young adult males. (5.2)**

---------- **INDICATIONS AND USAGE** ----------

INFLECTRA is a tumor necrosis factor (TNF) blocker indicated for:

Crohn's Disease (1.1):

- reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
- reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease.

Pediatric Crohn's Disease (1.2):

- reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy.

Ulcerative Colitis (1.3):

- reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.

Pediatric Ulcerative Colitis (1.4):

- reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy.

Rheumatoid Arthritis (1.5) in combination with methotrexate:

- reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active disease.

Ankylosing Spondylitis (1.6):

- reducing signs and symptoms in adult patients with active disease.

Psoriatic Arthritis (1.7):

- reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in adult patients.

Plaque Psoriasis (1.8):

- treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

---------- **DOSAGE AND ADMINISTRATION** ----------

Prior to treatment, ensure appropriate personnel and medication are available to treat reactions (e.g., hypersensitivity) that occur during infusion and shortly after infusion (2.11)

INFLECTRA is administered by intravenous infusion for at least 2 hours with an in-line filter (2.11)

Crohn's Disease (2.1)

- 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg every 8 weeks if they later lose their response.

Pediatric Crohn's Disease (≥ 6 years old) (2.2)

- 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Ulcerative Colitis (2.3)

- 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Pediatric Ulcerative Colitis (≥ 6 years old) (2.4)

- 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Rheumatoid Arthritis (2.5)

- In conjunction with methotrexate, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some patients may benefit from increasing the dose up to 10 mg/kg every 8 weeks or treating as often as every 4 weeks.

Ankylosing Spondylitis (2.6)

- 5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks.

Psoriatic Arthritis (2.7) and Plaque Psoriasis (2.8)

- 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

---------- **DOSAGE FORMS AND STRENGTHS** ----------

For injection: 100 mg of infliximab-dyyb as a lyophilized powder in a single-dose vial for reconstitution and dilution. (2.11, 3)

---------- **CONTRAINDICATIONS** ----------

- INFLECTRA doses >5 mg/kg in moderate or severe heart failure. (4)
- Previous severe hypersensitivity reaction to infliximab products or any inactive ingredients of INFLECTRA or to any murine proteins. (4)

---------- **WARNINGS AND PRECAUTIONS** ----------

- *Serious infections* – do not give INFLECTRA during an active infection. If an infection develops, monitor carefully and stop INFLECTRA if infection becomes serious. (5.1)
- *Invasive fungal infections* – for patients who develop a systemic illness on INFLECTRA, consider empiric antifungal therapy for those who reside or travel to regions where mycoses are endemic. (5.1)
- *Malignancies* – the incidence of malignancies, including invasive cervical cancer and lymphoma, was greater in infliximab-treated patients than in controls. Due to the risk of HSTCL carefully assess the risk/benefit especially if the patient has Crohn's disease or ulcerative colitis, is male, and is receiving azathioprine or 6-mercaptopurine treatment. (5.2)

- *Hepatitis B virus (HBV) reactivation* – test for HBV infection before starting INFLECTRA. Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop INFLECTRA and begin anti-viral therapy. (5.3)
- *Hepatotoxicity* – severe hepatic reactions, some fatal or necessitating liver transplantation. Stop INFLECTRA in cases of jaundice and/or marked liver enzyme elevations. (5.4)
- *Heart failure* –new onset or worsening symptoms may occur. (4, 5.5)
- *Cytopenias* – advise patients to seek immediate medical attention if signs and symptoms develop, and consider stopping INFLECTRA. (5.6)
- *Hypersensitivity* – serious infusion reactions including anaphylaxis or serum sickness-like reactions may occur. (5.7)
- *Cardiovascular and Cerebrovascular Reactions* – Cerebrovascular accidents, myocardial infarctions (some fatal), and arrhythmias have been reported during and within 24 hours of initiation of infliximab product infusion. Monitor patients during INFLECTRA infusion and if serious reaction occurs, discontinue infusion. (5.8)
- *Demyelinating disease* –exacerbation or new onset may occur. (5.9)
- *Lupus-like syndrome* –stop INFLECTRA if syndrome develops. (5.12)
- *Vaccinations and Use of Live vaccines/therapeutic infectious agents* – Prior to initiating INFLECTRA bring pediatric and adult patients up to date with all vaccinations. Live vaccines or therapeutic infectious agents should not be given with INFLECTRA. At least a six month waiting period following birth is recommended before the administration of live vaccines to infants exposed in utero to infliximab products. (5.13)

---------- **ADVERSE REACTIONS** ----------

Most common adverse reactions (>10%) – infections (e.g. upper respiratory, sinusitis, and pharyngitis), infusion-related reactions, headache, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact CELLTRION, Inc. at 1-800-383-7504 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- **DRUG INTERACTIONS** ----------

Other Biological Products– increased risk of serious infections (7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

* 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 product and the reference product. Biosimilarity of INFLECTRA has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

Revised: 4/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS and MALIGNANCY

SERIOUS INFECTIONS

Patients treated with infliximab products are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1)*, *Adverse Reactions (6.1)]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

INFLECTRA should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before INFLECTRA use and during therapy. Treatment for latent infection should be initiated prior to INFLECTRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

The risks and benefits of treatment with INFLECTRA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with INFLECTRA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including infliximab products *[see Warnings and Precautions (5.2)]*.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including infliximab products. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. The majority of reported cases have occurred in patients with Crohn's disease or ulcerative colitis and most were in adolescent and young adult males.

1 INDICATIONS AND USAGE

1.1 Crohn's Disease

INFLECTRA is indicated for:

- reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response to conventional therapy.
- reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing CD.

1.2 Pediatric Crohn's Disease

INFLECTRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active CD who have had an inadequate response to conventional therapy.

1.3 Ulcerative Colitis

INFLECTRA is indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy.

1.4 Pediatric Ulcerative Colitis

INFLECTRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active UC who have had an inadequate response to conventional therapy.

1.5 Rheumatoid Arthritis

INFLECTRA, in combination with methotrexate, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis (RA).

1.6 Ankylosing Spondylitis

INFLECTRA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS).

1.7 Psoriatic Arthritis

INFLECTRA is indicated for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in adult patients with psoriatic arthritis (PsA).

1.8 Plaque Psoriasis

INFLECTRA is indicated for the treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis (Ps) who are candidates for systemic therapy and when other systemic therapies are medically less appropriate. INFLECTRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician *[see Boxed Warning, Warnings and Precautions (5)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Adult Crohn's Disease

The recommended dosage of INFLECTRA is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of adults with moderately to severely active CD or fistulizing CD. For adult patients who respond and then lose their response, consideration may be given to treatment with 10 mg/kg every 8 weeks. Patients who do not respond by Week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue INFLECTRA in these patients.

2.2 Dosage in Pediatric Crohn's Disease

The recommended dosage of INFLECTRA for pediatric patients 6 years and older with moderately to severely active CD is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks.

2.3 Dosage in Adult Ulcerative Colitis

The recommended dosage of INFLECTRA is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of adult patients with moderately to severely active UC.

2.4 Dosage in Pediatric Ulcerative Colitis

The recommended dosage of INFLECTRA for pediatric patients 6 years and older with moderately to severely active UC is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks.

2.5 Dosage in Rheumatoid Arthritis

The recommended dosage of INFLECTRA is 3 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks thereafter for the treatment of moderately to severely active RA. INFLECTRA should be given in combination with methotrexate. For patients who have an incomplete response, consideration may be given to adjusting the dosage up to 10 mg/kg every 8 weeks or treating as often as every 4 weeks bearing in mind that risk of serious infections is increased at higher doses per infusion or more frequent dosing *[see Adverse Reactions (6.1)]*.

2.6 Dosage in Ankylosing Spondylitis

The recommended dosage of INFLECTRA is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks thereafter for the treatment of active AS.

2.7 Dosage in Psoriatic Arthritis

The recommended dosage of INFLECTRA is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of PsA. INFLECTRA can be used with or without methotrexate.

2.8 Dosage in Plaque Psoriasis

The recommended dosage of INFLECTRA in adult patients is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of chronic severe (i.e., extensive and/or

disabling) Ps.

2.9 Assessment for Latent and Active Tuberculosis

Prior to initiating INFLECTRA and periodically during therapy, patients should be evaluated for active tuberculosis and tested for latent infection *[see Warnings and Precautions (5.1)]*.

2.10 Administration Instructions Regarding Infusion Reactions

Prior to treatment, ensure appropriate personnel and medication are available to treat reactions (e.g., hypersensitivity, other reactions) that occur during infusion and shortly after infusion. Prior to infusion with INFLECTRA, patient may be premedicated with histamine-1 receptor antagonists, histamine-2 receptor antagonists, acetaminophen, and/or corticosteroids *[see Warnings and Precautions (5.7)]*.

For mild to moderate reactions during the infusion, consider slowing or stopping the infusion. Upon resolution of these reactions, may reinitiate at a lower infusion rate and/or with histamine-1 receptor antagonists, histamine-2 receptor antagonists, acetaminophen, and/or corticosteroids. Discontinue the infusion if the mild to moderate reactions reoccur.

Discontinue the infusion if severe hypersensitivity reactions occur during the infusion.

2.11 Reconstitution, Dilution, and Administration Instructions

INFLECTRA is intended for use under the guidance and supervision of a healthcare provider. The supplied lyophilized powder must be reconstituted and diluted prior to administration. The infusion solution should be prepared and administered by a trained medical professional using aseptic technique by the following procedure:

1. Calculate the dose, total volume of reconstituted INFLECTRA solution required and the number of INFLECTRA vials needed. More than one vial may be needed for a full dose.
2. Reconstitute each 100 mg INFLECTRA vial with 10 mL of Sterile Water for Injection, USP, to obtain a concentration of 10 mg/ml, using a syringe equipped with a 21-gauge or smaller needle as follows:

    - Remove the flip-top from the vial and wipe the top with an alcohol swab.
    - Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder, which has a cake-like appearance. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual.
    - Allow the reconstituted solution to stand for 5 minutes. Visually inspect the reconstituted solution for particulate matter and discoloration. The reconstituted solution should be colorless to light yellow and opalescent, and the solution may develop a few translucent particles as infliximab-dyyb is a protein. Do not use if the lyophilized powder has not fully dissolved or if opaque particles, discoloration, or other foreign particles are present. Do not store unused reconstituted INFLECTRA solution.

3. Dilute the total volume of the reconstituted INFLECTRA solution to 250 mL[1] with sterile 0.9% Sodium Chloride Injection, USP, (do not dilute with any other diluent) as follows:

    - Withdraw a volume from the 0.9% Sodium Chloride Injection, USP, 250 mL bottle or bag equal to the total volume of reconstituted INFLECTRA required for a dose. Slowly add the total volume of reconstituted INFLECTRA solution from the vial(s) to the 250 mL infusion bottle or bag.
    - Discard any unused portion of the reconstituted INFLECTRA solution remaining in the vial(s).
    - Gently invert the bag to mix the solution. The resulting infusion concentration should range between 0.4 mg/mL (minimum recommended concentration) and 4 mg/mL (maximum recommended concentration) of infliximab-dyyb.

4. The INFLECTRA infusion should begin within 3 hours of reconstitution and dilution. The infusion must be administered intravenously for at least 2 hours with an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 µm or less).
5. Given that the vials do not contain antibacterial preservatives, discard any unused portion of the infusion solution (do not store for reuse).

No physical biochemical compatibility studies have been conducted to evaluate the co-administration of INFLECTRA with other agents. INFLECTRA should not be infused concomitantly in the same intravenous line with other agents.

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[1] For volumes greater than 250 mL, either use a larger infusion bag (e.g. 500 mL) or multiple 250 mL infusion bags to ensure that the concentration of the infusion solution does not exceed 4 mg/mL.

3 DOSAGE FORMS AND STRENGTHS

For injection: 100 mg of infliximab-dyyb as a white lyophilized powder in a single-dose vial for reconstitution and dilution.

4 CONTRAINDICATIONS

The use of INFLECTRA at doses >5 mg/kg is contraindicated in patients with moderate or severe heart failure *[see Warnings and Precautions (5.5) and Adverse Reactions (6.1)]*.

INFLECTRA is contraindicated in patients with a previous severe hypersensitivity reaction to infliximab products or any of the inactive ingredients of INFLECTRA or any murine proteins [severe hypersensitivity reactions have included anaphylaxis, hypotension, and serum sickness] *[see Warnings and Precautions (5.7) and Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Patients treated with infliximab products are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death.

Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis, salmonellosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

Treatment with INFLECTRA should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with comorbid conditions and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection. The risks and benefits of treatment should be considered prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Tuberculosis

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving infliximab products, including patients who have previously received treatment for latent or active tuberculosis. Cases of active tuberculosis have also occurred in patients being treated with infliximab products during treatment for latent tuberculosis.

Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating INFLECTRA and periodically during therapy. Treatment of latent tuberculosis infection prior to therapy with TNF blockers has been shown to reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating INFLECTRA, even for patients previously vaccinated with Bacille Calmette-Guérin (BCG).

Anti-tuberculosis therapy should also be considered prior to initiation of INFLECTRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Tuberculosis should be strongly considered in patients who develop a new infection during INFLECTRA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Monitoring

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with INFLECTRA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with INFLECTRA.

INFLECTRA should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with INFLECTRA should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.

Invasive Fungal Infections

For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy.

5.2 Malignancies

Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF blockers (initiation of therapy ≤18 years of age), including infliximab products. Approximately half of these cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF blocker therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported postmarketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports.

Lymphomas

In the controlled portions of clinical trials of all the TNF blockers, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. In the controlled and open-label portions of infliximab clinical trials, 5 patients developed lymphomas among 5707 patients treated with infliximab (median duration of follow-up 1.0 years) vs. 0 lymphomas in 1600 control patients (median duration of follow-up 0.4 years). In RA patients, 2 lymphomas were observed for a rate of 0.08 cases per 100 patient-years of follow-up, which is approximately three-fold higher than expected in the general population. In the combined clinical trial population for RA, CD, PsA, AS, UC, and Ps, 5 lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow-up, which is approximately four-fold higher than expected in the general population. Patients with CD, RA or Ps, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies**,** may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blockers. Cases of acute and chronic leukemia have been reported with postmarketing TNF blocker use in RA and other diseases. Even in the absence of TNF blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Hepatosplenic T-cell Lymphoma (HSTCL)

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including infliximab products. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. The majority of reported cases have occurred in patients with CD or UC and most were in adolescent and young adult males. It is uncertain whether the occurrence of HSTCL is related to TNF blockers or TNF blockers in combination with these other immunosuppressants. When treating patients, consideration of whether to use INFLECTRA alone or in combination with other immunosuppressants such as azathioprine or 6-mercaptopurine should take into account a possibility that there is a higher risk of HSTCL with combination therapy versus an observed increased risk of immunogenicity and hypersensitivity reactions with infliximab product monotherapy from the clinical trial data from studies with infliximab *[see Warnings and Precautions (5.7) and Adverse Reactions (6.1)]*.

Skin Cancer

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blocker therapy, including infliximab products *[see Adverse Reactions (6.3)]*. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Cervical Cancer

A population-based retrospective cohort study using data from Swedish national health registries found a 2 to 3 fold increase in the incidence of invasive cervical cancer in women with RA treated with infliximab compared to biologics-naïve patients or the general population, particularly those over 60 years of age. A causal relationship between infliximab products and cervical cancer cannot be excluded. Periodic screening should continue in women treated with INFLECTRA *[see Adverse Reactions (6.3)]*.

Other Malignancies

In the controlled portions of clinical trials of some TNF blockers, including infliximab products, more malignancies (excluding lymphoma and nonmelanoma skin cancer [NMSC]) have been observed in patients receiving those TNF blockers compared with control patients. During the controlled portions of trials with infliximab, in patients with moderately to severely active RA, CD, PsA, AS, UC and Ps, 14 patients were diagnosed with malignancies (excluding lymphoma and NMSC) among 4019 infliximab-treated patients vs. 1 among 1597 control patients (at a rate of 0.52/100 patient-years among infliximab-treated patients vs. a rate of 0.11/100 patient-years among control patients), with median duration of follow-up 0.5 years for infliximab-treated patients and 0.4 years for

control patients. Of these, the most common malignancies were breast, colorectal, and melanoma. The rate of malignancies among infliximab-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected.

In a clinical trial exploring the use of infliximab in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, the majority of lung or head and neck origin, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking *[see Adverse Reactions (6.1)]*. Prescribers should exercise caution when considering the use of INFLECTRA in patients with moderate to severe COPD.

Ps patients should be monitored for nonmelanoma skin cancers (NMSCs), particularly those patients who have had prior prolonged phototherapy treatment. In the maintenance portion of clinical trials for infliximab, NMSCs were more common in patients with previous phototherapy *[see Adverse Reactions (6.1)]*.

The potential role of TNF blockers in the development of malignancies is not known *[see Adverse Reactions (6.1)]*. Rates in clinical trials for infliximab cannot be compared to rates in clinical trials of other TNF blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering INFLECTRA treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving INFLECTRA.

5.3 Hepatitis B Virus Reactivation

Use of TNF blockers, including infliximab products, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients should be tested for HBV infection before initiating TNF blocker therapy, including INFLECTRA. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, TNF blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, prescribers should exercise caution when considering resumption of TNF blocker therapy in this situation and monitor patients closely.

5.4 Hepatotoxicity

Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis, have been reported in postmarketing data in patients receiving infliximab products. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between 2 weeks to more than 1 year after initiation of infliximab products; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., ≥5 times the upper limit of normal) develop, INFLECTRA should be discontinued, and a thorough investigation of the abnormality should be undertaken. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving infliximab products without progression to severe hepatic injury *[see Adverse Reactions (6.1)]*.

5.5 Heart Failure

The use of INFLECTRA at doses > 5 mg/kg is contraindicated in patients with moderate or severe heart failure. A randomized, double-blind, placebo-controlled study evaluated the use of infliximab (5 mg/kg or 10 mg/kg at Weeks 0, 2 and 6) in patients with moderate or severe heart failure [New York Heart Association (NYHA) Functional Class III/IV]. Compared to patients who received placebo, there was a higher rate of mortality and a higher risk of hospitalization at Week 28 due to heart failure in patients who received the 10 mg/kg infliximab dose, and higher rates of cardiovascular adverse events in patients who received infliximab doses of 5 mg/kg and 10 mg/kg.

There have been postmarketing reports of new onset and worsening heart failure, with and without identifiable precipitating factors (e.g., pre-existing cardiovascular disease), in patients treated with infliximab products. Some of these patients have been under 50 years of age.

If a decision is made to administer INFLECTRA (≤ 5 mg/kg) to patients with moderate or severe heart failure or to administer INFLECTRA (any approved dose) to patients with mild heart failure, they should be closely monitored during therapy, and INFLECTRA should be discontinued if new or worsening symptoms of heart failure appear *[see Contraindications (4) and Adverse Reactions (6.1)]*.

5.6 Hematologic Reactions

Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving infliximab products. The causal relationship to infliximab product therapy remains unclear. Although no high-risk group(s)

has been identified, caution should be exercised in patients being treated with INFLECTRA who have ongoing or a history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever) while on INFLECTRA. Discontinuation of INFLECTRA therapy should be considered in patients who develop significant hematologic abnormalities.

5.7 Hypersensitivity

Infliximab products have been associated with hypersensitivity reactions that vary in their time of onset and required hospitalization in some cases. Most hypersensitivity reactions (including anaphylaxis, urticaria, dyspnea, and/or hypotension), have occurred during or within 2 hours of infliximab product infusion.

However, in some cases, serum sickness-like reactions have been observed in patients after initial therapy with infliximab products (i.e., as early as after the second dose), and when therapy with infliximab products was reinstituted following an extended period without treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia. These reactions were associated with a marked increase in antibodies to infliximab products, loss of detectable serum concentrations of infliximab products, and possible loss of drug efficacy.

INFLECTRA should be discontinued for severe hypersensitivity reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for immediate use in the event of a reaction *[see Dosage and Administration (2.10) and Adverse Reactions (6.1)]*.

In RA, CD and Ps clinical trials, re-administration of infliximab after a period of no treatment resulted in a higher incidence of infusion reactions relative to regular maintenance treatment *[see Adverse Reactions (6.1)]*. In general, the benefit-risk of readministration of INFLECTRA after a period of no-treatment, especially as a re-induction regimen given at weeks 0, 2 and 6, should be carefully considered. In the case where INFLECTRA maintenance therapy for Ps is interrupted, INFLECTRA should be reinitiated as a single dose followed by maintenance therapy.

5.8 Cardiovascular and Cerebrovascular Reactions During and After Infusion

Serious cerebrovascular accidents, myocardial ischemia/infarction (some fatal), hypotension, hypertension, and arrhythmias have been reported during and within 24 hours of initiation of infliximab product infusion. Cases of transient visual loss have been reported during or within 2 hours of infliximab product infusion. Monitor patients during infusion and if serious reaction occurs, discontinue infusion. Further management of reactions should be dictated by signs and symptoms *[see Adverse Reactions (6)]*.

5.9 Neurologic Reactions

Agents that inhibit TNF have been associated with CNS manifestation of systemic vasculitis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and optic neuritis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of INFLECTRA in patients with these neurologic disorders and should consider discontinuation of INFLECTRA if these disorders develop.

5.10 Concurrent Administration with Other Biological Products

Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another TNF blocker, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse reactions seen with the concurrent use of etanercept and anakinra therapy, similar toxicities may also result from the concurrent use of anakinra and other TNF blockers. Therefore, the concurrent use of INFLECTRA and anakinra is not recommended.

In clinical studies, concurrent administration of TNF blockers and abatacept have been associated with an increased risk of infections including serious infections compared with TNF blockers alone, without increased clinical benefit. Therefore, the concurrent use of INFLECTRA and abatacept is not recommended *[see Drug Interactions (7.1)]*.

There is insufficient information regarding the concurrent use of infliximab products with other biological products used to treat the same conditions as INFLECTRA. The concurrent use of INFLECTRA with these biological products is not recommended because of the possibility of an increased risk of infection *[see Drug Interactions (7.1)]*.

5.11 Switching Between Biological Disease-Modifying Antirheumatic Drugs (DMARDs)

Care should be taken when switching from one biologic to another, since overlapping biological activity may further increase the risk of infection.

5.12 Autoimmunity

Treatment with infliximab products may result in the formation of autoantibodies and in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with INFLECTRA, treatment should be discontinued *[see Adverse Reactions (6.1)]*.

5.13 Vaccinations and Use of Live Vaccines/Therapeutic Infectious Agents

Vaccinations

Prior to initiating INFLECTRA in pediatric and adult patients, update vaccinations in accordance with current vaccination guidelines.

Live Vaccines and Therapeutic Infectious Agents

In patients receiving TNF blockers, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines can result in clinical infections, including disseminated infections. The concurrent administration of live vaccines with INFLECTRA is not recommended.

Fatal outcome due to disseminated BCG infection has been reported in an infant who received a BCG vaccine after *in utero* exposure to infliximab products. Infliximab products are known to cross the placenta and have been detected up to 6 months following birth. At least a six month waiting period following birth is recommended before the administration of any live vaccine to infants exposed *in utero* to infliximab products.

Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g., BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with INFLECTRA.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

Adverse Reactions in Adults

The data described herein reflect exposure to infliximab in 4779 adult patients (1304 patients with RA, 1106 patients with CD, 202 with AS, 293 with PsA, 484 with UC, 1373 with Ps, and 17 patients with other conditions), including 2625 patients exposed beyond 30 weeks and 374 exposed beyond 1 year. *[*For information on adverse reactions in pediatric patients *see Adverse Reactions (6.1)]*. One of the most common reasons for discontinuation of treatment was infusion-related reactions (e.g., dyspnea, flushing, headache and rash).

Infusion-Related Reactions

Adverse Reactions During or Shortly After Infusion

An infusion reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 hour after an infusion. In all the clinical studies, approximately 20% of infliximab-treated patients experienced an infusion reaction compared with 10% of placebo-treated patients. Of infliximab-treated patients who had an infusion reaction during the induction period, 27% experienced an infusion reaction during the maintenance period. Of patients who did not have an infusion reaction during the induction period, 9% experienced an infusion reaction during the maintenance period.

Among all infliximab infusions, 3% were accompanied by nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary reactions (primarily chest pain, hypotension, hypertension or dyspnea), and <1% were accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Serious infusion reactions occurred in <1% of patients and included anaphylaxis, convulsions, erythematous rash and hypotension. Approximately 3% of patients discontinued treatment with infliximab because of infusion reactions, and all patients recovered with treatment and/or discontinuation of the infusion. Infliximab infusions beyond the initial infusion were not associated with a higher incidence of reactions. The infusion reaction rates remained stable in Ps through 1 year in Ps Study I. In psoriasis Study II, the rates were variable over time and somewhat higher following the final infusion than after the initial infusion. Across the 3 Ps studies, the percent of total infusions resulting in infusion reactions (i.e., an adverse event occurring within 1 hour) was 7% in the 3 mg/kg group, 4% in the 5 mg/kg group, and 1% in the placebo group.

Patients who became positive for antibodies to infliximab were more likely (approximately two to three-fold) to have an infusion reaction than were those who were negative. Use of concomitant immunosuppressant agents appeared to reduce the frequency of both antibodies to infliximab and infusion reactions *[see Adverse Reactions (6.2) and Drug Interactions (7.3)]*.

Infusion Reactions Following Re-administration

In a clinical trial of patients with moderate to severe Ps designed to assess the efficacy of long-term maintenance therapy versus re-treatment with an induction regimen of infliximab following disease flare, 4% (8/219) of patients in the re-treatment induction therapy arm experienced serious infusion reactions versus <1% (1/222) in the maintenance therapy arm. Patients enrolled in this trial did not receive any concomitant immunosuppressant therapy. In this study, the majority of serious infusion reactions occurred during the second infusion at Week 2. Symptoms included, but were not limited to, dyspnea, urticaria, facial edema, and hypotension. In all cases, treatment with infliximab was discontinued and/or other treatment instituted with complete resolution of signs and symptoms.

Delayed Reactions/Reactions Following Re-administration

In Ps studies, approximately 1% of patients treated with infliximab experienced a possible delayed hypersensitivity reaction, generally reported as serum sickness or a combination of arthralgia and/or myalgia with fever and/or rash. These reactions generally occurred within 2 weeks after repeat infusion.

Infections

In infliximab clinical studies, treated infections were reported in 36% of patients treated with infliximab (average of 51 weeks of follow-up) and in 25% of placebo-treated patients (average of 37 weeks of follow-up). The infections most frequently reported were respiratory tract infections (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. Among patients treated with infliximab, serious infections included pneumonia, cellulitis, abscess, skin ulceration, sepsis, and bacterial infection. In clinical trials, 7 opportunistic infections were reported; 2 cases each of coccidioidomycosis (1 case was fatal) and histoplasmosis (1 case was fatal), and 1 case each of pneumocystosis, nocardiosis and cytomegalovirus. Tuberculosis (TB) was reported in 14 patients, 4 of whom died due to miliary tuberculosis. Other cases of TB, including disseminated TB, also have been reported postmarketing. Most of these cases of TB occurred within the first 2 months after initiation of therapy with infliximab and may reflect recrudescence of latent disease *[see Warnings and Precautions (5.1)]*. In the 1-year placebo-controlled studies RA I and RA II, 5.3% of patients receiving infliximab every 8 weeks with MTX developed serious infections as compared to 3.4% of placebo patients receiving MTX. Of 924 patients receiving infliximab, 1.7% developed pneumonia and 0.4% developed TB, when compared to 0.3% and 0.0% in the placebo arm respectively. In a shorter (22-week) placebo-controlled study of 1082 RA patients randomized to receive placebo, 3 mg/kg or 10 mg/kg infusions with infliximab at 0, 2, and 6 weeks, followed by every 8 weeks with MTX, serious infections were more frequent in the 10 mg/kg infliximab group (5.3%) than the 3 mg/kg or placebo groups (1.7% in both). During the 54-week Crohn's II Study, 15% of patients with fistulizing CD developed a new fistula-related abscess.

In clinical studies with infliximab in patients with UC, infections treated with antimicrobials were reported in 27% of patients treated with infliximab (average of 41 weeks of follow-up) and in 18% of placebo-treated patients (average 32 weeks of follow-up). The types of infections, including serious infections, reported in patients with UC were similar to those reported in other clinical studies.

The onset of serious infections may be preceded by constitutional symptoms such as fever, chills, weight loss, and fatigue. The majority of serious infections, however, may also be preceded by signs or symptoms localized to the site of the infection.

Autoantibodies/Lupus-like Syndrome

Approximately half of patients treated with infliximab in clinical trials who were antinuclear antibody (ANA) negative at baseline developed a positive ANA during the trial compared with approximately one-fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately one-fifth of patients treated with infliximab compared with 0% of placebo-treated patients. Reports of lupus and lupus-like syndromes, however, remain uncommon.

Malignancies

In controlled trials, more patients treated with infliximab developed malignancies than placebo-treated patients *[see Warnings and Precautions (5.2)]*.

In a randomized controlled clinical trial exploring the use of infliximab in patients with moderate to severe COPD who were either current smokers or ex-smokers, 157 patients were treated with infliximab at doses similar to those used in RA and CD. Of these infliximab-treated patients, 9 developed a malignancy, including 1 lymphoma, for a rate of 7.67 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 3.51 – 14.56). There was 1 reported malignancy among 77 control patients for a rate of 1.63 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 0.04 – 9.10). The majority of the malignancies developed in the lung or head and neck *[see Warnings and Precautions (5.2)]*.

Adverse Reactions in Patients with NYHA Class III/IV Heart Failure

In a randomized, double-blind study evaluating infliximab in moderate or severe heart failure (NYHA Class III/IV; left ventricular ejection fraction ≤35%), 150 patients were randomized to receive treatment with 3 infusions of infliximab at 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks. Higher incidences of mortality and hospitalization due to worsening heart failure were observed in patients receiving the 10 mg/kg infliximab dose. At 1 year, 8 patients in the 10 mg/kg infliximab group had died compared with 4 deaths each in the 5 mg/kg infliximab and the placebo groups. There were trends toward increased dyspnea, hypotension, angina, and dizziness in both the 10 mg/kg and 5 mg/kg infliximab treatment groups, versus placebo. Infliximab products have not been studied in patients with mild heart failure (NYHA Class I/II) *[see Contraindications (4) and Warnings and Precautions (5.5)]*.

Hepatotoxicity

Severe liver injury, including acute liver failure and autoimmune hepatitis, has been reported in patients receiving infliximab products *[see Warnings and Precautions (5.4)]*. Reactivation of hepatitis B virus has occurred in patients receiving TNF blockers, including infliximab products, who are chronic carriers of this virus *[see Warnings and Precautions (5.3)]*.

In clinical trials in RA, CD, UC, AS, Ps, and PsA, elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving infliximab than in controls (Table 1), both when infliximab was given as monotherapy and when it was used in combination with other immunosuppressive agents. In general, patients who developed ALT and AST elevations

were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of infliximab, or modification of concomitant medications.

Table 1 Proportion of Patients with Elevated ALT in Clinical Trials in Adults

	Proportion of patients with elevated ALT					
	>1 to 3 × ULN		≥3 × ULN		≥5 × ULN	
	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab
Rheumatoid arthritis*	24%	34%	3%	4%	<1%	<1%
Crohn's disease†	34%	39%	4%	5%	0%	2%
Ulcerative colitis‡	12%	17%	1%	2%	<1%	<1%
Ankylosing spondylitis§	15%	51%	0%	10%	0%	4%
Psoriatic arthritis¶	16%	50%	0%	7%	0%	2%
Plaque psoriasis#	24%	49%	<1%	8%	0%	3%

* Placebo patients received methotrexate while patients treated with infliximab received both infliximab and methotrexate. Median follow-up was 58 weeks.

† Placebo patients in the 2 Phase 3 trials in CD received an initial dose of 5 mg/kg infliximab at study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo maintenance group and then later crossed over to infliximab are included in the infliximab group in ALT analysis. Median follow-up was 54 weeks.

‡ Median follow-up was 30 weeks. Specifically, the median duration of follow-up was 30 weeks for placebo and 31 weeks for infliximab.

§ Median follow-up was 24 weeks for the placebo group and 102 weeks for infliximab group.

¶ Median follow-up was 39 weeks for infliximab group and 18 weeks for the placebo group.

ALT values are obtained in 2 Phase 3 Ps studies with median follow-up of 50 weeks for infliximab and 16 weeks for placebo.

Adverse Reactions in Psoriasis Studies

During the placebo-controlled portion across the 3 clinical trials up to week 16, the proportion of patients who experienced at least 1 serious adverse reaction (SAE; defined as resulting in death, life threatening, requires hospitalization, or persistent or significant disability/incapacity) was 0.5% in the 3 mg/kg infliximab group, 1.9% in the placebo group, and 1.6% in the 5 mg/kg infliximab group.

Among patients in the 2 Phase 3 studies, 12.4% of patients receiving infliximab 5 mg/kg every 8 weeks through 1 year of maintenance treatment experienced at least 1 SAE in Study I. In Study II, 4.1% and 4.7% of patients receiving infliximab 3 mg/kg and 5 mg/kg every 8 weeks, respectively, through 1 year of maintenance treatment experienced at least 1 SAE.

One death due to bacterial sepsis occurred 25 days after the second infusion of 5 mg/kg of infliximab. Serious infections included sepsis, and abscesses. In Study I, 2.7% of patients receiving infliximab 5 mg/kg every 8 weeks through 1 year of maintenance treatment experienced at least 1 serious infection. In Study II, 1.0% and 1.3% of patients receiving infliximab 3 mg/kg and 5 mg/kg, respectively, through 1 year of treatment experienced at least 1 serious infection. The most common serious infection (requiring hospitalization) was abscess (skin, throat, and peri-rectal) reported by 5 (0.7%) patients in the 5 mg/kg infliximab group. Two active cases of tuberculosis were reported: 6 weeks and 34 weeks after starting infliximab.

In the placebo-controlled portion of the Ps studies, 7 of 1123 patients who received infliximab at any dose were diagnosed with at least one NMSC compared to 0 of 334 patients who received placebo.

In the Ps studies, 1% (15/1373) of patients experienced serum sickness or a combination of arthralgia and/or myalgia with fever, and/or rash, usually early in the treatment course. Of these patients, 6 required hospitalization due to fever, severe myalgia, arthralgia, swollen joints, and immobility.

Other Adverse Reactions in Adults

Safety data are available from 4779 infliximab-treated adult patients, including 1304 with RA, 1106 with CD, 484 with UC, 202 with AS, 293 with PsA, 1373 with Ps and 17 with other conditions. [For information on other adverse reactions in pediatric patients, *see Adverse Reactions (6.1)]*. Adverse reactions reported in ≥5% of all patients with RA receiving 4 or more infusions are in Table 2. The types and frequencies of adverse reactions observed were similar in infliximab-treated RA, AS, PsA, Ps and CD patients except for abdominal pain, which occurred in 26% of infliximab-treated patients with CD. In the CD studies, there were insufficient numbers and duration of follow-up for patients who never received infliximab to provide meaningful comparisons.

Table 2 Adverse Reactions that Occurred in ≥ 5% of Patients who Received ≥ 4 Infliximab Infusions for RA

	Placebo (n=350)	Infliximab (n=1129)
Average weeks of follow-up	59 weeks	66 weeks
Upper respiratory tract infection	25%	32%
Nausea	20%	21%
Headache	14%	18%
Sinusitis	8%	14%
Diarrhea	12%	12%
Abdominal pain	8%	12%
Pharyngitis	8%	12%
Coughing	8%	12%
Bronchitis	9%	10%
Rash	5%	10%
Dyspepsia	7%	10%
Fatigue	7%	9%
Urinary tract infection	6%	8%
Pain	7%	8%
Arthralgia	7%	8%
Pruritus	2%	7%
Fever	4%	7%
Hypertension	5%	7%
Moniliasis	3%	5%

The most common serious adverse reactions observed in clinical trials were infections *[see Adverse Reactions (6.1)]*. Other serious, medically relevant adverse reactions ≥0.2% or clinically significant adverse reactions by body system were as follows:

- *Body as a whole:* allergic reaction, edema
- *Blood:* pancytopenia
- *Cardiovascular:* hypotension
- *Gastrointestinal:* constipation, intestinal obstruction
- *Central and Peripheral Nervous:* dizziness
- *Heart Rate and Rhythm:* bradycardia
- *Liver and Biliary:* hepatitis
- *Metabolic and Nutritional:* dehydration
- *Platelet, Bleeding and Clotting:* thrombocytopenia
- *Neoplasms:* lymphoma
- *Red Blood Cell:* anemia, hemolytic anemia
- *Resistance Mechanism:* cellulitis, sepsis, serum sickness, sarcoidosis
- *Respiratory:* lower respiratory tract infection (including pneumonia), pleurisy, pulmonary edema
- *Skin and Appendages:* increased sweating
- *Vascular (Extracardiac):* thrombophlebitis
- *White Cell and Reticuloendothelial:* leukopenia, lymphadenopathy

Adverse Reactions in Pediatric Patients

Adverse Reactions in Pediatric Patients with Crohn's Disease

There were some differences in the adverse reactions observed in the pediatric patients receiving infliximab compared to those observed in adults with CD. These differences are discussed in the following paragraphs.

The following adverse reactions were reported more commonly in 103 randomized pediatric CD patients administered 5 mg/kg infliximab through 54 weeks than in 385 adult CD patients receiving a similar treatment regimen: anemia (11%), leukopenia (9%), flushing (9%), viral infection (8%), neutropenia (7%), bone fracture (7%), bacterial infection (6%), and respiratory tract allergic reaction (6%).

Infections were reported in 56% of randomized pediatric patients in Study Peds Crohn's and in 50% of adult patients in Study Crohn's I. In Study Peds Crohn's, infections were reported more frequently for patients who received every 8-week as opposed to every 12-week infusions (74% and 38%, respectively), while serious infections were reported for 3 patients in the every 8-week and 4 patients in the every 12-week maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Pneumonia was reported for 3 patients, (2 in the every 8-week and 1 in the every 12-week maintenance treatment groups). Herpes zoster was reported for 2 patients in the every 8-week maintenance treatment group.

In Study Peds Crohn's, 18% of randomized patients experienced 1 or more infusion reactions, with no notable difference between treatment groups. Of the 112 patients in Study Peds Crohn's, there were no serious infusion reactions, and 2 patients had non-serious anaphylactoid reactions.

Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 18% of pediatric patients in CD clinical trials; 4% had ALT elevations ≥3 × ULN, and 1% had elevations ≥5 × ULN. (Median follow-up was 53 weeks).

Adverse Reactions in Pediatric Patients with Ulcerative Colitis

Overall, the adverse reactions reported in the pediatric UC trial and adult UC (Study UC I and Study UC II) studies were generally consistent. In a pediatric UC trial, the most common adverse reactions were upper respiratory tract infection, pharyngitis, abdominal pain, fever, and headache.

Infections were reported in 31 (52%) of 60 treated patients in the pediatric UC trial and 22 (37%) required oral or parenteral antimicrobial treatment. The proportion of patients with infections in the pediatric UC trial was similar to that in the pediatric CD study (Study Peds Crohn's) but higher than the proportion in the adults' UC studies (Study UC I and Study UC II). The overall incidence of infections in the pediatric UC trial was 13/22 (59%) in the every 8 week maintenance treatment group. Upper respiratory tract infection (7/60 [12%]) and pharyngitis (5/60 [8%]) were the most frequently reported respiratory system infections. Serious infections were reported in 12% (7/60) of all treated patients.

Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 17% (10/60) of pediatric patients in the pediatric UC trial; 7% (4/60) had ALT elevations ≥3 × ULN, and 2% (1/60) had elevations ≥5 × ULN (median follow-up was 49 weeks).

Overall, 8 of 60 (13%) treated patients experienced one or more infusion reactions, including 4 of 22 (18%) patients in the every 8-week treatment maintenance group. No serious infusion reactions were reported.

In the pediatric UC trial, 45 patients were in the 12 to 17 year age group and 15 in the 6 to 11 year age group. The numbers of patients in each subgroup are too small to make any definitive conclusions about the effect of age on safety events. There were higher proportions of patients with serious adverse events (40% vs. 18%) and discontinuation due to adverse events (40% vs. 16%) in the younger age group than in the older age group. While the proportion of patients with infections was also higher in the younger age group (60% vs. 49%), for serious infections, the proportions were similar in the two age groups (13% in the 6 to 11 year age group vs. 11% in the 12 to 17 year age group). Overall proportions of adverse reactions, including infusion reactions, were similar between the 6 to 11 and 12 to 17 year age groups (13%).

6.2 Immunogenicity

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

Treatment with infliximab products can be associated with the development of antibodies to infliximab products. An enzyme immunoassay (EIA) method was originally used to measure anti-infliximab antibodies in clinical studies of infliximab. The EIA method is subject to interference by serum infliximab, possibly resulting in an underestimation of the rate of patient antibody formation. A separate, drug-tolerant electrochemiluminescence immunoassay (ECLIA) method for detecting antibodies to infliximab was subsequently developed and validated. This method is 60-fold more sensitive than the original EIA. With the ECLIA method, all clinical samples can be classified as either positive or negative for antibodies to infliximab without the need for the inconclusive category.

The incidence of antibodies to infliximab was based on the original EIA method in all clinical studies of infliximab except for the Phase 3 study in pediatric patients with UC where the incidence of antibodies to infliximab was detected using both the EIA and ECLIA methods.

Immunogenicity in Adult Patients

The incidence of antibodies to infliximab in patients with RA and CD given a 3-dose induction regimen followed by maintenance dosing was approximately 10% as assessed through 1 to 2 years of infliximab treatment. A higher incidence of antibodies to infliximab was observed in CD patients receiving infliximab after drug-free intervals >16 weeks. In a PsA study in which 191 patients received 5 mg/kg with or without MTX, antibodies to infliximab occurred in 15% of patients. The majority of antibody-

positive patients had low titers. Antibody development was lower among RA and CD patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX. Patients who were antibody-positive were more likely to have higher rates of clearance, have reduced efficacy, and to experience an infusion reaction than were patients who were antibody negative *[see Adverse Reactions (6.1)]*. In the Ps Study II, which included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 36% of patients treated with 5 mg/kg every 8 weeks for 1 year, and in 51% of patients treated with 3 mg/kg every 8 weeks for 1 year.

In the Ps Study III, which also included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 20% of patients treated with 5 mg/kg induction (weeks 0, 2 and 6), and in 27% of patients treated with 3 mg/kg induction. Despite the increase in antibody formation, the infusion reaction rates in Studies I and II in patients treated with 5 mg/kg induction followed by every 8 week maintenance for 1 year and in Study III in patients treated with 5 mg/kg induction (14.1% – 23.0%) and serious infusion reaction rates (<1%) were similar to those observed in other study populations. The clinical significance of apparent increased immunogenicity on efficacy and infusion reactions in Ps patients as compared to patients with other diseases treated with infliximab products over the long term is not known.

Immunogenicity in Pediatric Patients with Crohn's Disease

In Study Peds Crohn's, in which all patients received stable doses of 6-MP, AZA, or MTX, excluding inconclusive samples, 3 of 24 patients had antibodies to infliximab. Although 105 patients were tested for antibodies to infliximab, 81 patients were classified as inconclusive because they could not be ruled as negative due to assay interference by the presence of infliximab in the sample.

Immunogenicity in Pediatric Patients with Ulcerative Colitis

In the pediatric UC trial, 58 patients were evaluated for antibodies to infliximab using the EIA as well as the drug-tolerant ECLIA. With the EIA, 4 of 58 (7%) patients had antibodies to infliximab. With the ECLIA, 30 of 58 (52%) patients had antibodies to infliximab. The higher incidence of antibodies to infliximab by the ECLIA method was due to the 60-fold higher sensitivity compared to the EIA method. While EIA-positive patients generally had undetectable trough infliximab concentrations, ECLIA-positive patients could have detectable trough concentrations of infliximab because the ECLIA assay is more sensitive and drug-tolerant.

6.3 Postmarketing Experience

Adverse reactions, some with fatal outcomes, have been identified during post approval use of infliximab products in adult and pediatric patients. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Postmarketing Adverse Reactions in Adults and Pediatric Patients

- Neutropenia *[see Warnings and Precautions (5.6)]*, agranulocytosis (including infants exposed in utero to infliximab products), idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura.
- Interstitial lung disease (including pulmonary fibrosis/interstitial pneumonitis and rapidly progressive disease).
- Pericardial effusion, systemic and cutaneous vasculitis.
- Erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, linear IgA bullous dermatosis (LABD), acute generalized exanthematous pustulosis (AGEP), new onset and worsening psoriasis (all subtypes including pustular, primarily palmoplantar), lichenoid reactions.
- Peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy) transverse myelitis, and neuropathies (additional neurologic reactions have also been observed) *[see Warnings and Precautions (5.9)]*.
- Acute liver failure, jaundice, hepatitis, and cholestasis *[*see *Warnings and Precautions (5.4)]*
- Serious infections *[see Warnings and Precautions (5.1)]* and vaccine breakthrough infection including bovine tuberculosis (disseminated BCG infection) following vaccination in an infant exposed in utero to infliximab products *[see Warnings and Precautions (5.13)]*.
- Malignancies, including leukemia, melanoma, Merkel cell carcinoma, and cervical cancer *[see Warnings and Precautions (5.2)]*
- Anaphylactic reactions, including anaphylactic shock, laryngeal/pharyngeal edema and severe bronchospasm, and seizure have been associated with administration of infliximab products.
- Transient visual loss have been reported in association with infliximab products during or within 2 hours of infusion. Cerebrovascular accidents, myocardial ischemia/infarction (some fatal), and arrhythmia occurring within 24 hours of initiation of infusion have also been reported *[see Warnings and Precautions (5.8)]*.

Postmarketing Serious Adverse Reactions in Pediatric Patients

The following serious adverse reactions have been reported in the postmarketing experience in pediatric patients: infections (some fatal) including opportunistic infections and tuberculosis, infusion reactions, hypersensitivity reactions, malignancies, including hepatosplenic T-cell lymphomas *[see Boxed Warning* and *Warnings and Precautions (5.2)]*, transient hepatic enzyme abnormalities, lupus-like syndromes, and the development of autoantibodies.

7 DRUG INTERACTIONS

7.1 Other Biological Products

The combination of INFLECTRA with other biological products used to treat the same conditions as INFLECTRA is not recommended *[see Warnings and Precautions (5.10)]*.

An increased risk of serious infections was seen in clinical studies of other TNF blockers used in combination with anakinra or abatacept, with no added clinical benefit. Because of the nature of the adverse reactions seen with these combinations with TNF blocker therapy, similar toxicities may also result from the combination of anakinra or abatacept with other TNF blockers. Therefore, the combination of INFLECTRA and anakinra or abatacept is not recommended *[see Warnings and Precautions (5.10)]*.

The concomitant use of tocilizumab with biological DMARDs such as TNF antagonists, including INFLECTRA, should be avoided because of the possibility of increased immunosuppression and increased risk of infection.

7.2 Methotrexate and Other Concomitant Medications

Specific drug interaction studies, including interactions with methotrexate (MTX), have not been conducted. The majority of patients in RA or CD clinical studies received one or more concomitant medications. In RA, concomitant medications besides MTX were nonsteroidal anti-inflammatory agents (NSAIDs), folic acid, corticosteroids and/or narcotics. Concomitant CD medications were antibiotics, antivirals, corticosteroids, 6-MP/AZA and aminosalicylates. In PsA clinical trials, concomitant medications included MTX in approximately half of the patients as well as NSAIDs, folic acid and corticosteroids. Concomitant MTX use may decrease the incidence of anti-drug antibody production and increase infliximab product concentrations.

7.3 Immunosuppressants

Patients with CD who received immunosuppressants tended to experience fewer infusion reactions compared to patients on no immunosuppressants *[see Adverse Reactions (6.1)]*. Serum infliximab concentrations appeared to be unaffected by baseline use of medications for the treatment of CD including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and aminosalicylates.

7.4 Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-1, IL-6, IL-10, IFN) during chronic inflammation. Therefore, it is expected that for a molecule that antagonizes cytokine activity, such as infliximab products, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of INFLECTRA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

7.5 Live Vaccines/Therapeutic Infectious Agents

It is recommended that live vaccines not be given concurrently with INFLECTRA. It is also recommended that live vaccines not be given to infants after *in utero* exposure to infliximab products for at least 6 months following birth *[see Warnings and Precautions (5.13)]*.

It is recommended that therapeutic infectious agents not be given concurrently with INFLECTRA *[see Warnings and Precautions (5.13)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available observational studies in pregnant women exposed to infliximab products showed no increased risk of major malformations among live births as compared to those exposed to non-biologics. However, findings on other birth and maternal outcomes were not consistent across studies of different study design and conduct *(see Data)*.

Monoclonal antibodies such as infliximab products are transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in utero* exposed infant (see Clinical Considerations). Because infliximab products do not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with infliximab products. In a developmental study conducted in mice using an analogous antibody, no evidence of maternal toxicity or fetal harm was observed *(see Data)*.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and

15–20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data suggest that there is an increased risk of adverse pregnancy outcomes in women with inflammatory bowel disease or rheumatoid arthritis associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2.5 kg) and small for gestational age at birth.

Fetal/Neonatal Adverse Reactions

As with other IgG antibodies, infliximab products cross the placenta. Infliximab products have been detected in the serum of infants up to 6 months following birth. Consequently, these infants may be at increased risk of infection, including disseminated infection which can become fatal. At least a six month waiting period following birth is recommended before the administration of live vaccines (e.g., BCG vaccine or other live vaccines, such as the rotavirus vaccine) to these infants *[see Warnings and Precautions (5.13)]*. Cases of agranulocytosis in infants exposed in utero have also been reported *[see Adverse Reactions (6.3)]*.

Data

Human Data

Two prospective cohort studies were conducted assessing birth outcomes as well as the health status of infants up to the age of one year in women exposed to infliximab compared to non-biologic comparators including methotrexate, azathioprine, 6-mercaptopurine and systemic corticosteroids used for the treatment of similar diseases. The first study was conducted in an IBD pregnancy registry in the United States and assessed pregnancy outcomes in 294 women with inflammatory bowel disease exposed to infliximab during pregnancy compared with 515 women on a non-biologic treatment. Infliximab exposure was not associated with increased rates of major congenital malformations, miscarriage/stillbirth, infants of low birth weight, small for gestational age, or infection in the first year of life. The second study among IBD and non-IBD patients in Sweden, Finland, and Denmark compared 97, 7, and 166 women exposed to infliximab to 2,693, 2,499 and 1,268 women on non-biologic systemic therapy, respectively. In this study, comparing pooled data across the three countries, exposure to infliximab was not associated with increased rates of congenital anomalies or infant death. Infliximab in combination with immunosuppressants (mainly systemic corticosteroids and azathioprine) was associated with increased rates of preterm birth, small for gestational age, low birth weight, and infant hospitalization for infection compared with non-biologic systemic treatment. Although the study did not show any associations with infliximab monotherapy, the analyses could have been underpowered to detect an association. There were additional methodological limitations with these studies that may account for the study findings in both studies: the concomitant use of other medications or treatments was not controlled and disease severity was not assessed; in the U.S. study, patient reported outcomes were collected without clinical validation. These methodological limitations hinder interpretation of the study results.

Animal Data

Because infliximab products do not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with infliximab products. An embryofetal development study was conducted in pregnant mice using cV1q anti-mouse TNFα, an analogous antibody that selectively inhibits the functional activity of mouse TNFα. This antibody administered in mice, during the period of organogenesis on gestation days (GDs) 6 and 12, at IV doses up to 40 mg/kg produced no evidence of maternal toxicity, fetal mortality, or structural abnormalities. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Analyses of fetal samples on GD 14 indicated placental transfer of the antibody and exposure of the fetuses during organogenesis. In a peri-and post-natal development study in mice, no maternal toxicity or adverse developmental effects in offspring were observed when dams were administered IV doses of 10 or 40 mg/kg of the analogous antibody on GDs 6, 12 and 18 and lactation days 3, 9 and 15.

8.2 Lactation

Risk Summary

Published literature show that infliximab is present at low levels in human milk. Systemic exposure in a breastfed infant is expected to be low because infliximab products are largely degraded in the gastrointestinal tract. A U.S. multi-center study of 168 women treated with infliximab for inflammatory bowel disease (breast milk samples obtained, n=29) showed that infants exposed to infliximab through breast milk had no increase in rates of infections and developed normally. There are no data on the effects of infliximab products on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for INFLECTRA and any potential adverse effects on the breastfed child from INFLECTRA or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of infliximab products have been established in pediatric patients 6 to 17 years of age for induction and maintenance treatment of CD and UC. *[see Dosage and Administration (2.2, 2.4) and Adverse Reactions (6.1)]*. However, the safety and effectiveness of infliximab products in pediatric patients <6 years of age with CD or UC have not been established. The safety

and effectiveness of infliximab products in the treatment of pediatric patients with Ps and juvenile rheumatoid arthritis (JRA) have not been established.

Pediatric Crohn's Disease

The safety and effectiveness of infliximab products have been established for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active CD who have had an inadequate response to conventional therapy. The use of infliximab for this indication is supported by evidence from a randomized, open-label pediatric CD study in 112 pediatric patients aged 6 years and older *[see Clinical Studies (14.2)]*.

Infliximab has been studied only in combination with conventional immunosuppressive therapy in pediatric CD. The longer term (greater than 1 year) safety and effectiveness of infliximab products in pediatric CD patients have not been established in clinical trials.

Postmarketing cases of HSTCL have been reported in pediatric patients treated with TNF blockers including infliximab products. Due to the risk of HSTCL, a careful risk-benefit assessment should be made when INFLECTRA is used in combination with other immunosuppressants in pediatric CD patients *[see Boxed Warning, Warnings and Precautions (5.2)]*.

Pediatric Ulcerative Colitis

The safety and effectiveness of infliximab products for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients aged 6 years and older with moderately to severely active UC who have had an inadequate response to conventional therapy have been established. The use of infliximab for this indication is supported by evidence from adequate and well-controlled studies of infliximab in adults with additional safety and pharmacokinetic data from an open-label pediatric UC Study in 60 pediatric patients aged 6 years and older *[see Dosage and Administration (2.4), Adverse Reactions (6.1), and Clinical Studies (14.4)]*. The effectiveness of infliximab in inducing and maintaining mucosal healing in pediatric UC was not established. Although 41 patients had a Mayo endoscopy subscore of 0 or 1 at the Week 8 endoscopy, the induction phase was open-label and lacked a control group. Only 9 patients had an optional endoscopy at Week 54. Approximately half of the patients were on concomitant immunomodulators (AZA, 6-MP, MTX) at study start.

Due to the risk of HSTCL, a careful risk-benefit assessment should be made when INFLECTRA is used in combination with other immunosuppressants in pediatric UC patients *[see Boxed Warning and Warnings and Precautions (5.2)]*.

The longer term (greater than 1 year) safety and effectiveness of infliximab products in pediatric UC patients have not been established in clinical trials.

Juvenile Rheumatoid Arthritis (JRA)

The safety and effectiveness of infliximab products in the treatment of pediatric patients with juvenile rheumatoid arthritis (JRA) have not been established.

The safety and efficacy of infliximab in patients with JRA were evaluated in a multicenter, randomized, placebo-controlled, double-blind study for 14 weeks, followed by a double-blind, all-active treatment extension, for a maximum of 44 weeks. Patients with active JRA between the ages of 4 and 17 years who had been treated with MTX for at least 3 months were enrolled. Concurrent use of folic acid, oral corticosteroids (≤0.2 mg/kg/day of prednisone or equivalent), NSAIDs, and/or disease modifying antirheumatic drugs (DMARDs) was permitted.

Doses of 3 mg/kg of infliximab or placebo were administered intravenously at Weeks 0, 2 and 6. Patients randomized to placebo crossed-over to receive 6 mg/kg of infliximab at Weeks 14, 16, and 20, and then every 8 weeks through Week 44. Patients who completed the study continued to receive open-label treatment with infliximab for up to 2 years in a companion extension study.

The study failed to establish the efficacy of infliximab in the treatment of JRA. Key observations in the study included a high placebo response rate and a higher rate of immunogenicity than what has been observed in adults. Additionally, a higher rate of clearance of infliximab was observed than had been observed in adults.

Population pharmacokinetic analysis showed that in pediatric patients with JRA with a body weight of up to 35 kg receiving 6 mg/kg infliximab and pediatric patients with JRA with body weight greater than 35 kg up to adult body weight receiving 3 mg/kg infliximab, the steady state area under the concentration curve (AUCss) was similar to that observed in adults receiving 3 mg/kg of infliximab.

A total of 60 patients with JRA were treated with doses of 3 mg/kg and 57 patients were treated with doses of 6 mg/kg. The proportion of patients with infusion reactions who received 3 mg/kg infliximab was 35% (21/60) over 52 weeks compared with 18% (10/57) in patients who received 6 mg/kg over 38 weeks. The most common infusion reactions reported were vomiting, fever, headache, and hypotension. In the 3 mg/kg infliximab group, 4 patients had a serious infusion reaction and 3 patients reported a possible anaphylactic reaction (2 of which were among the serious infusion reactions). In the 6 mg/kg infliximab group, 2 patients had a serious infusion reaction, 1 of whom had a possible anaphylactic reaction. Two of the 6 patients who experienced serious infusion reactions received infliximab by rapid infusion (duration of less than 2 hours). Antibodies to infliximab developed in 38% (20/53) of patients who received 3 mg/kg infliximab compared with 12% (6/49) of patients who received 6 mg/kg.

A total of 68% (41/60) of patients who received 3 mg/kg of infliximab in combination with MTX experienced an infection over 52 weeks compared with 65% (37/57) of patients who received 6 mg/kg of infliximab in combination with MTX over 38 weeks. The

most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was pneumonia. Other notable infections included primary varicella infection in 1 patient and herpes zoster in 1 patient.

8.5 Geriatric Use

Of the total number of infliximab-treated patients in RA and Ps clinical studies, 256 (9.6%) were 65 years old and over, while 17 (0.6%) were 75 years old and over. In these trials, no overall differences in safety or effectiveness were observed between geriatric patients (patients ≥65 years old) and younger adult patients (patients 18 to 65 years old). However, the incidence of serious adverse reactions in geriatric patients was higher in both infliximab and control groups compared to younger adult patients.

Of the total number of infliximab-treated patients in CD, UC, AS, and PsA clinical studies, 76 (3.2%) were 65 years old and over, while 9 (0.4%) were 75 years old and over. In the CD, UC, AS, and PsA studies, there were insufficient numbers of geriatric patients to determine whether they respond differently from younger adults.

The incidence of serious infections in infliximab-treated geriatric patients was greater than in infliximab-treated younger adult patients; therefore close monitoring of geriatric patients for the development of serious infections is recommended *[see Warnings and Precautions (5.1), and Adverse Reactions (6.1)]*.

10 OVERDOSAGE

Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects *[see Warnings and Precautions (5)]* and appropriate symptomatic treatment instituted immediately.

11 DESCRIPTION

Infliximab-dyyb, a tumor necrosis factor (TNF) blocker, is a chimeric IgG1κ monoclonal antibody (composed of human constant and murine variable regions). It has a molecular weight of approximately 149.1 kilodaltons. Infliximab-dyyb is produced by a recombinant murine myeloma cell line, SP2/0.

INFLECTRA (infliximab-dyyb) for injection is supplied as a sterile, preservative-free, white, lyophilized powder for intravenous infusion after reconstitution and dilution. Following reconstitution with 10 mL of Sterile Water for Injection, USP, the final concentration is 10 mg/mL and the resulting pH is approximately 7.2. Each single-dose vial contains 100 mg infliximab-dyyb, dibasic sodium phosphate, dihydrate (6.1 mg), monobasic sodium phosphate, monohydrate (2.2 mg), polysorbate 80 (0.5 mg), and sucrose (500 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Infliximab products neutralize the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibit binding of TNFα with its receptors. Infliximab products do not neutralize TNFβ (lymphotoxin-α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of proinflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab products can be lysed *in vitro* or *in vivo*. Infliximab products inhibit the functional activity of TNFα in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes and epithelial cells. The relationship of these biological response markers to the mechanism(s) by which infliximab products exert their clinical effects is unknown. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab products prevent disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and when administered after disease onset, allow eroded joints to heal.

12.2 Pharmacodynamics

Elevated concentrations of TNFα have been found in involved tissues and fluids of patients with RA, CD, UC, AS, PsA and Ps. In RA, treatment with infliximab products reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion [E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)], chemoattraction [IL-8 and monocyte chemotactic protein (MCP-1)] and tissue degradation [matrix metalloproteinase (MMP) 1 and 3]. In CD, treatment with infliximab products reduced infiltration of inflammatory cells and TNFα production in inflamed areas of the intestine, and reduced the proportion of mononuclear cells from the lamina propria able to express TNFα and interferon. After treatment with infliximab products, patients with RA or CD exhibited decreased levels of serum IL-6 and C-reactive protein (CRP) compared to baseline. Peripheral blood lymphocytes from infliximab product-treated patients showed no

significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared to cells from untreated patients. In PsA, treatment with infliximab products resulted in a reduction in the number of T-cells and blood vessels in the synovium and psoriatic skin lesions as well as a reduction of macrophages in the synovium. In Ps, infliximab products treatment may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which infliximab products exert their clinical effects is unknown.

12.3 Pharmacokinetics

In adults, single intravenous (IV) infusions of 3 mg/kg to 20 mg/kg (two times the maximum recommended dose for any indication) of infliximab showed a linear relationship between the dose administered and the maximum serum concentration. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment. Pharmacokinetic results for single doses of 3 mg/kg to 10 mg/kg in RA, 5 mg/kg in CD, and 3 mg/kg to 5 mg/kg in Ps indicate that the median terminal half-life of infliximab is 7.7 to 9.5 days.

Following an initial dose of infliximab, repeated infusions at 2 and 6 weeks resulted in predictable concentration-time profiles following each treatment. No systemic accumulation of infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4- or 8-week intervals. Development of antibodies to infliximab increased infliximab clearance. At 8 weeks after a maintenance dose of 3 to 10 mg/kg of infliximab, median infliximab serum concentrations ranged from approximately 0.5 to 6 mcg/mL; however, infliximab concentrations were not detectable (<0.1 mcg/mL) in patients who became positive for antibodies to infliximab. No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight, or gender. It is not known if there are differences in clearance or volume of distribution in patients with marked impairment of hepatic or renal function.

Infliximab pharmacokinetic characteristics (including peak and trough concentrations and terminal half-life) were similar in pediatric (aged 6 to 17 years) and adult patients with CD or UC following the administration of 5 mg/kg of infliximab.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 6-month study in CD-1 mice was conducted to assess the tumorigenic potential of cV1q anti-mouse TNFα, an analogous antibody. No evidence of tumorigenicity was observed in mice that received intravenous doses of 10 mg/kg or 40 mg/kg cV1q given weekly. The relevance of this study for human risk is unknown. No impairment of fertility or reproductive performance indices were observed in male or female mice that received cV1q, an analogous mouse antibody, at intravenous doses up to 40 mg/kg given weekly.

14 CLINICAL STUDIES

14.1 Adult Crohn's Disease

Active Crohn's Disease in Adults

The safety and efficacy of single and multiple doses of infliximab were assessed in 2 randomized, double-blind, placebo-controlled clinical studies in 653 adult patients with moderate to severely active CD [Crohn's Disease Activity Index (CDAI) ≥220 and ≤400] with an inadequate response to prior conventional therapies. Concomitant stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents were permitted and 92% of patients continued to receive at least one of these medications.

In the single-dose trial of 108 adult patients, 16% (4/25) of placebo patients achieved a clinical response (decrease in CDAI ≥70 points) at Week 4 vs. 81% (22/27) of patients receiving 5 mg/kg infliximab (P<0.001, two-sided, Fisher's Exact test). Additionally, 4% (1/25) of placebo patients and 48% (13/27) of patients receiving 5 mg/kg of infliximab achieved clinical remission (CDAI<150) at Week 4.

In a multidose trial (ACCENT I [Study Crohn's I]), 545 adult patients received 5 mg/kg at Week 0 and were then randomized to one of three treatment groups; the placebo maintenance group received placebo at Weeks 2 and 6, and then every 8 weeks; the 5 mg/kg maintenance group received 5 mg/kg at Weeks 2 and 6, and then every 8 weeks; and the 10 mg/kg maintenance group received 5 mg/kg at Weeks 2 and 6, and then 10 mg/kg every 8 weeks. Patients in response at Week 2 were randomized and analyzed separately from those not in responses at Week 2. Corticosteroid taper was permitted after Week 6.

At Week 2, 57% (311/545) of patients were in clinical response. At Week 30, a significantly greater proportion of these patients in the 5 mg/kg and 10 mg/kg maintenance groups achieved clinical remission compared to patients in the placebo maintenance group (Table 3).

Additionally, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg infliximab maintenance groups were in clinical remission and were able to discontinue corticosteroid use compared to patients in the placebo maintenance group at Week 54 (Table 3).

Table 3 Clinical Remission and Steroid Withdrawal in Adult Patients with CD (Study Crohn's I)

	Single 5-mg/kg Dose*	Three-Dose Induction†	
	Placebo Maintenance	Infliximab Maintenance q 8wks	
		5 mg/kg	10 mg/kg
Week 30			
Clinical remission	25/102 25%	41/104 39%	48/105 46%
P-value‡		0.022	0.001
Week 54			
Patients in remission able to discontinue corticosteroid use§	6/54 11%	14/56 25%	18/53 34%
P-value‡		0.059	0.005

* Infliximab at Week 0

† Infliximab 5 mg/kg administered at Weeks 0, 2 and 6

‡ P-values represent pairwise comparisons to placebo

§ Of those receiving corticosteroids at baseline

Patients in the infliximab maintenance groups (5 mg/kg and 10 mg/kg) had a longer time to loss of response than patients in the placebo maintenance group (Figure 1). At Weeks 30 and 54, significant improvement from baseline was seen among the 5 mg/kg and 10 mg/kg groups treated with infliximab compared to the placebo group in the disease-specific inflammatory bowel disease questionnaire (IBDQ), particularly the bowel and systemic components, and in the physical component summary score of the general health-related quality of life questionnaire SF-36.

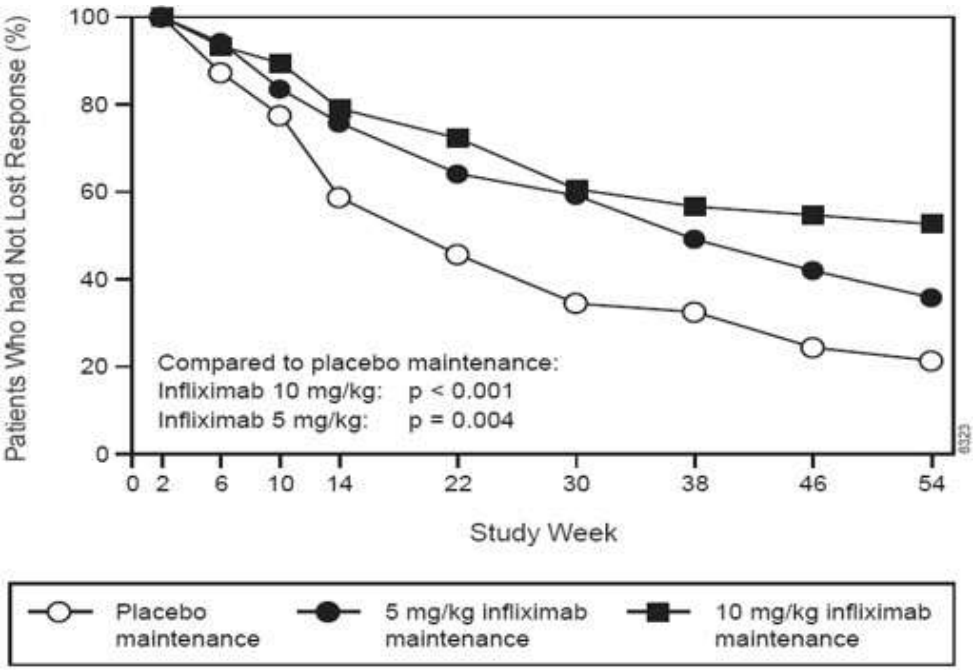

Figure 1 Kaplan-Meier Estimate of the Proportion of Adults with CD Who Had Not Lost Response Through Week 54 (Study Crohn's I)

In a subset of 78 patients who had mucosal ulceration at baseline and who participated in an endoscopic substudy, 13 of 43 patients in infliximab maintenance group had endoscopic evidence of mucosal healing compared to 1 of 28 patients in the placebo group at Week 10. Of the patients treated with infliximab showing mucosal healing at Week 10, 9 of 12 patients also showed mucosal healing at Week 54.

Patients who achieved a response and subsequently lost response were eligible to receive infliximab on an episodic basis at a dose that was 5 mg/kg higher than the dose to which they were randomized. The majority of such patients responded to the higher dose. Among patients who were not in response at Week 2, 59% (92/157) of maintenance patients on infliximab responded by Week 14 compared to 51% (39/77) of placebo maintenance patients. Among patients who did not respond by Week 14, additional therapy did not result in significantly more responses *[see Dosage and Administration (2)]*.

Fistulizing Crohn's Disease in Adults

The safety and efficacy of infliximab were assessed in 2 randomized, double-blind, placebo-controlled studies in adult patients with fistulizing CD with fistula(s) that were of at least 3 months duration. Concurrent use of stable doses of corticosteroids, 5-aminosalicylates, antibiotics, MTX, 6-MP and/or AZA was permitted.

In the first trial, 94 adult patients received 3 doses of either placebo or infliximab at Weeks 0, 2 and 6. Fistula response (≥50% reduction in number of enterocutaneous fistulas draining upon gentle compression on at least 2 consecutive visits without an increase in medication or surgery for CD) was seen in 68% (21/31) of patients in the 5 mg/kg infliximab group (P=0.002) and 56% (18/32) of patients in the 10 mg/kg infliximab group (P=0.021) vs. 26% (8/31) of patients in the placebo arm. The median time to onset of response and median duration of response in patients treated with infliximab was 2 and 12 weeks, respectively. Closure of all fistulas was achieved in 52% patients treated with infliximab compared with 13% of placebo-treated patients (P<0.001).

In the second trial (ACCENT II [Study Crohn's II]), adult patients who were enrolled had to have at least 1 draining enterocutaneous (perianal, abdominal) fistula. All patients received 5 mg/kg of infliximab at Weeks 0, 2 and 6. Patients were randomized to placebo or 5 mg/kg maintenance with infliximab at Week 14. Patients received maintenance doses at Week 14 and then every 8 weeks through Week 46. Patients who were in fistula response (fistula response was defined the same as in the first trial) at both Weeks 10 and 14 were randomized separately from those not in response. The primary endpoint was time from randomization to loss of response among those patients who were in fistula response.

Among the randomized patients (273 of the 296 initially enrolled), 87% had perianal fistulas and 14% had abdominal fistulas. Eight percent also had rectovaginal fistulas. Greater than 90% of the patients had received previous immunosuppressive and antibiotic therapy.

At Week 14, 65% (177/273) of patients were in fistula response. Patients randomized to maintenance with infliximab had a longer time to loss of fistula response compared to the placebo maintenance group (Figure 2). At Week 54, 38% (33/87) of patients treated with infliximab had no draining fistulas compared with 22% (20/90) of placebo-treated patients (P=0.02). Compared to placebo maintenance, patients on maintenance treatment with infliximab had a trend toward fewer hospitalizations.

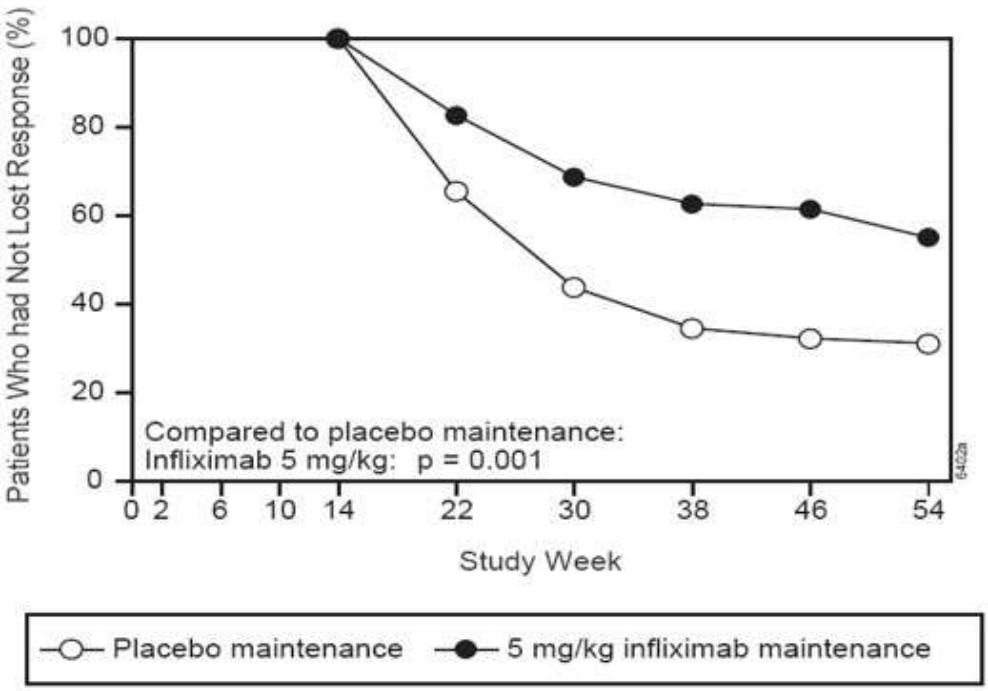

Figure 2 Life Table Estimates of the Proportion of Adult CD Patients Who Had Not Lost Fistula Response Through Week 54 (Study Crohn's II)

Patients who achieved a fistula response and subsequently lost response were eligible to receive maintenance therapy with infliximab at a dose that was 5 mg/kg higher than the dose to which they were randomized. Of the placebo maintenance patients, 66% (25/38) responded to 5 mg/kg infliximab, and 57% (12/21) of maintenance patients on infliximab responded to 10 mg/kg.

Patients who had not achieved a response by Week 14 were unlikely to respond to additional doses of infliximab.

Similar proportions of patients in either group developed new fistulas (17% overall) and similar numbers developed abscesses (15% overall).

14.2 Pediatric Crohn's Disease

The safety and efficacy of infliximab were assessed in a randomized, open-label study (Study Peds Crohn's) in 112 pediatric patients aged 6 to 17 years old with moderately to severely active CD and an inadequate response to conventional therapies. The median age was 13 years and the median Pediatric Crohn's Disease Activity Index (PCDAI) was 40 (on a scale of 0 to 100). All patients were required to be on a stable dose of 6-MP, AZA, or MTX; 35% were also receiving corticosteroids at baseline.

All patients received induction dosing of 5 mg/kg of infliximab at Weeks 0, 2, and 6. At Week 10, 103 patients were randomized to a maintenance regimen of 5 mg/kg of infliximab given either every 8 weeks or every 12 weeks.

At Week 10, 88% of patients were in clinical response (defined as a decrease from baseline in the PCDAI score of ≥15 points and total PCDAI score of ≤30 points), and 59% were in clinical remission (defined as PCDAI score of ≤10 points).

The proportion of pediatric patients achieving clinical response at Week 10 compared favorably with the proportion of adults achieving a clinical response in Study Crohn's I. The study definition of clinical response in Study Peds Crohn's was based on the PCDAI score, whereas the CDAI score was used in the adult Study Crohn's I.

At both Week 30 and Week 54, the proportion of patients in clinical response was greater in the every 8-week treatment group than in the every 12-week treatment group (73% vs. 47% at Week 30, and 64% vs. 33% at Week 54). At both Week 30 and Week 54, the proportion of patients in clinical remission was also greater in the every 8-week treatment group than in the every 12-week treatment group (60% vs. 35% at Week 30, and 56% vs. 24% at Week 54), (Table 4).

For patients in Study Peds Crohn's receiving corticosteroids at baseline, the proportion of patients able to discontinue corticosteroids while in remission at Week 30 was 46% for the every 8-week maintenance group and 33% for the every 12-week maintenance group. At Week 54, the proportion of patients able to discontinue corticosteroids while in remission was 46% for the every 8-week maintenance group and 17% for the every 12-week maintenance group.

Table 4 Response and Remission in Study Peds Crohn's

	5 mg/kg Infliximab	
	Every 8 Week Treatment Group	**Every 12 Week Treatment Group**
Patients randomized	52	51
Clinical Response*		
Week 30	73%†	47%
Week 54	64%†	33%
Clinical Remission‡		
Week 30	60%§	35%
Week 54	56%†	24%

* Defined as a decrease from baseline in the PCDAI score of ≥15 points and total score of ≤30 points.

† *P*-value <0.01

‡ Defined as a PCDAI score of ≤10 points.

§ *P*-value <0.05

14.3 Adult Ulcerative Colitis

The safety and efficacy of infliximab were assessed in 2 randomized, double-blind, placebo-controlled clinical studies in 728 adult patients with moderately to severely active UC (Mayo score 6 to 12 [of possible range 0 to 12], Endoscopy subscore ≥2) with an inadequate response to conventional oral therapies (Studies UC I and UC II). Concomitant treatment with stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents was permitted. Corticosteroid taper was permitted after Week 8. Patients were randomized at Week 0 to receive either placebo, 5 mg/kg infliximab or 10 mg/kg infliximab at Weeks 0, 2, 6, and every 8 weeks thereafter through Week 46 in Study UC I, and at Weeks 0, 2, 6, and every 8 weeks thereafter through Week 22 in Study UC II. In Study UC II, patients were allowed to continue blinded therapy to Week 46 at the investigator's discretion.

Adult patients in Study UC I had failed to respond or were intolerant to oral corticosteroids, 6-MP, or AZA. Adult patients in Study UC II had failed to respond or were intolerant to the above treatments and/or aminosalicylates. Similar proportions of patients in Studies UC I and UC II were receiving corticosteroids (61% and 51%, respectively), 6-MP/AZA (49% and 43%) and aminosalicylates (70% and 75%) at baseline. More patients in Study UC II than UC I were taking solely aminosalicylates for UC (26% vs. 11%, respectively). Clinical response was defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.

Clinical Response, Clinical Remission, and Mucosal Healing

In both Study UC I and Study UC II, greater percentages of patients in both infliximab groups achieved clinical response, clinical remission and mucosal healing than in the placebo group. Each of these effects was maintained through the end of each trial (Week 54

in Study UC I, and Week 30 in Study UC II). In addition, a greater proportion of patients in infliximab groups demonstrated sustained response and sustained remission than in the placebo groups (Table 5).

Of patients on corticosteroids at baseline, greater proportions of adult patients in groups treated with infliximab were in clinical remission and able to discontinue corticosteroids at Week 30 compared with the patients in the placebo treatment groups (22% in infliximab treatment groups vs. 10% in placebo group in Study UC I; 23% in infliximab treatment groups vs. 3% in placebo group in Study UC II). In Study UC I, this effect was maintained through Week 54 (21% in infliximab treatment groups vs. 9% in placebo group). The infliximab-associated response was generally similar in the 5 mg/kg and 10 mg/kg dose groups.

Table 5 Response, Remission and Mucosal Healing in Adult UC Studies (Studies UC I and UC II)

	Study UC I			Study UC II		
	Placebo	**5 mg/kg Infliximab**	**10 mg/kg Infliximab**	**Placebo**	**5 mg/kg Infliximab**	**10 mg/kg Infliximab**
Patients randomized	121	121	122	123	121	120
Clinical Response[*,†]						
Week 8	37%	69%[‡]	62%[‡]	29%	65%[‡]	69%[‡]
Week 30	30%	52%[‡]	51%[§]	26%	47%[‡]	60%[‡]
Week 54	20%	45%[‡]	44%[‡]	NA	NA	NA
Sustained Response[†]						
(Clinical response at both Week 8 and 30)	23%	49%[‡]	46%[‡]	15%	41%[‡]	53%[‡]
(Clinical response at Weeks 8, 30 and 54)	14%	39%[‡]	37%[‡]	NA	NA	NA
Clinical Remission[¶,†]						
Week 8	15%	39%[‡]	32%[§]	6%	34%[‡]	28%[‡]
Week 30	16%	34%[§]	37%[‡]	11%	26%[§]	36%[‡]
Week 54	17%	35%[§]	34%[§]	NA	NA	NA
Sustained Remission[†]						
(Clinical remission at both Week 8 and 30)	8%	23%[§]	26%[‡]	2%	15%[‡]	23%[‡]
(Clinical remission at Weeks 8, 30 and 54)	7%	20%[§]	20%[§]	NA	NA	NA
Mucosal Healing[#,†]						
Week 8	34%	62%[‡]	59%[‡]	31%	60%[‡]	62%[‡]

[*] Defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1. (The Mayo score consists of the sum of four subscores: stool frequency, rectal bleeding, physician's global assessment and endoscopy findings).

[†] Patients who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in clinical response, clinical remission or mucosal healing from the time of the event onward.

[‡] $P<0.001$,

[§] $P<0.01$

[¶] Defined as a Mayo score ≤2 points, no individual subscore >1.

[#] Defined as a 0 or 1 on the endoscopy subscore of the Mayo score.

	Study UC I			Study UC II		
	Placebo	5 mg/kg Infliximab	10 mg/kg Infliximab	Placebo	5 mg/kg Infliximab	10 mg/kg Infliximab
Week 30	25%	50%‡	49%‡	30%	46%§	57%‡
Week 54	18%	45%‡	47%‡	NA	NA	NA

* Defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1. (The Mayo score consists of the sum of four subscores: stool frequency, rectal bleeding, physician's global assessment and endoscopy findings).

† Patients who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in clinical response, clinical remission or mucosal healing from the time of the event onward.

‡ $P<0.001$,

§ $P<0.01$

¶ Defined as a Mayo score ≤2 points, no individual subscore >1.

Defined as a 0 or 1 on the endoscopy subscore of the Mayo score.

The improvement with infliximab was consistent across all Mayo subscores through Week 54 (Study UC I shown in Table 6; Study UC II through Week 30 was similar).

Table 6 Proportion of Adult UC Patients in Study UC I with Mayo Subscores Indicating Inactive or Mild Disease Through Week 54

	Study UC I		
		Infliximab	
	Placebo (n=121)	5 mg/kg (n=121)	10 mg/kg (n=122)
Stool frequency			
Baseline	17%	17%	10%
Week 8	35%	60%	58%
Week 30	35%	51%	53%
Week 54	31%	52%	51%
Rectal bleeding			
Baseline	54%	40%	48%
Week 8	74%	86%	80%
Week 30	65%	74%	71%
Week 54	62%	69%	67%
Physician's Global Assessment			
Baseline	4%	6%	3%
Week 8	44%	74%	64%
Week 30	36%	57%	55%
Week 54	26%	53%	53%
Endoscopy findings			
Baseline	0%	0%	0%
Week 8	34%	62%	59%
Week 30	26%	51%	52%
Week 54	21%	50%	51%

14.4 Pediatric Ulcerative Colitis

The safety and effectiveness of infliximab products for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients aged 6 years and older with moderately to severely active UC who have had an inadequate response to conventional therapy are supported by evidence from adequate and well-controlled studies of infliximab in adults. Additional safety and pharmacokinetic data were collected in an open-label pediatric UC trial in 60 pediatric patients aged 6 through 17 years (median age 14.5 years) with moderately to severely active UC (Mayo score of 6 to 12; Endoscopic subscore ≥2) and an inadequate response to conventional therapies. At baseline, the median Mayo score was 8, 53% of patients were receiving immunomodulator therapy (6-

MP/AZA/MTX), and 62% of patients were receiving corticosteroids (median dose 0.5 mg/kg/day in prednisone equivalents). Discontinuation of immunomodulators and corticosteroid taper were permitted after Week 0.

All patients received induction dosing of 5 mg/kg infliximab at Weeks 0, 2, and 6. Patients who did not respond to infliximab at Week 8 received no further infliximab and returned for safety follow-up. At Week 8, 45 patients were randomized to a maintenance regimen of 5 mg/kg infliximab given either every 8 weeks through Week 46 or every 12 weeks through Week 42. Patients were allowed to change to a higher dose and/or more frequent administration schedule if they experienced loss of response.

Clinical response at Week 8 was defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, including a decrease in the rectal bleeding subscore by ≥1 points or achievement of a rectal bleeding subscore of 0 or 1.

Clinical remission at Week 8 was measured by the Mayo score, defined as a Mayo score of ≤2 points with no individual subscore >1. Clinical remission was also assessed at Week 8 and Week 54 using the Pediatric Ulcerative Colitis Activity Index (PUCAI)[1] score and was defined by a PUCAI score of <10 points.

Endoscopies were performed at baseline and at Week 8. A Mayo endoscopy subscore of 0 indicated normal or inactive disease and a subscore of 1 indicated mild disease (erythema, decreased vascular pattern, or mild friability).

Of the 60 patients treated, 44 were in clinical response at Week 8. Of 32 patients taking concomitant immunomodulators at baseline, 23 achieved clinical response at Week 8, compared to 21 of 28 of those not taking concomitant immunomodulators at baseline. At Week 8, 24 of 60 patients were in clinical remission as measured by the Mayo score and 17 of 51 patients were in remission as measured by the PUCAI score.

At Week 54, 8 of 21 patients in the every 8-week maintenance group and 4 of 22 patients in the every 12-week maintenance group achieved remission as measured by the PUCAI score.

During maintenance phase, 23 of 45 randomized patients (9 in the every 8-week group and 14 in the every 12-week group) required an increase in their dose and/or increase in frequency of infliximab administration due to loss of response. Nine of the 23 patients who required a change in dose had achieved remission at Week 54. Seven of those patients received the 10 mg/kg every 8-week dosing.

14.5 Rheumatoid Arthritis

The safety and efficacy of infliximab in adult patients with RA were assessed in 2 multicenter, randomized, double-blind, pivotal trials: ATTRACT (Study RA I) and ASPIRE (Study RA II). Concurrent use of stable doses of folic acid, oral corticosteroids (≤10 mg/day) and/or non-steroidal anti-inflammatory drugs (NSAIDs) was permitted.

Study RA I was a placebo-controlled study of 428 patients with active RA despite treatment with MTX. Patients enrolled had a median age of 54 years, median disease duration of 8.4 years, median swollen and tender joint count of 20 and 31 respectively, and were on a median dose of 15 mg/wk of MTX. Patients received either placebo+MTX or one of 4 doses/schedules of the infliximab+MTX: 3 mg/kg or 10 mg/kg infliximab by IV infusion at Weeks 0, 2 and 6 followed by additional infusions every 4 or 8 weeks in combination with MTX.

Study RA II was a placebo-controlled study of 3 active treatment arms in 1004 MTX naïve patients of 3 or fewer years' duration active RA. Patients enrolled had a median age of 51 years with a median disease duration of 0.6 years, median swollen and tender joint count of 19 and 31, respectively, and >80% of patients had baseline joint erosions. At randomization, all patients received MTX (optimized to 20 mg/wk by Week 8) and either placebo, 3 mg/kg or 6 mg/kg of infliximab at Weeks 0, 2, and 6 and every 8 weeks thereafter.

Data on use of infliximab products without concurrent MTX are limited *[see Adverse Reactions (6.1)]*.

Clinical Response

In Study RA I, all doses/schedules of infliximab+MTX resulted in improvement in signs and symptoms as measured by the American College of Rheumatology response criteria (ACR 20) with a higher percentage of patients achieving an ACR 20, 50 and 70 compared to placebo+MTX (Table 7). This improvement was observed at Week 2 and maintained through Week 102. Greater effects on each component of the ACR 20 were observed in all patients treated with infliximab+MTX compared to placebo+MTX (Table 8). More patients treated with infliximab reached a major clinical response than placebo-treated patients (Table 7).

In Study RA II, after 54 weeks of treatment, both doses of infliximab+MTX resulted in statistically significantly greater response in signs and symptoms compared to MTX alone as measured by the proportion of patients achieving ACR 20, 50 and 70 responses (Table 7). More patients treated with infliximab reached a major clinical response than placebo-treated patients (Table 7).

Table 7 ACR Response (percent of patients) in Adult RA Patients (Studies RA I and RA II)

Response	Study RA I					Study RA II		
		Infliximab+MTX					Infliximab+MTX	
		3 mg/kg		10 mg/kg			3 mg/kg	6 mg/kg
	Placebo +MTX (n=88)	q8 wks (n=86)	q4 wks (n=86)	q8 wks (n=87)	q4 wks (n=81)	Placebo +MTX (n=274)	q8 wks (n=351)	q8 wks (n=355)
ACR 20								
Week 30	20%	50%*	50% *	52% *	58% *	N/A	N/A	N/A
Week 54	17%	42% *	48% *	59% *	59% *	54%	62% †	66% *
ACR 50								
Week 30	5%	27% *	29% *	31% *	26% *	N/A	N/A	N/A
Week 54	9%	21% †	34% *	40% *	38% *	32%	46% *	50% *
ACR 70								
Week 30	0%	8%‡	11% ‡	18% *	11% *	N/A	N/A	N/A
Week 54	2%	11% †	18% *	26% *	19% *	21%	33% ‡	37% *
Major clinical response§	0%	7% †	8% ‡	15% *	6% †	8%	12%	17% *

* $P \leq 0.001$

† $P < 0.05$

‡ $P < 0.01$

§ A major clinical response was defined as a 70% ACR response for 6 consecutive months (consecutive visits spanning at least 26 weeks) through Week 102 for Study RA I and Week 54 for Study RA II.

Table 8 Components of ACR 20 at Baseline and 54 Weeks (Study RA I)

Parameter (medians)	Placebo+MTX (n=88)		Infliximab+MTX* (n=340)	
	Baseline	Week 54	Baseline	Week 54
No. of Tender Joints	24	16	32	8
No. of Swollen Joints	19	13	20	7
Pain†	6.7	6.1	6.8	3.3
Physician's Global Assessment†	6.5	5.2	6.2	2.1
Patient's Global Assessment†	6.2	6.2	6.3	3.2
Disability Index (HAQ-DI)‡	1.8	1.5	1.8	1.3
CRP (mg/dL)	3.0	2.3	2.4	0.6

* All doses/schedules of infliximab+MTX

† Visual Analog Scale (0=best, 10=worst)

‡ Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0=best, 3=worst)

Radiographic Response

Structural damage in both hands and feet was assessed radiographically at Week 54 by the change from baseline in the van der Heijde-modified Sharp (vdH-S) score, a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet.

In Study RA I, approximately 80% of patients had paired X-ray data at 54 weeks and approximately 70% at 102 weeks. The inhibition of progression of structural damage was observed at 54 weeks (Table 9) and maintained through 102 weeks.

In Study RA II, >90% of patients had at least 2 evaluable X-rays. Inhibition of progression of structural damage was observed at Weeks 30 and 54 (Table 9) in infliximab+MTX groups compared to MTX alone. Patients treated with infliximab+MTX demonstrated less progression of structural damage compared to MTX alone, whether baseline acute-phase reactants (ESR and CRP) were normal or elevated: patients with elevated baseline acute-phase reactants treated with MTX alone demonstrated a mean progression in vdH-S score of 4.2 units compared to patients treated with infliximab+MTX who demonstrated 0.5 units of progression; patients with normal baseline acute phase reactants treated with MTX alone demonstrated a mean progression in vdH-S score of 1.8 units

compared to infliximab+MTX who demonstrated 0.2 units of progression. Of patients receiving infliximab+MTX, 59% had no progression (vdH-S score ≤0 unit) of structural damage compared to 45% of patients receiving MTX alone. In a subset of patients who began the study without erosions, infliximab+MTX maintained an erosion-free state at 1 year in a greater proportion of patients than MTX alone, 79% (77/98) vs. 58% (23/40), respectively (P<0.01). Fewer patients in infliximab+MTX groups (47%) developed erosions in uninvolved joints compared to MTX alone (59%).

Table 9 Radiographic Change from Baseline to Week 54 in Adult RA Patients (Studies RA I and RA II)

	Study RA I			Study RA II		
		Infliximab+MTX			Infliximab+MTX	
		3 mg/kg	10 mg/kg		3 mg/kg	6 mg/kg
	Placebo + MTX (n=64)	q8 wks (n=71)	q8 wks (n=77)	Placebo + MTX (n=282)	q8 wks (n=359)	q8 wks (n=363)
Total Score						
Baseline						
Mean	79	78	65	11.3	11.6	11.2
Median	55	57	56	5.1	5.2	5.3
Change from baseline						
Mean	6.9	1.3*	0.2*	3.7	0.4*	0.5*
Median	4.0	0.5	0.5	0.4	0.0	0.0
Erosion Score						
Baseline						
Mean	44	44	33	8.3	8.8	8.3
Median	25	29	22	3.0	3.8	3.8
Change from baseline						
Mean	4.1	0.2*	0.2*	3.0	0.3*	0.1*
Median	2.0	0.0	0.5	0.3	0.0	0.0
JSN Score						
Baseline						
Mean	36	34	31	3.0	2.9	2.9
Median	26	29	24	1.0	1.0	1.0
Change from baseline						
Mean	2.9	1.1*	0.0*	0.6	0.1*	0.2
Median	1.5	0.0	0.0	0.0	0.0	0.0

* P<0.001 for each outcome against placebo.

Physical Function Response

Physical function and disability were assessed using the Health Assessment Questionnaire (HAQ-DI) and the general health-related quality of life questionnaire SF-36.

In Study RA I, all doses/schedules of infliximab+MTX showed significantly greater improvement from baseline in HAQ-DI and SF-36 physical component summary score averaged over time through Week 54 compared to placebo+MTX, and no worsening in the SF-36 mental component summary score. The median (interquartile range) improvement from baseline to Week 54 in HAQ-DI was 0.1 (-0.1, 0.5) for the placebo+MTX group and 0.4 (0.1, 0.9) for infliximab+MTX (p<0.001). Both HAQ-DI and SF-36 effects were maintained through Week 102. Approximately 80% of patients in all doses/schedules of infliximab+MTX remained in the trial through 102 weeks.

In Study RA II, both treatment groups of infliximab showed greater improvement in HAQ-DI from baseline averaged over time through Week 54 compared to MTX alone; 0.7 for infliximab+MTX vs. 0.6 for MTX alone (P≤0.001). No worsening in the SF-36 mental component summary score was observed.

14.6 Ankylosing Spondylitis

The safety and efficacy of infliximab were assessed in a randomized, multicenter, double-blind, placebo-controlled study in 279 adult patients with active AS. Patients were between 18 and 74 years of age, and had AS as defined by the modified New York criteria for

Ankylosing Spondylitis. Patients were to have had active disease as evidenced by both a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score >4 (possible range 0–10) and spinal pain >4 (on a Visual Analog Scale [VAS] of 0–10). Patients with complete ankylosis of the spine were excluded from study participation, and the use of Disease Modifying Anti-Rheumatic Drugs (DMARDs) and systemic corticosteroids were prohibited. Doses of 5 mg/kg of infliximab or placebo were administered intravenously at Weeks 0, 2, 6, 12 and 18.

At 24 weeks, improvement in the signs and symptoms of AS, as measured by the proportion of patients achieving a 20% improvement in ASAS response criteria (ASAS 20), was seen in 60% of patients in the infliximab-treated group vs. 18% of patients in the placebo group (p<0.001). Improvement was observed at Week 2 and maintained through Week 24 (Figure 3 and Table 10).

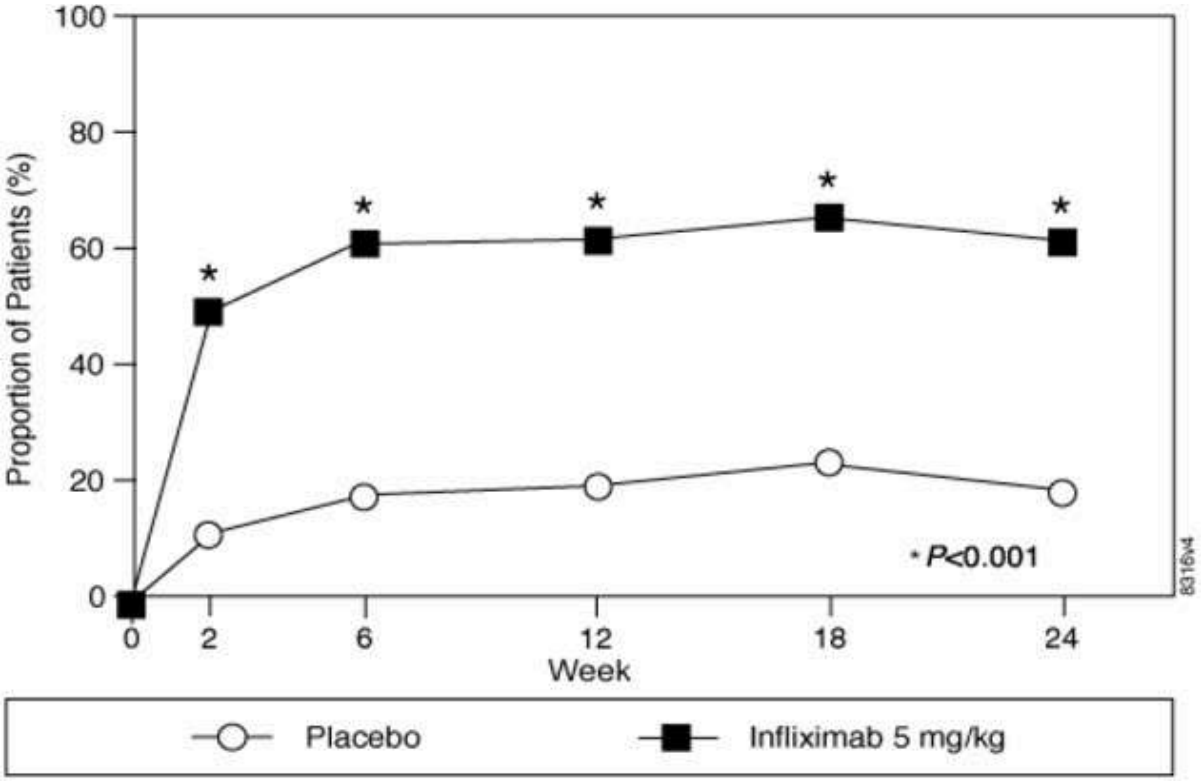

Figure 3 Proportion of Adult AS Patients Who Achieved ASAS 20 Response

At 24 weeks, the proportions of patients achieving a 50% and a 70% improvement in the signs and symptoms of AS, as measured by ASAS response criteria (ASAS 50 and ASAS 70, respectively), were 44% and 28%, respectively, for patients receiving infliximab, compared to 9% and 4%, respectively, for patients receiving placebo (*P*<0.001, infliximab vs. placebo). A low level of disease activity (defined as a value <20 [on a scale of 0 – 100 mm] in each of the 4 ASAS response parameters) was achieved in 22% of patients treated with infliximab vs. 1% in placebo-treated patients (*P*<0.001).

Table 10 Components of AS Disease Activity

	Placebo (n=78)		Infliximab 5 mg/kg (n=201)		
	Baseline	**24 Weeks**	**Baseline**	**24 Weeks**	**P-value**
ASAS 20 response Criteria (Mean)					
Patient Global Assessment*	6.6	6.0	6.8	3.8	<0.001
Spinal pain*	7.3	6.5	7.6	4.0	<0.001
BASFI†	5.8	5.6	5.7	3.6	<0.001

* Measured on a VAS with 0="none" and 10="severe"

† Bath Ankylosing Spondylitis Functional Index (BASFI), average of 10 questions

‡ Inflammation, average of last 2 questions on the 6-question BASDAI

§ CRP normal range 0–1.0 mg/dL

¶ Spinal mobility normal values: modified Schober's test: >4 cm; chest expansion:>6 cm; tragus to wall: <15 cm; lateral spinal flexion: >10 cm

	Placebo (n=78)		Infliximab 5 mg/kg (n=201)		
	Baseline	24 Weeks	Baseline	24 Weeks	P-value
Inflammation‡	6.9	5.8	6.9	3.4	<0.001
Acute Phase Reactants					
Median CRP§ (mg/dL)	1.7	1.5	1.5	0.4	<0.001
Spinal Mobility (cm, Mean)					
Modified Schober's test¶	4.0	5.0	4.3	4.4	0.75
Chest expansion¶	3.6	3.7	3.3	3.9	0.04
Tragus to wall¶	17.3	17.4	16.9	15.7	0.02
Lateral spinal flexion¶	10.6	11.0	11.4	12.9	0.03

* Measured on a VAS with 0="none" and 10="severe"

† Bath Ankylosing Spondylitis Functional Index (BASFI), average of 10 questions

‡ Inflammation, average of last 2 questions on the 6-question BASDAI

§ CRP normal range 0–1.0 mg/dL

¶ Spinal mobility normal values: modified Schober's test: >4 cm; chest expansion:>6 cm; tragus to wall: <15 cm; lateral spinal flexion: >10 cm

The median improvement from baseline in the general health-related quality-of-life questionnaire SF-36 physical component summary score at Week 24 was 10.2 for the infliximab group vs. 0.8 for the placebo group (P<0.001). There was no change in the SF-36 mental component summary score in either the infliximab group or the placebo group.

Results of this study were similar to those seen in a multicenter double-blind, placebo-controlled study of 70 patients with AS.

14.7 Psoriatic Arthritis

Safety and efficacy of infliximab were assessed in a multicenter, double-blind, placebo-controlled study in 200 adult patients with active PsA despite DMARD or NSAID therapy (≥5 swollen joints and ≥5 tender joints) with 1 or more of the following subtypes: arthritis involving DIP joints (n=49), arthritis mutilans (n=3), asymmetric peripheral arthritis (n=40), polyarticular arthritis (n=100), and spondylitis with peripheral arthritis (n=8). Patients also had Ps with a qualifying target lesion ≥2 cm in diameter. Forty-six percent of patients continued on stable doses of methotrexate (≤25 mg/week). During the 24-week double-blind phase, patients received either 5 mg/kg infliximab or placebo at Weeks 0, 2, 6, 14, and 22 (100 patients in each group). At Week 16, placebo patients with <10% improvement from baseline in both swollen and tender joint counts were switched to infliximab induction (early escape). At Week 24, all placebo-treated patients crossed over to infliximab induction. Dosing continued for all patients through Week 46.

Clinical Response

Treatment with infliximab resulted in improvement in signs and symptoms, as assessed by the ACR criteria, with 58% of patients treated with infliximab achieving ACR 20 at Week 14, compared with 11% of placebo-treated patients (P<0.001). The response was similar regardless of concomitant use of methotrexate. Improvement was observed as early as Week 2. At 6 months, the ACR 20/50/70 responses were achieved by 54%, 41%, and 27%, respectively, of patients receiving infliximab compared to 16%, 4%, and 2%, respectively, of patients receiving placebo. Similar responses were seen in patients with each of the subtypes of PsA, although few patients were enrolled with the arthritis mutilans and spondylitis with peripheral arthritis subtypes.

Compared to placebo, treatment with infliximab resulted in improvements in the components of the ACR response criteria, as well as in dactylitis and enthesopathy (Table 11). The clinical response was maintained through Week 54. Similar ACR responses were observed in an earlier randomized, placebo-controlled study of 104 PsA patients, and the responses were maintained through 98 weeks in an open-label extension phase.

Table 11 Components of ACR 20 and Percentage of Adult PsA Patients with 1 or More Joints with Dactylitis and Percentage of Adult PsA Patients with Enthesopathy at Baseline and Week 24

Patients Randomized	Placebo (n=100)		Infliximab 5 mg/kg* (n=100)	
	Baseline	Week 24	Baseline	Week 24

Patients Randomized	Placebo (n=100)		Infliximab 5 mg/kg* (n=100)	
	Baseline	Week 24	Baseline	Week 24
Parameter (medians)				
No. of Tender Joints†	24	20	20	6
No. of Swollen Joints‡	12	9	12	3
Pain§	6.4	5.6	5.9	2.6
Physician's Global Assessment§	6.0	4.5	5.6	1.5
Patient's Global Assessment§	6.1	5.0	5.9	2.5
Disability Index (HAQ-DI)¶	1.1	1.1	1.1	0.5
CRP (mg/dL)#	1.2	0.9	1.0	0.4
% Patients with 1 or more digits with dactylitis	41	33	40	15
% Patients with enthesopathy	35	36	42	22

* P<0.001 for percent change from baseline in all components of ACR 20 at Week 24, P<0.05 for % of patients with dactylitis, and P=0.004 for % of patients with enthesopathy at Week 24

† Scale 0–68

‡ Scale 0–66

§ Visual Analog Scale (0=best, 10=worst)

¶ Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0=best, 3=worst)

Normal range 0–0.6 mg/dL

Improvement in Psoriasis Area and Severity Index (PASI) in PsA patients with baseline body surface area (BSA) ≥3% (n=87 placebo, n=83 infliximab) was achieved at Week 14, regardless of concomitant methotrexate use, with 64% of patients treated with infliximab achieving at least 75% improvement from baseline vs. 2% of placebo-treated patients; improvement was observed in some patients as early as Week 2. At 6 months, the PASI 75 and PASI 90 responses were achieved by 60% and 39%, respectively, of patients receiving infliximab compared to 1% and 0%, respectively, of patients receiving placebo. The PASI response was generally maintained through Week 54. *[See Clinical Studies (14.8)]*.

Radiographic Response

Structural damage in both hands and feet was assessed radiographically by the change from baseline in the van der Heijde-Sharp (vdH-S) score, modified by the addition of hand DIP joints. The total modified vdH-S score is a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing (JSN) in the hands and feet. At Week 24, patients treated with infliximab had less radiographic progression than placebo-treated patients (mean change of -0.70 vs. 0.82, *P*<0.001). Patients treated with infliximab also had less progression in their erosion scores (-0.56 vs 0.51) and JSN scores (-0.14 vs 0.31). The patients in the infliximab group demonstrated continued inhibition of structural damage at Week 54. Most patients showed little or no change in the vdH-S score during this 12-month study (median change of 0 in both patients who initially received infliximab or placebo). More patients in the placebo group (12%) had readily apparent radiographic progression compared with the infliximab group (3%).

Physical Function

Physical function status was assessed using the HAQ Disability Index (HAQ-DI) and the SF-36 Health Survey. Patients treated with infliximab demonstrated significant improvement in physical function as assessed by HAQ-DI (median percent improvement in HAQ-DI score from baseline to Week 14 and 24 of 43% for infliximab-treated patients vs 0% for placebo-treated patients).

During the placebo-controlled portion of the trial (24 weeks), 54% of patients treated with infliximab achieved a clinically meaningful improvement in HAQ-DI (≥0.3 unit decrease) compared to 22% of placebo-treated patients. Patients treated with infliximab also demonstrated greater improvement in the SF-36 physical and mental component summary scores than placebo-treated patients. The responses were maintained for up to 2 years in an open-label extension study.

14.8 Plaque Psoriasis

The safety and efficacy of infliximab were assessed in 3 randomized, double-blind, placebo-controlled studies in patients 18 years of age and older with chronic, stable Ps involving ≥10% BSA, a minimum PASI score of 12, and who were candidates for systemic therapy or phototherapy. Patients with guttate, pustular, or erythrodermic psoriasis were excluded from these studies. No concomitant anti-psoriatic therapies were allowed during the study, with the exception of low-potency topical corticosteroids on the face and groin after Week 10 of study initiation.

Study I (EXPRESS) evaluated 378 patients who received placebo or infliximab at a dose of 5 mg/kg at Weeks 0, 2, and 6 (induction therapy), followed by maintenance therapy every 8 weeks. At Week 24, the placebo group crossed over to infliximab induction therapy (5 mg/kg), followed by maintenance therapy every 8 weeks. Patients originally randomized to infliximab continued to receive infliximab 5 mg/kg every 8 weeks through Week 46. Across all treatment groups, the median baseline PASI score was 21 and the baseline Static Physician Global Assessment (sPGA) score ranged from moderate (52% of patients) to marked (36%) to severe (2%). In addition, 75% of patients had a BSA >20%. Seventy-one percent of patients previously received systemic therapy, and 82% received phototherapy.

Study II (EXPRESS II) evaluated 835 patients who received placebo or infliximab at doses of 3 mg/kg or 5 mg/kg at Weeks 0, 2, and 6 (induction therapy). At Week 14, within each infliximab dose group, patients were randomized to either scheduled (every 8 weeks) or as needed (PRN) maintenance treatment through Week 46. At Week 16, the placebo group crossed over to infliximab induction therapy (5 mg/kg), followed by maintenance therapy every 8 weeks. Across all treatment groups, the median baseline PASI score was 18, and 63% of patients had a BSA >20%. Fifty-five percent of patients previously received systemic therapy, and 64% received a phototherapy.

Study III (SPIRIT) evaluated 249 patients who had previously received either psoralen plus ultraviolet A treatment (PUVA) or other systemic therapy for their psoriasis. These patients were randomized to receive either placebo or infliximab at doses of 3 mg/kg or 5 mg/kg at Weeks 0, 2, and 6. At Week 26, patients with a sPGA score of moderate or worse (greater than or equal to 3 on a scale of 0 to 5) received an additional dose of the randomized treatment. Across all treatment groups, the median baseline PASI score was 19, and the baseline sPGA score ranged from moderate (62% of patients) to marked (22%) to severe (3%). In addition, 75% of patients had a BSA >20%. Of the enrolled patients, 114 (46%) received the Week 26 additional dose.

In Studies I, II and III, the primary endpoint was the proportion of patients who achieved a reduction in score of at least 75% from baseline at Week 10 by the PASI (PASI 75). In Study I and Study III, another evaluated outcome included the proportion of patients who achieved a score of "cleared" or "minimal" by the sPGA. The sPGA is a 6-category scale ranging from "5 = severe" to "0 = cleared" indicating the physician's overall assessment of the psoriasis severity focusing on induration, erythema, and scaling. Treatment success, defined as "cleared" or "minimal," consisted of none or minimal elevation in plaque, up to faint red coloration in erythema, and none or minimal fine scale over <5% of the plaque.

Study II also evaluated the proportion of patients who achieved a score of "clear" or "excellent" by the relative Physician's Global Assessment (rPGA). The rPGA is a 6-category scale ranging from "6 = worse" to "1 = clear" that was assessed relative to baseline. Overall lesions were graded with consideration to the percent of body involvement as well as overall induration, scaling, and erythema. Treatment success, defined as "clear" or "excellent," consisted of some residual pinkness or pigmentation to marked improvement (nearly normal skin texture; some erythema may be present). The results of these studies are presented in Table 12.

Table 12 Adult Psoriasis Studies I, II, and III, Percentage of Patients who Achieved PASI75 and Percentage who Achieved Treatment "Success" with Physician's Global Assessment at Week 10

	Placebo	Infliximab	
		3 mg/kg	5 mg/kg
Psoriasis Study I - patients randomized*	77	---	301
PASI 75	2 (3%)	---	242 (80%)†
sPGA	3 (4%)	---	242 (80%)†
Psoriasis Study II - patients randomized*	208	313	314
PASI 75	4 (2%)	220 (70%)†	237 (75%)†
rPGA	2 (1%)	217 (69%)†	234 (75%)†
Psoriasis Study III - patients randomized‡	51	99	99
PASI 75	3 (6%)	71 (72%)†	87 (88%)†
sPGA	5 (10%)	71 (72%)†	89 (90%)†

* Patients with missing data at Week 10 were considered as nonresponders.

† $P<0.001$ compared with placebo

‡ Patients with missing data at Week 10 were imputed by last observation.

In Study I, in the subgroup of patients with more extensive Ps who had previously received phototherapy, 85% of patients on 5 mg/kg infliximab achieved a PASI 75 at Week 10 compared with 4% of patients on placebo.

In Study II, in the subgroup of patients with more extensive Ps who had previously received phototherapy, 72% and 77% of patients on 3 mg/kg and 5 mg/kg infliximab achieved a PASI 75 at Week 10 respectively compared with 1% on placebo. In Study II, among

patients with more extensive Ps who had failed or were intolerant to phototherapy, 70% and 78% of patients on 3 mg/kg and 5 mg/kg infliximab achieved a PASI 75 at Week 10 respectively, compared with 2% on placebo.

Maintenance of response was studied in a subset of 292 and 297 patients treated with infliximab in the 3 mg/kg and 5 mg/kg groups; respectively, in Study II. Stratified by PASI response at Week 10 and investigational site, patients in the active treatment groups were re-randomized to either a scheduled or as needed maintenance (PRN) therapy, beginning on Week 14.

The groups that received a maintenance dose every 8 weeks appear to have a greater percentage of patients maintaining a PASI 75 through week 50 as compared to patients who received the as-needed or PRN doses, and the best response was maintained with the 5 mg/kg every 8-week dose. These results are shown in Figure 4. At Week 46, when infliximab serum concentrations were at trough level, in the every 8-week dose group, 54% of patients in the 5 mg/kg group compared to 36% in the 3 mg/kg group achieved PASI 75. The lower percentage of PASI 75 responders in the 3 mg/kg every 8-week dose group compared to the 5 mg/kg group was associated with a lower percentage of patients with detectable trough serum infliximab levels.

This may be related in part to higher antibody rates *[see Adverse Reactions (6.1)]*. In addition, in a subset of patients who had achieved a response at Week 10, maintenance of response appears to be greater in patients who received infliximab every 8 weeks at the 5 mg/kg dose. Regardless of whether the maintenance doses are PRN or every 8 weeks, there is a decline in response in a subpopulation of patients in each group over time. The results of Study I through Week 50 in the 5 mg/kg every 8 weeks maintenance dose group were similar to the results from Study II.

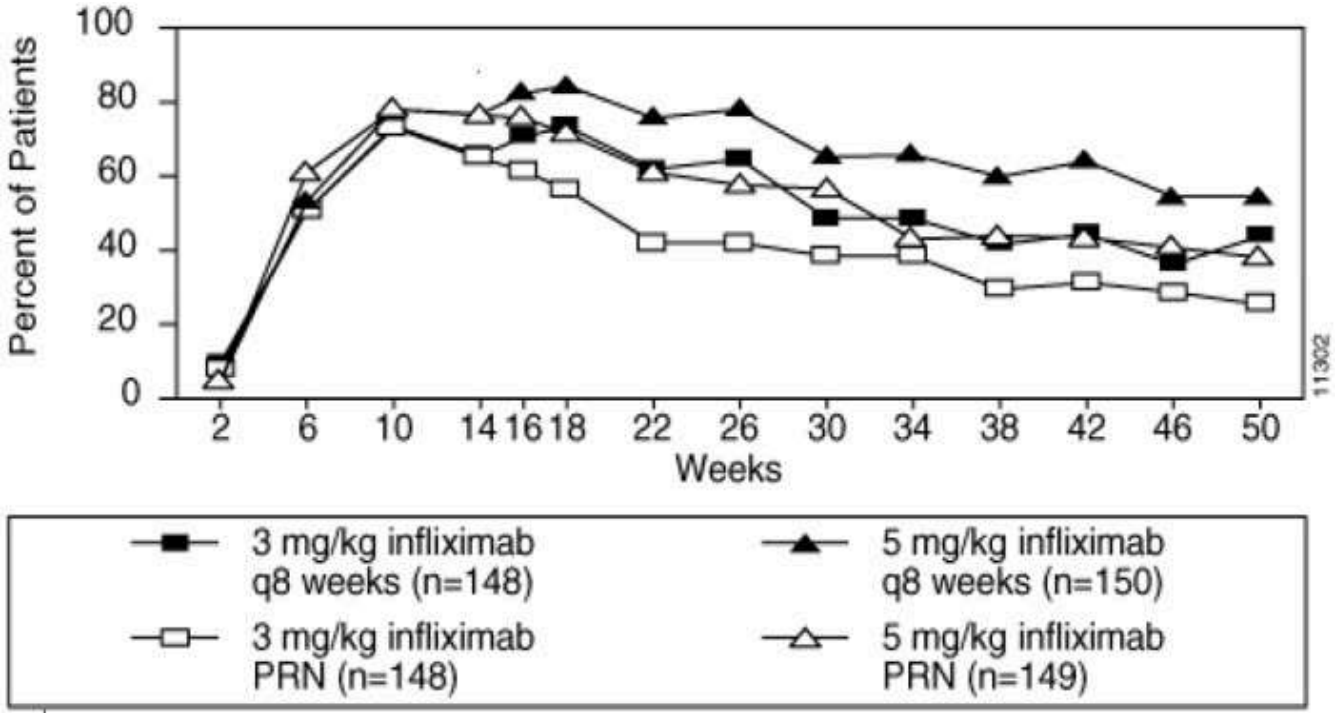

Figure 4 Proportion of Adult Ps Patients Who Achieved ≥75% Improvement in PASI from Baseline through Week 50 (patients randomized at Week 14)

Efficacy and safety of infliximab treatment beyond 50 weeks have not been evaluated in patients with Ps.

15 REFERENCES

1. Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: A prospective multicenter study. *Gastroenterology*. 2007;133:423–432.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

INFLECTRA (infliximab-dyyb) for injection is supplied as one single-dose vial individually packaged in a carton (NDC 0069-0809-01 100 mg vial).

Each single-dose vial contains 100 mg of infliximab-dyyb as a sterile, preservative-free, white lyophilized powder for reconstitution and dilution (more than one vial may be needed for a full dose) *[see Dosage and Administration (2.11)]*.

Storage and Handling

Store unopened INFLECTRA® vials in a refrigerator at 2°C to 8°C (36°F to 46°F).

If needed, unopened INFLECTRA vials may be stored at room temperature up to a maximum of 30°C (86°F) for a single period up to 6 months but not exceeding the original expiration date. The new expiration date must be written in the space provided on the carton. Once removed from the refrigerator, INFLECTRA cannot be returned to the refrigerator.

Not made with natural rubber latex.

For storage condition of the reconstituted and diluted product for administration, *see Dosage and Administration (2.11)*.

17 PATIENT COUNSELING INFORMATION

Advise the patient or their caregiver to read the FDA-Approved Patient Labeling (Medication Guide).

Patients or their caregivers should be advised of the potential benefits and risks of INFLECTRA. Healthcare providers should instruct their patients or their caregivers to read the Medication Guide before starting INFLECTRA therapy and to reread it each time they receive an infusion.

Infections

Inform patients that INFLECTRA increases the risk for developing serious infections. Instruct patients of the importance of contacting their healthcare provider if they develop any symptoms of an infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections *[see Warnings and Precautions (5.1, 5.3)]*.

Malignancies

Malignancies have been reported among children, adolescents and young adults who received treatment with TNF blockers. Patients should be counseled about the risk of lymphoma and other malignancies while receiving INFLECTRA *[see Warnings and Precautions (5.2)]*.

Hepatotoxicity

Instruct patients to seek medical attention if they develop signs or symptoms of hepatotoxicity (e.g., jaundice) *[see Warnings and Precautions (5.4)]*.

Heart Failure

Instruct patients to seek medical attention and consult their prescriber if they develop signs or symptoms of heart failure *[see Contraindications (4) and Warnings and Precautions (5.5)]*.

Hematologic Reactions

Instruct patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever) while on INFLECTRA *[see Warnings and Precautions (5.6)]*.

Hypersensitivity

Advise patients to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions *[see Warnings and Precautions (5.7)]*.

Cardiovascular and Cerebrovascular Reactions During and After Infusion

Advise patients to seek immediate medical attention if they develop any new or worsening symptoms of cardiovascular and cerebrovascular reactions which have been reported during and within 24 hours of initiation of INFLECTRA infusion *[see Warnings and Precautions (5.8)]*.

Neurologic Reactions

Advise patients to seek medical attention if they develop signs or symptoms of neurologic reactions *[see Warnings and Precautions (5.9)]*.

Live Vaccines/Therapeutic Infectious Agents

Instruct INFLECTRA-treated patients to avoid receiving live vaccines or therapeutic infectious agents *[see Warnings and Precautions (5.13)]*.

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MEDICATION GUIDE
INFLECTRA® (In-flec-tra)
(infliximab-dyyb)
for injection, for intravenous use

Read the Medication Guide that comes with INFLECTRA before you receive the first treatment, and before each time you get a treatment of INFLECTRA. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment.

What is the most important information I should know about INFLECTRA?

INFLECTRA may cause serious side effects, including:

1. Risk of infection

INFLECTRA is a medicine that affects your immune system. INFLECTRA can lower the ability of your immune system to fight infections. Serious infections have happened in patients receiving INFLECTRA. These infections include tuberculosis (TB) and infections caused by viruses, fungi, or bacteria that have spread throughout the body. Some patients have died from these infections.

- Your doctor should test you for TB before starting INFLECTRA.
- Your doctor should monitor you closely for signs and symptoms of TB during treatment with INFLECTRA.

Before starting INFLECTRA, tell your doctor if you:

- think you have an infection. You should not start receiving INFLECTRA if you have any kind of infection.
- are being treated for an infection.
- have signs of an infection, such as a fever, cough, flu-like symptoms.
- have any open cuts or sores on your body.
- get a lot of infections or have infections that keep coming back.
- have diabetes or an immune system problem. People with these conditions have a higher chance for infections.
- have TB, or have been in close contact with someone with TB.
- live or have lived in certain parts of the country (such as the Ohio and Mississippi River valleys) where there is an increased risk for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, or blastomycosis). These infections may develop or become more severe if you receive INFLECTRA. If you do not know if you have lived in an area where histoplasmosis, coccidioidomycosis, or blastomycosis is common, ask your doctor.
- have or have had hepatitis B.
- use the medicines KINERET (anakinra), ORENCIA (abatacept), ACTEMRA (tocilizumab), or other medicines called biologics used to treat the same conditions as INFLECTRA.

After starting INFLECTRA, if you have an infection, any sign of an infection including a fever, cough, flu-like symptoms, or have open cuts or sores on your body, call your doctor right away. INFLECTRA can make you more likely to get infections or make any infection that you have worse.

2. Risk of Cancer

- There have been cases of unusual cancers in children and teenage patients using tumor necrosis factor (TNF) blocker medicines, such as INFLECTRA.
- For children and adults receiving TNF blocker medicines, including INFLECTRA, the chances of getting lymphoma or other cancers may increase.
- Some people receiving TNF blockers, including INFLECTRA, developed a rare type of cancer called hepatosplenic T-cell lymphoma. This type of cancer often results in death. Most of these people were male teenagers or young men. Also, most

people were being treated for Crohn's disease or ulcerative colitis with a TNF blocker and another medicine called azathioprine or 6-mercaptopurine.
- People who have been treated for rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis for a long time may be more likely to develop lymphoma. This is especially true for people with very active disease.
- Some people treated with infliximab products, such as INFLECTRA, have developed certain kinds of skin cancer. If any changes in the appearance of your skin or growths on your skin occur during or after your treatment with INFLECTRA, tell your doctor.
- Patients with Chronic Obstructive Pulmonary Disease (COPD), a specific type of lung disease, may have an increased risk for getting cancer while being treated with INFLECTRA.
- Some women being treated for rheumatoid arthritis with infliximab products have developed cervical cancer. For women receiving INFLECTRA, including those over 60 years of age, your doctor may recommend that you continue to be regularly screened for cervical cancer.
- Tell your doctor if you have ever had any type of cancer. Discuss with your doctor any need to adjust medicines you may be taking.

See the section "**What are the possible side effects of INFLECTRA?**" below for more information.

What is INFLECTRA?

INFLECTRA is a prescription medicine that is approved for patients with:

- Rheumatoid Arthritis - adults with moderately to severely active rheumatoid arthritis, along with the medicine methotrexate.
- Crohn's Disease - children 6 years and older and adults with Crohn's disease who have not responded well to other medicines.
- Ankylosing Spondylitis in adults
- Psoriatic Arthritis in adults
- Plaque Psoriasis - adult patients with plaque psoriasis that is chronic (does not go away) severe, extensive, and/or disabling.
- Ulcerative Colitis – children 6 years and older and adults with moderately to severely active ulcerative colitis who have not responded well to other medicines.

INFLECTRA blocks the action of a protein in your body called tumor necrosis factor-alpha (TNF-alpha). TNF-alpha is made by your body's immune system. People with certain diseases have too much TNF-alpha that can cause the immune system to attack normal healthy parts of the body. INFLECTRA can block the damage caused by too much TNF-alpha**.**

It is not known if INFLECTRA is safe and effective in children under 6 years of age.

Who should not receive INFLECTRA?

You should not receive INFLECTRA if you have:

- heart failure, unless your doctor has examined you and decided that you are able to receive INFLECTRA. Talk to your doctor about your heart failure.
- had an allergic reaction to infliximab products or any of the ingredients in INFLECTRA. See the end of this Medication Guide for a complete list of ingredients in INFLECTRA.

What should I tell my doctor before starting treatment with INFLECTRA?

Your doctor will assess your health before each treatment.

Tell your doctor about all of your medical conditions, including if you:

- have an infection (see "**What is the most important information I should know about INFLECTRA?**").
- have other liver problems including liver failure.
- have heart failure or other heart conditions. If you have heart failure, it may get worse while you receive INFLECTRA.
- have or have had any type of cancer.
- have had phototherapy (treatment with ultraviolet light or sunlight along with a medicine to make your skin sensitive to light) for psoriasis. You may have a higher chance of getting skin cancer while receiving INFLECTRA.
- have COPD (Chronic Obstructive Pulmonary Disease), a specific type of lung disease. Patients with COPD may have an increased risk of getting cancer while receiving INFLECTRA.
- have or have had a condition that affects your nervous system such as:
    - multiple sclerosis, or Guillain-Barré syndrome, or
    - if you experience any numbness or tingling, or
    -

if you have had a seizure.

- have recently received or are scheduled to receive a vaccine. **Adults and children receiving INFLECTRA should not receive live vaccines (for example, the Bacille Calmette-Guérin [BCG] vaccine) or treatment with a weakened bacteria** (such as BCG for bladder cancer). Adults and children should have all of their vaccines brought up to date before starting treatment with INFLECTRA.
- are pregnant or plan to become pregnant, are breastfeeding or plan to breastfeed. You and your doctor should decide if you should receive INFLECTRA while you are pregnant or breastfeeding.

If you have a baby and you were receiving INFLECTRA during your pregnancy, it is important to tell your baby's doctor and other healthcare professionals about your INFLECTRA use so they can decide when your baby should receive any vaccine. Certain vaccinations can cause infections.
If you received INFLECTRA while you were pregnant, your baby may be at higher risk for getting an infection. If your baby receives a live vaccine within 6 months after birth, your baby may develop infections with serious complications that can lead to death. This includes live vaccines such as the BCG, rotavirus, or any other live vaccines. For other types of vaccines, talk with your doctor.

How should I receive INFLECTRA?

- You will be given INFLECTRA through a needle placed in a vein (IV or intravenous infusion) in your arm.
- Your doctor may decide to give you medicine before starting the INFLECTRA infusion to prevent or lessen side effects.
- Only a healthcare professional should prepare the medicine and administer it to you.
- INFLECTRA will be given to you over a period of about 2 hours.
- If you have side effects from INFLECTRA, the infusion may need to be adjusted or stopped. In addition, your healthcare professional may decide to treat your symptoms.
- A healthcare professional will monitor you during the INFLECTRA infusion and for a period of time afterward for side effects. Your doctor may do certain tests while you are receiving INFLECTRA to monitor you for side effects and to see how well you respond to the treatment.
- Your doctor will determine the right dose of INFLECTRA for you and how often you should receive it. Make sure to discuss with your doctor when you will receive infusions and to come in for all your infusions and follow-up appointments.

What should I avoid while receiving INFLECTRA?
Do not take INFLECTRA together with medicines such as KINERET (anakinra), ORENCIA (abatacept), ACTEMRA (tocilizumab), or other medicines called biologics that are used to treat the same conditions as INFLECTRA.
Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. These include any other medicines to treat Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis or psoriasis.
Know the medicines you take. Keep a list of your medicines and show them to your doctor and pharmacist when you get a new medicine.

What are the possible side effects of INFLECTRA?
INFLECTRA can cause serious side effects, including:
See "**What is the most important information I should know about INFLECTRA?**".
Serious Infections

- Some patients, especially those 65 years and older have had serious infections while receiving infliximab products, such as INFLECTRA. These serious infections include TB and infections caused by viruses, fungi, or bacteria that have spread throughout the body or cause infections in certain areas (such as skin). Some patients die from these infections. If you get an infection while receiving treatment with INFLECTRA your doctor will treat your infection and may need to stop your INFLECTRA treatment.
- Tell your doctor right away if you have any of the following signs of an infection while receiving or after receiving INFLECTRA:

  - a fever
  - feel very tired
  - have a cough
  - have flu-like symptoms
  - warm, red, or painful skin

-

Your doctor will examine you for TB and perform a test to see if you have TB. If your doctor feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with INFLECTRA and during treatment with INFLECTRA.

- Even if your TB test is negative, your doctor should carefully monitor you for TB infections while you are receiving INFLECTRA. Patients who had a **negative** TB skin test before receiving infliximab products have developed active TB.
- If you are a chronic carrier of the hepatitis B virus, the virus can become active while you are being treated with INFLECTRA. In some cases, patients have died as a result of hepatitis B virus being reactivated. Your doctor should do a blood test for hepatitis B virus before you start treatment with INFLECTRA and occasionally while you are being treated. Tell your doctor if you have any of the following symptoms:

  - feel unwell
  - poor appetite
  - tiredness (fatigue)
  - fever, skin rash, or joint pain

Heart Failure
If you have a heart problem called congestive heart failure, your doctor should check you closely while you are receiving INFLECTRA. Your congestive heart failure may get worse while you are receiving INFLECTRA. Be sure to tell your doctor of any new or worse symptoms including:

- shortness of breath
- swelling of ankles or feet
- sudden weight gain

Treatment with INFLECTRA may need to be stopped if you get new or worse congestive heart failure.

Other Heart Problems
Some patients have experienced a heart attack (some of which led to death), low blood flow to the heart, or abnormal heart rhythm within 24 hours of beginning their infusion of infliximab products. Symptoms may include chest discomfort or pain, arm pain, stomach pain, shortness of breath, anxiety, lightheadedness, dizziness, fainting, sweating, nausea, vomiting, fluttering or pounding in your chest, and/or a fast or a slow heartbeat. Tell your doctor right away if you have any of these symptoms.

Liver Injury
Some patients receiving infliximab products have developed serious liver problems. Tell your doctor if you have:

- jaundice (skin and eyes turning yellow)
- dark brown-colored urine
- pain on the right side of your stomach area (right-sided abdominal pain)
- fever
- extreme tiredness (severe fatigue)

Blood Problems
In some patients receiving infliximab products, the body may not make enough of the blood cells that help fight infections or help stop bleeding. Tell your doctor if you:

- have a fever that does not go away
- bruise or bleed very easily
- look very pale

Nervous System Disorders
Some patients receiving infliximab products have developed problems with their nervous system. Tell your doctor if you have:

- changes in your vision
- numbness or tingling in any part of your body
- seizures
- weakness in your arms or legs

Some patients have experienced a stroke within approximately 24 hours of their infusion with infliximab products. Tell your doctor right away if you have symptoms of a stroke which may include: numbness or weakness of the face, arm or leg, especially on one side of the body; sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes, sudden trouble walking, dizziness, loss of balance or coordination or a sudden, severe headache.

Allergic Reactions
Some patients have had allergic reactions to infliximab products. Some of these reactions were severe. These reactions can happen while you are getting your INFLECTRA treatment or shortly afterward. Your doctor may need to stop or pause your treatment with INFLECTRA and may give you medicines to treat the allergic reaction. Signs of an allergic reaction can include:

- hives (red, raised, itchy patches of skin)
- difficulty breathing
- chest pain
- high or low blood pressure
- fever
- chills

Some patients treated with infliximab products have had delayed allergic reactions. The delayed reactions occurred within 3 to 12 days after receiving treatment with infliximab products. Tell your doctor right away if you have any of these signs of delayed allergic reaction to INFLECTRA:

- fever
- rash
- headache
- sore throat
- muscle or joint pain
- swelling of the face and hands
- difficulty swallowing

Lupus-like Syndrome
Some patients have developed symptoms that are like the symptoms of Lupus. If you develop any of the following symptoms, your doctor may decide to stop your treatment with INFLECTRA.

- chest discomfort or pain that does not go away
- shortness of breath
- joint pain
- rash on the cheeks or arms that gets worse in the sun

Psoriasis
Some people receiving infliximab products had new psoriasis or worsening of psoriasis they already had. Tell your doctor if you develop red scaly patches or raised bumps on the skin that are filled with pus. Your doctor may decide to stop your treatment with INFLECTRA.
The most common side effects of infliximab products include:

- respiratory infections, such as sinus infections and sore throat
- headache
- coughing
- stomach pain

Infusion reactions can happen up to 2 hours after your infusion of INFLECTRA. Symptoms of infusion reactions may include:

- fever
- chills
- chest pain
- low blood pressure or high blood pressure
- shortness of breath
- rash
- itching

Children with Crohn's disease showed some differences in side effects of treatment compared with adults with Crohn's disease. The side effects that happened more in children were: anemia (low red blood cells), leukopenia (low white blood cells), flushing (redness or blushing), viral infections, neutropenia (low neutrophils, the white blood cells that fight infection), bone fracture, bacterial infection and allergic reactions of the breathing tract. Among patients who received infliximab for ulcerative colitis in clinical studies, more children had infections as compared with adults.
Tell your doctor about any side effect that bothers you or does not go away.
These are not all of the side effects with INFLECTRA. Ask your doctor or pharmacist for more information.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about INFLECTRA
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
You can ask your doctor or pharmacist for information about INFLECTRA that is written for health professionals.
For more information go to www.pfizer.com or call 1-800-383-7504.

What are the ingredients in INFLECTRA?
The active ingredient is infliximab-dyyb.
The inactive ingredients in INFLECTRA include: dibasic sodium phosphate dihydrate, monobasic sodium phosphate monohydrate, polysorbate 80, and sucrose. No preservatives are present.
Not made with natural rubber latex.

Manufactured by: CELLTRION, Inc. 23, Academy-ro, Yeonsu-gu, Incheon, 22014,
Republic of Korea

This Medication Guide has been approved by the U.S. Food and Drug Administration

Revised: April 2023

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For more information go to www.pfizer.com or call 1-800-383-7504.

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U.S. Food and Drug Administration

Revised: April 2023

Revised: 5/2023

Pfizer Laboratories Div Pfizer Inc

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

RUXIENCE® (rituximab-pvvr) injection, for intravenous use
Initial U.S. Approval: 2019

RUXIENCE (rituximab-pvvr) is biosimilar* to RITUXAN (rituximab)

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

See full prescribing information for complete boxed warning.

- **Fatal infusion-related reactions within 24 hours of rituximab infusion; approximately 80% of fatal reactions occurred with first infusion. Monitor patients and discontinue RUXIENCE infusion for severe reactions (5.1, 6.1).**
- **Severe mucocutaneous reactions, some with fatal outcomes (5.2).**
- **Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death (5.3).**
- **Progressive multifocal leukoencephalopathy (PML) resulting in death (5.4, 6.3).**

RECENT MAJOR CHANGES

Dosage and Administration, Administration and Storage (2.8)	10/2023

INDICATIONS AND USAGE

RUXIENCE is a CD20-directed cytolytic antibody indicated for the treatment of:

- Adult patients with Non-Hodgkin's Lymphoma (NHL) (1.1).
  - 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.
- Adult patients with Chronic Lymphocytic Leukemia (CLL) (1.2).
  - Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC).
- Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies (1.3).
- Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids (1.4).

DOSAGE AND ADMINISTRATION

- Administer only as an intravenous infusion (2.1).
- Do not administer as an intravenous push or bolus (2.1).
- RUXIENCE should only be administered by a healthcare professional with appropriate medical support to manage severe infusion-related reactions that can be fatal if they occur (2.1).

- The dose for adult B-cell NHL is 375 mg/m^2 (2.2).
- The dose for CLL is 375 mg/m^2 in the first cycle and 500 mg/m^2 in Cycles 2–6, in combination with FC, administered every 28 days (2.3).
- The dose as a component of Zevalin® (ibritumomab tiuxetan) Therapeutic Regimen is 250 mg/m^2 (2.4).
- The dose for RA in combination with methotrexate is two-1,000 mg intravenous infusions separated by 2 weeks (one course) every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks. Methylprednisolone 100 mg intravenous or equivalent glucocorticoid is recommended 30 minutes prior to each infusion (2.5).
- The induction dose for adult patients with active GPA and MPA in combination with glucocorticoids is 375 mg/m^2 once weekly for 4 weeks. The follow up dose for adult patients with GPA and MPA who have achieved disease control with induction treatment, in combination with glucocorticoids is two 500 mg intravenous infusions separated by two weeks, followed by a 500 mg intravenous infusion every 6 months thereafter based on clinical evaluation (2.6).

---------- **DOSAGE FORMS AND STRENGTHS** ----------

- Injection: 100 mg/10 mL (10 mg/mL) and 500 mg/50 mL (10 mg/mL) solution in single-dose vials (3).

---------- **CONTRAINDICATIONS** ----------

None (4).

---------- **WARNINGS AND PRECAUTIONS** ----------

- Tumor lysis syndrome: Administer aggressive intravenous hydration, anti-hyperuricemic agents, monitor renal function (5.5).
- Infections: Withhold RUXIENCE and institute appropriate anti-infective therapy (5.6).
- Cardiac adverse reactions: Discontinue infusions in case of serious or life-threatening events (5.7).
- Renal toxicity: Discontinue in patients with rising serum creatinine or oliguria (5.8).
- Bowel obstruction and perforation: Consider and evaluate for abdominal pain, vomiting, or related symptoms (5.9).
- Immunizations: Live virus vaccinations prior to or during RUXIENCE treatment are not recommended (5.10).
- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception (5.11).

---------- **ADVERSE REACTIONS** ----------

Most common adverse reactions in clinical trials were:

- NHL (greater than or equal to 25%): infusion-related reactions, fever, lymphopenia, chills, infection and asthenia (6.1).
- CLL (greater than or equal to 25%): infusion-related reactions and neutropenia (6.1).
- RA (greater than or equal to 10%): upper respiratory tract infection, nasopharyngitis, urinary tract infection, and bronchitis (other important adverse reactions include infusion-related reactions, serious infections, and cardiovascular events) (6.1).
- GPA and MPA (greater than or equal to 15%): infections, nausea, diarrhea, headache, muscle spasms, anemia, peripheral edema, infusion-related reactions (6.1).

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.

---------- **DRUG INTERACTIONS** ----------

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

---------- **USE IN SPECIFIC POPULATIONS** ----------

- Lactation: Advise not to breastfeed (8.2).
- Geriatric Use: In CLL patients older than 70 years of age, exploratory analyses suggest no benefit with the addition of rituximab to FC (8.5).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

*

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 product and the reference product. Biosimilarity of RUXIENCE has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

Revised: 10/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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

Infusion-Related Reactions

Administration of rituximab products 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 *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*.

Severe Mucocutaneous Reactions

Severe, including fatal, mucocutaneous reactions can occur in patients receiving rituximab products *[see Warnings and Precautions (5.2)]*.

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 *[see Warnings and Precautions (5.3)]*.

Progressive Multifocal Leukoencephalopathy (PML)

Progressive Multifocal Leukoencephalopathy (PML), including fatal PML, can occur in patients receiving rituximab products *[see Warnings and Precautions (5.4), Adverse Reactions (6.3)]*.

1 INDICATIONS AND USAGE

1.1 Non-Hodgkin's Lymphoma (NHL)

RUXIENCE is indicated for the treatment of adult patients with:

- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent.
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy.
- Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.
- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens.

1.2 Chronic Lymphocytic Leukemia (CLL)

RUXIENCE, in combination with fludarabine and cyclophosphamide (FC), is indicated for the treatment of adult patients with previously untreated and previously treated CD20-positive CLL.

1.3 Rheumatoid Arthritis (RA)

RUXIENCE, in combination with methotrexate, is indicated for the treatment of adult patients with moderately-to severely-active rheumatoid arthritis who have had an inadequate response to one or more Tumor Necrosis Factor (TNF) antagonist therapies.

1.4 Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)

RUXIENCE, in combination with glucocorticoids, is indicated for the treatment of adult patients with Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA).

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Information

Administer only as an intravenous infusion *[see Dosage and Administration (2.8)]*. Do not administer as an intravenous push or bolus.

RUXIENCE should only be administered by a healthcare professional with appropriate medical support to manage severe infusion-related reactions that can be fatal if they occur *[see Warnings and Precautions (5.1)]*.

Premedicate before each infusion *[see Dosage and Administration (2.7)]*.

Prior to First Infusion

Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with RUXIENCE *[see Warnings and Precautions (5.3)]*. Obtain complete blood counts (CBC) including platelets prior to the first dose.

During RUXIENCE Therapy

In patients with lymphoid malignancies, during treatment with RUXIENCE monotherapy, obtain complete blood counts (CBC) with differential and platelet counts prior to each RUXIENCE course. During treatment with RUXIENCE and chemotherapy, obtain CBC with differential and platelet counts at weekly to monthly intervals and more frequently in patients who develop cytopenias *[see Adverse Reactions (6.1)]*. In patients with RA, GPA or MPA, obtain CBC with differential and platelet counts at two to four month intervals during RUXIENCE therapy. Continue to monitor for cytopenias after final dose and until resolution.

- **First Infusion**

  Standard Infusion: Initiate infusion at a rate of 50 mg/hour. In the absence of infusion toxicity, increase infusion rate by 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.
- **Subsequent Infusions**
  Standard Infusion: Initiate infusion at a rate of 100 mg/hour. In the absence of infusion toxicity, increase rate by 100 mg/hour increments at 30-minute intervals, to a maximum of 400 mg/hour.
  For Previously Untreated Follicular NHL and DLBCL Adult Patients: If patients did not experience a Grade 3 or 4 infusion-related adverse event during Cycle 1, a 90-minute infusion can be administered in Cycle 2 with a glucocorticoid-containing chemotherapy regimen.
  Initiate at a rate of 20% of the total dose given in the first 30 minutes and the remaining 80% of the total dose given over the next 60 minutes. If the 90-minute infusion is tolerated in Cycle 2, the same rate can be used when administering the remainder of the treatment regimen (through Cycle 6 or 8).
  Patients who have clinically significant cardiovascular disease or who have a circulating lymphocyte count greater than or equal to 5,000/mm^3 before Cycle 2 should not be administered the 90-minute infusion *[see Clinical Studies (14.4)]*.
- Interrupt the infusion or slow the infusion rate for infusion-related reactions *[see Boxed Warning, Warnings and Precautions (5.1)]*. Continue the infusion at one-half the previous rate upon improvement of symptoms.

2.2 Recommended Dose for Non-Hodgkin's Lymphoma (NHL)

The recommended dose is 375 mg/m^2 as an intravenous infusion according to the following schedules:

- **Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**
  Administer once weekly for 4 or 8 doses.
- **Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**
  Administer once weekly for 4 doses.
-

Previously Untreated, Follicular, CD20-Positive, B-Cell NHL
Administer on Day 1 of each cycle of chemotherapy for up to 8 doses. In patients with complete or partial response, initiate RUXIENCE maintenance eight weeks following completion of a rituximab product in combination with chemotherapy. 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**
  Following completion of 6–8 cycles of CVP chemotherapy, administer once weekly for 4 doses at 6-month intervals to a maximum of 16 doses.
- **Diffuse Large B-Cell NHL**
  Administer on Day 1 of each cycle of chemotherapy for up to 8 infusions.

2.3 Recommended Dose for Chronic Lymphocytic Leukemia (CLL)

The recommended dose is 375 mg/m^2 the day prior to the initiation of FC chemotherapy, then 500 mg/m^2 on Day 1 of Cycles 2–6 (every 28 days).

2.4 Recommended Dose as a Component of Zevalin® for Treatment of NHL

When used as part of the Zevalin therapeutic regimen, infuse 250 mg/m^2 in accordance with the Zevalin package insert. Refer to the Zevalin package insert for full prescribing information regarding the Zevalin therapeutic regimen.

2.5 Recommended Dose for Rheumatoid Arthritis (RA)

- Administer RUXIENCE as two-1,000 mg intravenous infusions separated by 2 weeks.
- Glucocorticoids administered as methylprednisolone 100 mg intravenous or its equivalent 30 minutes prior to each infusion are recommended to reduce the incidence and severity of infusion-related reactions.
- 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 methotrexate.

2.6 Recommended Dose for Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)

Induction Treatment of Adult Patients with Active GPA/MPA

- Administer RUXIENCE as a 375 mg/m^2 intravenous infusion once weekly for 4 weeks for patients with active GPA or MPA.
- Glucocorticoids administered as methylprednisolone 1,000 mg intravenously per day for 1 to 3 days followed by oral prednisone as per clinical practice. This regimen should begin within 14 days prior to or with the initiation of RUXIENCE and may continue during and after the 4 week induction course of RUXIENCE treatment.

Follow up Treatment of Adult Patients with GPA/MPA who have Achieved Disease Control with Induction Treatment

- Administer RUXIENCE as two 500 mg intravenous infusions separated by two weeks, followed by a 500 mg intravenous infusion every 6 months thereafter based on clinical evaluation.
- If induction treatment of active disease was with a rituximab product, initiate follow up treatment with RUXIENCE within 24 weeks after the last induction infusion with a rituximab product or based on clinical evaluation, but no sooner than 16 weeks after the last induction infusion with a rituximab product.
- If induction treatment of active disease was with other standard of care immunosuppressants, initiate RUXIENCE follow up treatment within the 4 week period that follows achievement of disease control.

2.7 Recommended Dose for Premedication and Prophylactic Medications

Premedicate with acetaminophen and an antihistamine before each infusion of RUXIENCE. For adult patients administered RUXIENCE according to the 90-minute infusion rate, the glucocorticoid component of their chemotherapy regimen should be administered prior to infusion *[see Clinical Studies (14.4)]*.

For RA, GPA and MPA patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion.

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

PCP prophylaxis is also recommended for patients with GPA and MPA during treatment and for at least 6 months following the last RUXIENCE infusion.

2.8 Administration and Storage

Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. RUXIENCE should be a clear to slightly opalescent, colorless to pale brownish-yellow liquid. Do not use vial if particulates or discoloration is present.

Administration

Use a sterile needle and syringe to prepare RUXIENCE. Withdraw the necessary amount of RUXIENCE and dilute to a final concentration of 1 mg/mL to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride Injection or 5% Dextrose Injection. Gently invert the bag to mix the solution. Do not mix or dilute with other drugs. Discard any unused portion left in the vial.

Storage

If not used immediately, store diluted RUXIENCE solutions as shown in the table below.

Diluted RUXIENCE Solution Storage Conditions

Diluent Used to Prepare Solution for Infusion	Diluted RUXIENCE Solution Storage Conditions
0.9% Sodium Chloride Injection, USP	Store RUXIENCE solution diluted in 0.9% Sodium Chloride Injection, USP refrigerated at 2°C to 8°C (36°F to 46°F) for up to 16 days after preparation.
5% Dextrose Injection, USP	Store RUXIENCE solution diluted in 5% Dextrose Injection, USP refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours after preparation.

No incompatibilities between RUXIENCE and polyvinylchloride bags have been observed.

3 DOSAGE FORMS AND STRENGTHS

Injection: RUXIENCE is a clear to slightly opalescent, colorless to pale brownish-yellow solution for intravenous infusion:

- 100 mg/10 mL (10 mg/mL) in a single-dose vial
- 500 mg/50 mL (10 mg/mL) in a single-dose vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion-Related Reactions

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

Premedicate patients with an antihistamine and acetaminophen prior to dosing. For RA, GPA and MPA patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion. Institute medical management (e.g., 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 pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells (greater than or equal to 25,000/mm^3) *[see Warnings and Precautions (5.7), Adverse Reactions (6.1)]*.

5.2 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 re-administration of rituximab products to patients with severe mucocutaneous reactions has not been determined.

5.3 Hepatitis B Virus (HBV) Reactivation

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

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

Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with 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 RUXIENCE 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.

5.4 Progressive Multifocal Leukoencephalopathy (PML)

JC virus infection resulting in 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.

5.5 Tumor Lysis Syndrome (TLS)

Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, sometimes fatal, can occur within 12–24 hours after the first infusion of rituximab products in patients with NHL. A high number of circulating malignant cells (greater than or equal to 25,000/mm^3) or high tumor burden, confers a greater risk of TLS.

Administer aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high risk for TLS. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated *[see Warnings and Precautions (5.8)]*.

5.6 Infections

Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of rituximab product-based therapy. Infections have been reported in some patients with prolonged hypogammaglobulinemia (defined as hypogammaglobulinemia greater than 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 *[see Adverse Reactions (6.1, 6.3)]*. RUXIENCE is not recommended for use in patients with severe, active infections.

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

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

5.9 Bowel Obstruction and Perforation

Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving rituximab 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.

5.10 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 and administer non live 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.

5.11 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. Advise females of reproductive potential to use effective contraception while receiving RUXIENCE and for 12 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.12 Concomitant Use with Other Biologic Agents and DMARDS other than Methotrexate in RA, GPA and MPA

Limited data are available on the safety of the use of biologic agents or disease modifying anti-rheumatic drugs (DMARDs) other than methotrexate in RA patients exhibiting peripheral B-cell depletion following treatment with rituximab. 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.

5.13 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 four 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 *[see Clinical Studies (14.6)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Infusion-related reactions *[see Warnings and Precautions (5.1)]*
- Severe mucocutaneous reactions *[see Warnings and Precautions (5.2)]*
- Hepatitis B reactivation with fulminant hepatitis *[see Warnings and Precautions (5.3)]*

- Progressive multifocal leukoencephalopathy *[see Warnings and Precautions (5.4)]*
- Tumor lysis syndrome *[see Warnings and Precautions (5.5)]*
- Infections *[see Warnings and Precautions (5.6)]*
- Cardiovascular adverse reactions *[see Warnings and Precautions (5.7)]*
- Renal toxicity *[see Warnings and Precautions (5.8)]*
- Bowel obstruction and perforation *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

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

B-Cell Malignancies

The data described below reflect exposure to rituximab in 3,092 patients, with exposures ranging from a single infusion up to 2 years. Rituximab was studied in both single-arm and controlled trials (n=356 and n=2,427). The population included 1,180 patients with low grade or follicular lymphoma, 927 patients with DLBCL, 676 patients with CLL, and 309 patients with another indication. Most NHL patients received rituximab as an infusion of 375 mg/m^2 per infusion, given as a single agent weekly for up to 8 doses, in combination with chemotherapy for up to 8 doses, or following chemotherapy for up to 16 doses. CLL patients received rituximab 375 mg/m^2 as an initial infusion followed by 500 mg/m^2 for up to 5 doses, in combination with fludarabine and cyclophosphamide. Seventy-one percent of CLL patients received 6 cycles and 90% received at least 3 cycles of rituximab-based therapy.

The most common adverse reactions of rituximab (incidence greater than or equal to 25%) observed in clinical trials of patients with NHL were infusion-related reactions, fever, lymphopenia, chills, infection, and asthenia.

The most common adverse reactions of rituximab (incidence greater than or equal to 25%) observed in clinical trials of patients with CLL were: infusion-related reactions and neutropenia.

Infusion-Related Reactions

In the majority of patients with NHL, infusion-related reactions consisting of fever, chills/rigors, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension occurred during the first rituximab infusion. Infusion-related reactions typically occurred within 30 to 120 minutes of beginning the first infusion and resolved with slowing or interruption of the rituximab infusion and with supportive care (diphenhydramine, acetaminophen, and intravenous saline). The incidence of infusion-related reactions was highest during the first infusion (77%) and decreased with each subsequent infusion *[see Warnings and Precautions (5.1)]*. In adult patients with previously untreated follicular NHL or previously untreated DLBCL, who did not experience a Grade 3 or 4 infusion-related reaction in Cycle 1 and received a 90-minute infusion of rituximab at Cycle 2, the incidence of Grade 3–4 infusion-related reactions on the day of, or day after the infusion was 1.1% (95% CI [0.3%, 2.8%]). For Cycles 2–8, the incidence of Grade 3–4 infusion-related reactions on the day of or day after the 90-minute infusion, was 2.8% (95% CI [1.3%, 5.0%]) *[see Warnings and Precautions (5.1), Clinical Studies (14.4)]*.

Infections

Serious infections (NCI CTCAE Grade 3 or 4), including sepsis, occurred in less than 5% of patients with NHL in the single-arm studies. The overall incidence of infections was 31% (bacterial 19%, viral 10%, unknown 6%, and fungal 1%) *[see Warnings and Precautions (5.6)]*.

In randomized, controlled studies where rituximab was administered following chemotherapy for the treatment of follicular or low-grade NHL, the rate of infection was higher among patients who received rituximab. In diffuse large B-cell lymphoma patients, viral infections occurred more frequently in those who received rituximab.

Cytopenias and Hypogammaglobulinemia

In patients with NHL receiving rituximab monotherapy, NCI-CTC Grade 3 and 4 cytopenias were reported in 48% of patients. These included lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1–588 days) and of neutropenia was 13 days (range, 2–116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following rituximab therapy occurred during the single-arm studies.

In studies of monotherapy, rituximab-induced B-cell depletion occurred in 70% to 80% of patients with NHL. Decreased IgM and IgG serum levels occurred in 14% of these patients.

In CLL trials, the frequency of prolonged neutropenia and late-onset neutropenia was higher in patients treated with rituximab in combination with fludarabine and cyclophosphamide (R-FC) compared to patients treated with FC. Prolonged neutropenia is defined as Grade 3–4 neutropenia that has not resolved between 24 and 42 days after the last dose of study treatment. Late-onset neutropenia is defined as Grade 3–4 neutropenia starting at least 42 days after the last treatment dose.

In patients with previously untreated CLL, the frequency of prolonged neutropenia was 8.5% for patients who received R-FC (n=402) and 5.8% for patients who received FC (n=398). In patients who did not have prolonged neutropenia, the frequency of late-onset neutropenia was 14.8% of 209 patients who received R-FC and 4.3% of 230 patients who received FC.

For patients with previously treated CLL, the frequency of prolonged neutropenia was 24.8% for patients who received R-FC (n=274) and 19.1% for patients who received FC (n=274). In patients who did not have prolonged neutropenia, the frequency of late-onset neutropenia was 38.7% in 160 patients who received R-FC and 13.6% of 147 patients who received FC.

Relapsed or Refractory, Low-Grade NHL

Adverse reactions presented in Table 1 occurred in 356 patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL treated in single-arm studies of rituximab administered as a single agent *[see Clinical Studies (14.1)]*. Most patients received rituximab 375 mg/m^2 weekly for 4 doses.

Table 1. Incidence of Adverse Reactions in Greater than or Equal to 5% of Patients with Relapsed or Refractory, Low-Grade or Follicular NHL, Receiving Single-agent Rituximab (N=356)[*,†]

	All Grades (%)	Grade 3 and 4 (%)
Any Adverse Reactions	99	57
Body as a Whole	86	10
Fever	53	1
Chills	33	3
Infection	31	4
Asthenia	26	1
Headache	19	1
Abdominal Pain	14	1
Pain	12	1
Back Pain	10	1
Throat Irritation	9	0
Flushing	5	0
Heme and Lymphatic System	67	48
Lymphopenia	48	40
Leukopenia	14	4
Neutropenia	14	6
Thrombocytopenia	12	2
Anemia	8	3
Skin and Appendages	44	2
Night Sweats	15	1
Rash	15	1
Pruritus	14	1
Urticaria	8	1
Respiratory System	38	4
Increased Cough	13	1
Rhinitis	12	1
Bronchospasm	8	1
Dyspnea	7	1
Sinusitis	6	0
Metabolic and Nutritional Disorders	38	3
Angioedema	11	1
Hyperglycemia	9	1
Peripheral Edema	8	0
LDH Increase	7	0
Digestive System	37	2
Nausea	23	1
Diarrhea	10	1
Vomiting	10	1

[*] Adverse reactions observed up to 12 months following rituximab.

[†] Adverse reactions graded for severity by NCI-CTC criteria.

	All Grades (%)	Grade 3 and 4 (%)
Nervous System	32	1
Dizziness	10	1
Anxiety	5	1
Musculoskeletal System	26	3
Myalgia	10	1
Arthralgia	10	1
Cardiovascular System	25	3
Hypotension	10	1
Hypertension	6	1

* Adverse reactions observed up to 12 months following rituximab.

† Adverse reactions graded for severity by NCI-CTC criteria.

In these single-arm rituximab studies, bronchiolitis obliterans occurred during and up to 6 months after rituximab infusion.

Previously Untreated, Low-Grade or Follicular, NHL

In NHL Study 4, patients in the R-CVP arm experienced a higher incidence of infusional toxicity and neutropenia compared to patients in the CVP arm. The following adverse reactions occurred more frequently (greater than or equal to 5%) in patients receiving R-CVP compared to CVP alone: rash (17% vs. 5%), cough (15% vs. 6%), flushing (14% vs. 3%), rigors (10% vs. 2%), pruritus (10% vs. 1%), neutropenia (8% vs. 3%), and chest tightness (7% vs. 1%) *[see Clinical Studies (14.2)]*.

In NHL Study 5, detailed safety data collection was limited to serious adverse reactions, Grade greater than or equal to 2 infections, and Grade greater than or equal to 3 adverse reactions. In patients receiving rituximab as single-agent maintenance therapy following rituximab plus chemotherapy, infections were reported more frequently compared to the observation arm (37% vs. 22%). Grade 3-4 adverse reactions occurring at a higher incidence (greater than or equal to 2%) in the rituximab group were infections (4% vs. 1%) and neutropenia (4% vs. less than 1%).

In NHL Study 6, the following adverse reactions were reported more frequently (greater than or equal to 5%) in patients receiving rituximab following CVP compared to patients who received no further therapy: fatigue (39% vs. 14%), anemia (35% vs. 20%), peripheral sensory neuropathy (30% vs. 18%), infections (19% vs. 9%), pulmonary toxicity (18% vs. 10%), hepato-biliary toxicity (17% vs. 7%), rash and/or pruritus (17% vs. 5%), arthralgia (12% vs. 3%), and weight gain (11% vs. 4%). Neutropenia was the only Grade 3 or 4 adverse reaction that occurred more frequently (greater than or equal to 2%) in the rituximab arm compared with those who received no further therapy (4% vs. 1%) *[see Clinical Studies (14.3)]*.

DLBCL

In NHL Studies 7 (NCT00003150) and 8, *[see Clinical Studies (14.3)]*, the following adverse reactions, regardless of severity, were reported more frequently (greater than or equal to 5%) in patients age greater than or equal to 60 years receiving R-CHOP as compared to CHOP alone: pyrexia (56% vs. 46%), lung disorder (31% vs. 24%), cardiac disorder (29% vs. 21%), and chills (13% vs. 4%). Detailed safety data collection in these studies was primarily limited to Grade 3 and 4 adverse reactions and serious adverse reactions.

In NHL Study 8, a review of cardiac toxicity determined that supraventricular arrhythmias or tachycardia accounted for most of the difference in cardiac disorders (4.5% for R-CHOP vs. 1.0% for CHOP).

The following Grade 3 or 4 adverse reactions occurred more frequently among patients in the R-CHOP arm compared with those in the CHOP arm: thrombocytopenia (9% vs. 7%) and lung disorder (6% vs. 3%). Other Grade 3 or 4 adverse reactions occurring more frequently among patients receiving R-CHOP were viral infection (NHL Study 8), neutropenia (NHL Studies 8 and 9 (NCT00064116)), and anemia (NHL Study 9).

CLL

The data below reflect exposure to rituximab in combination with fludarabine and cyclophosphamide in 676 patients with CLL in CLL Study 1 (NCT00281918) or CLL Study 2 (NCT00090051) *[see Clinical Studies (14.5)]*. The age range was 30–83 years and 71% were men. Detailed safety data collection in CLL Study 1 was limited to Grade 3 and 4 adverse reactions and serious adverse reactions.

Infusion-related adverse reactions were defined by any of the following adverse events occurring during or within 24 hours of the start of infusion: nausea, pyrexia, chills, hypotension, vomiting, and dyspnea.

In CLL Study 1, the following Grade 3 and 4 adverse reactions occurred more frequently in R-FC-treated patients compared to FC-treated patients: infusion-related reactions (9% in R-FC arm), neutropenia (30% vs. 19%), febrile neutropenia (9% vs. 6%), leukopenia (23% vs. 12%), and pancytopenia (3% vs. 1%).

In CLL Study 2, the following Grade 3 or 4 adverse reactions occurred more frequently in R-FC-treated patients compared to FC-treated patients: infusion-related reactions (7% in R-FC arm), neutropenia (49% vs. 44%), febrile neutropenia (15% vs. 12%), thrombocytopenia (11% vs. 9%), hypotension (2% vs. 0%), and hepatitis B (2% vs. less than 1%). Fifty-nine percent of R-FC-treated patients experienced an infusion-related reaction of any severity.

Rheumatoid Arthritis

The data presented below reflect the experience in 2,578 RA patients treated with rituximab in controlled and long-term studies[1] 1 with a total exposure of 5,014 patient years.

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 placebo-controlled studies, patients received 2 × 500 mg or 2 × 1,000 mg intravenous infusions of rituximab or placebo, in combination with methotrexate, during a 24-week period. From these studies, 938 patients treated with rituximab (2 × 1,000 mg) or placebo have been pooled (see Table 2). Adverse reactions reported in greater than or equal to 5% of patients were hypertension, nausea, upper respiratory tract infection, arthralgia, pyrexia and pruritus (see Table 2). The rates and types of adverse reactions in patients who received rituximab 2 × 500 mg were similar to those observed in patients who received rituximab 2 × 1,000 mg.

Table 2[*]Incidence of All Adverse Reactions[†] Occurring in Greater than or Equal to 2% and at Least 1% Greater than Placebo Among Rheumatoid Arthritis Patients in Clinical Studies Up to Week 24 (Pooled)

Adverse Reaction	Placebo + MTX N=398 n (%)	Rituximab + MTX N=540 n (%)
Hypertension	21 (5)	43 (8)
Nausea	19 (5)	41 (8)
Upper Respiratory Tract Infection	23 (6)	37 (7)
Arthralgia	14 (4)	31 (6)
Pyrexia	8 (2)	27 (5)
Pruritus	5 (1)	26 (5)
Chills	9 (2)	16 (3)
Dyspepsia	3 (<1)	16 (3)
Rhinitis	6 (2)	14 (3)
Paresthesia	3 (<1)	12 (2)
Urticaria	3 (<1)	12 (2)
Abdominal Pain Upper	4 (1)	11 (2)
Throat Irritation	0 (0)	11 (2)
Anxiety	5 (1)	9 (2)
Migraine	2 (<1)	9 (2)
Asthenia	1 (<1)	9 (2)

[*] These data are based on 938 patients treated in Phase 2 and 3 studies of rituximab (2 × 1,000 mg) or placebo administered in combination with methotrexate.

[†] Coded using MedDRA.

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[1] [1] Pooled studies: NCT00074438, NCT00422383, NCT00468546, NCT00299130, NCT00282308, NCT00266227, NCT02693210, NCT02093026 and NCT02097745.

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 less than 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. The proportion of patients experiencing acute infusion-related reactions decreased with subsequent courses of rituximab. The administration of intravenous glucocorticoids prior to

rituximab infusions reduced the incidence and severity of such reactions, however, there was no clear benefit from the administration of oral glucocorticoids for the prevention of acute infusion-related reactions. Patients in clinical studies also received antihistamines and acetaminophen prior to rituximab infusions.

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 2,578 RA patients, the rate of serious infections was 4.31 per 100 patient years. The most common serious infections (greater than or equal to 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. Thirteen serious infections were observed in 186.1 patient years (6.99 per 100 patient years) prior to exposure and 10 were observed in 182.3 patient years (5.49 per 100 patient years) after exposure.

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 2,578 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 three 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.

Hypophosphatemia and Hyperuricemia

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

In the experience with rituximab in RA patients, newly-occurring hypophosphatemia was observed in 21% (528/2570) of patients and newly-occurring hyperuricemia was observed in 2% (56/2570) of patients. The majority of the observed hypophosphatemia occurred at the time of the infusions and was transient.

Retreatment in Patients with RA

In the experience with rituximab in RA patients, 2,578 patients have been exposed to rituximab and have received up to 10 courses of rituximab in RA clinical trials, with 1,890, 1,043, and 425 patients having received at least two, three, and four 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 *[see Clinical Studies (14.6), Dosage and Administration (2.5)]*.

<u>Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)</u>

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

The data presented below from GPA/MPA Study 1 (NCT00104299) reflect the experience in 197 adult patients with active GPA and MPA treated with rituximab or cyclophosphamide in a single controlled study, which was conducted in two phases: a 6 month randomized, double-blind, double-dummy, active-controlled remission induction phase and an additional 12 month remission maintenance phase *[see Clinical Studies (14.7)]*. In the 6-month remission induction phase, 197 patients with GPA and MPA were randomized to either rituximab 375 mg/m^2 once weekly for 4 weeks plus glucocorticoids, or oral cyclophosphamide 2 mg/kg daily (adjusted for renal function, white blood cell count, and other factors) plus glucocorticoids to induce remission. Once remission was achieved or at the end of the 6 month remission induction period, the cyclophosphamide group received azathioprine to maintain remission. The rituximab group did not receive additional therapy to maintain remission. The primary analysis was at the end of the 6 month remission induction period and the safety results for this period are described below.

Adverse reactions presented below in Table 3 were adverse events which occurred at a rate of greater than or equal to 10% in the rituximab group. This table reflects experience in 99 GPA and MPA patients treated with rituximab, with a total of 47.6 patient years of observation and 98 GPA and MPA patients treated with cyclophosphamide, with a total of 47.0 patient years of observation. Infection was the most common category of adverse events reported (47–62%) and is discussed below.

Table 3 Incidence of All Adverse Reactions Occurring in Greater than or Equal to 10% of Rituximab-treated Patients with active GPA and MPA in the GPA/MPA Study 1 Up to Month 6*

Adverse Reaction	Rituximab N=99 n (%)	Cyclophosphamide N=98 n (%)
Nausea	18 (18%)	20 (20%)
Diarrhea	17 (17%)	12 (12%)
Headache	17 (17%)	19 (19%)
Muscle Spasms	17 (17%)	15 (15%)
Anemia	16 (16%)	20 (20%)
Peripheral Edema	16 (16%)	6 (6%)
Insomnia	14 (14%)	12 (12%)
Arthralgia	13 (13%)	9 (9%)
Cough	13 (13%)	11 (11%)
Fatigue	13 (13%)	21 (21%)
Increased ALT	13 (13%)	15 (15%)
Hypertension	12 (12%)	5 (5%)
Epistaxis	11 (11%)	6 (6%)
Dyspnea	10 (10%)	11 (11%)
Leukopenia	10 (10%)	26 (27%)
Rash	10 (10%)	17 (17%)

* The study design allowed for crossover or treatment by best medical judgment, and 13 patients in each treatment group received a second therapy during the 6 month study period.

Infusion-Related Reactions

Infusion-related reactions in GPA/MPA Study 1 were defined as any adverse event occurring within 24 hours of an infusion and considered to be infusion-related by investigators. Among the 99 patients treated with rituximab, 12% experienced at least one infusion-related reaction, compared with 11% of the 98 patients in the cyclophosphamide group. Infusion-related reactions included cytokine release syndrome, flushing, throat irritation, and tremor. In the rituximab group, the proportion of patients experiencing an infusion-related reaction was 12%, 5%, 4%, and 1% following the first, second, third, and fourth infusions, respectively. Patients were pre-medicated 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% (61/99) of patients in the rituximab group experienced an infection of any type compared to 47% (46/98) patients in the cyclophosphamide group 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% in the rituximab-treated patients and 10% in the cyclophosphamide treated patients, 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.

Follow up Treatment of Adult Patients with GPA/MPA who have Achieved Disease Control with Induction Treatment (GPA/MPA Study 2)

In GPA/MPA Study 2 (NCT00748644), an open-label, controlled, clinical study *[see Clinical Studies (14.7)]*, evaluating the efficacy and safety of non-U.S.-licensed rituximab versus azathioprine as follow up treatment in adult patients with GPA, MPA or renal-limited ANCA-associated vasculitis who had achieved disease control after induction treatment with cyclophosphamide, a total of 57 GPA and MPA patients in disease remission received follow up treatment with two 500 mg intravenous infusions of non-U.S.-

licensed rituximab, separated by two weeks on Day 1 and Day 15, followed by a 500 mg intravenous infusion every 6 months for 18 months.

The safety profile was consistent with the safety profile for rituximab in RA, GPA, and MPA.

Infusion-Related Reactions

In GPA/MPA Study 2, 7/57 (12%) patients in the non-U.S.-licensed 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 (less than 4%). One patient had two serious IRRs, two 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-U.S.-licensed 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.

Long-term, Observational Study with Rituximab in Patients with GPA/MPA (GPA/MPA Study 3)

In a long-term observational safety study (NCT01613599), 97 patients with GPA or MPA received treatment with rituximab (mean of 8 infusions [range 1–28]) for up to 4 years, according to physician standard practice and discretion. Majority of patients received doses ranging from 500 mg to 1,000 mg, approximately every 6 months. The safety profile was consistent with the safety profile for rituximab in RA, GPA and MPA.

6.2 Immunogenicity

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

Using an ELISA assay, anti-rituximab antibody was detected in 4 of 356 (1.1%) patients with low-grade or follicular NHL receiving single-agent rituximab. Three of the four patients had an objective clinical response.

A total of 273/2578 (11%) patients with RA tested positive for anti-rituximab antibodies at any time after receiving rituximab. Anti-rituximab 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 anti-rituximab antibody positive and negative patients, and most reactions were mild to moderate. Four anti-rituximab antibody positive patients had serious infusion-related reactions, and the temporal relationship between anti-rituximab antibody positivity and infusion-related reaction was variable.

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

6.3 Postmarketing Experience

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

- Hematologic: prolonged pancytopenia, marrow hypoplasia, Grade 3–4 prolonged or late-onset neutropenia, hyperviscosity syndrome in Waldenstrom's macroglobulinemia, prolonged hypogammaglobulinemia *[see Warnings and Precautions (5.6)]*.
- Cardiac: fatal cardiac failure.
- Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like syndrome, serum sickness, polyarticular arthritis, and vasculitis with rash.
- Infection: viral infections, including progressive multifocal leukoencephalopathy (PML), increase in fatal infections in HIV-associated lymphoma, and a reported increased incidence of Grade 3 and 4 infections *[see Warnings and Precautions (5.6)]*.
- Neoplasia: disease progression of Kaposi's sarcoma.
- Skin: severe mucocutaneous reactions, pyoderma gangrenosum (including genital presentation).
- Gastrointestinal: bowel obstruction and perforation.
- Pulmonary: fatal bronchiolitis obliterans and fatal interstitial lung disease.
- Nervous system: Posterior Reversible Encephalopathy Syndrome (PRES)/Reversible Posterior Leukoencephalopathy Syndrome (RPLS).

7 DRUG INTERACTIONS

Formal drug interaction studies have not been performed with rituximab products. In patients with CLL, rituximab did not alter systemic exposure to fludarabine or cyclophosphamide. In clinical trials of patients with RA, concomitant administration of methotrexate or cyclophosphamide did not alter the pharmacokinetics of rituximab.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on human data, rituximab products can cause adverse developmental outcomes including B-cell lymphocytopenia in infants exposed in-utero *(see Clinical Considerations)*. In animal reproduction studies, intravenous administration of rituximab to pregnant cynomolgus monkeys during the period of organogenesis caused lymphoid B-cell depletion in the newborn offspring at doses resulting in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Advise pregnant women of the risk to a fetus.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated populations is unknown. The estimated background risk in the U.S. general population of major birth defects is 2%–4% and of miscarriage is 15%–20% of clinically recognized pregnancies.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Human Data

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

Animal Data

An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received rituximab via the intravenous route during early gestation (organogenesis period; post coitum Days 20 through 50). Rituximab was administered as loading doses on post coitum (PC) Days 20, 21, and 22, at 15, 37.5, or 75 mg/kg/day, and then weekly on PC Days 29, 36, 43, and 50, at 20, 50, or 100 mg/kg/week. The 100 mg/kg/week dose resulted in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Rituximab crosses the monkey placenta. Exposed offspring did not exhibit any teratogenic effects but did have decreased lymphoid tissue B cells.

A subsequent pre- and postnatal reproductive toxicity study in cynomolgus monkeys was completed to assess developmental effects including the recovery of B cells and immune function in infants exposed to rituximab in-utero. Animals were treated with a loading dose of 0, 15, or 75 mg/kg every day for 3 days, followed by weekly dosing with 0, 20, or 100 mg/kg dose. Subsets of pregnant females were treated from PC Day 20 through postpartum Day 78, PC Day 76 through PC Day 134, and from PC Day 132 through delivery and postpartum Day 28. Regardless of the timing of treatment, decreased B cells and immunosuppression were noted in the offspring of rituximab-treated pregnant animals. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months postpartum.

8.2 Lactation

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

8.3 Females and Males of Reproductive Potential

Rituximab products can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

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

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with RUXIENCE and for 12 months after the last dose.

8.4 Pediatric Use

The safety and effectiveness of RUXIENCE have not been established in pediatric patients with NHL, CLL or RA.

Rituximab was not studied in pediatric patients with polyarticular juvenile idiopathic arthritis (PJIA) due to concerns regarding the potential for prolonged immunosuppression as a result of B-cell depletion in the developing juvenile immune system.

8.5 Geriatric Use

Diffuse Large B-Cell NHL

Among patients with DLBCL evaluated in three randomized, active-controlled trials, 927 patients received rituximab in combination with chemotherapy. Of these, 396 (43%) were age 65 or greater and 123 (13%) were age 75 or greater. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse reactions, mostly supraventricular arrhythmias, occurred more frequently among elderly patients. Serious pulmonary adverse reactions were also more common among the elderly, including pneumonia and pneumonitis.

Low-Grade or Follicular Non-Hodgkin's Lymphoma

Patients with previously untreated follicular NHL evaluated in NHL Study 5 were randomized to rituximab as single-agent maintenance therapy (n=505) or observation (n=513) after achieving a response to rituximab in combination with chemotherapy. Of these, 123 (24%) patients in the rituximab arm were age 65 or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other clinical studies of rituximab in low-grade or follicular, CD20-positive, B-cell NHL did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects.

Chronic Lymphocytic Leukemia

Among patients with CLL evaluated in two randomized active-controlled trials, 243 of 676 rituximab-treated patients (36%) were 65 years of age or older; of these, 100 rituximab-treated patients (15%) were 70 years of age or older.

In exploratory analyses defined by age, there was no observed benefit from the addition of rituximab to fludarabine and cyclophosphamide among patients 70 years of age or older in CLL Study 1 or in CLL Study 2; there was also no observed benefit from the addition of rituximab to fludarabine and cyclophosphamide among patients 65 years of age or older in CLL Study 2 *[see Clinical Studies (14.5)]*. Patients 70 years or older received lower dose intensity of fludarabine and cyclophosphamide compared to younger patients, regardless of the addition of rituximab. In CLL Study 1, the dose intensity of rituximab was similar in older and younger patients, however in CLL Study 2 older patients received a lower dose intensity of rituximab.

The incidence of Grade 3 and 4 adverse reactions was higher among patients receiving R-FC who were 70 years or older compared to younger patients for neutropenia [44% vs. 31% (CLL Study 1); 56% vs. 39% (CLL Study 2)], febrile neutropenia [16% vs. 6% (NHL Study 10 (NCT00719472))], anemia [5% vs. 2% (CLL Study 1); 21% vs. 10% (CLL Study 2)], thrombocytopenia [19% vs. 8% (CLL Study 2)], pancytopenia [7% vs. 2% (CLL Study 1); 7% vs. 2% (CLL Study 2)], and infections [30% vs. 14% (CLL Study 2)].

Rheumatoid Arthritis

Among the 2,578 patients in global RA studies completed to date, 12% were 65–75 years old and 2% were 75 years old and older. The incidences of adverse reactions were similar between older and younger patients. The rates of serious adverse reactions, including serious infections, malignancies, and cardiovascular events were higher in older patients.

Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis

Of the 99 rituximab-treated GPA and MPA patients in GPA/MPA Study 1, 36 (36%) were 65 years old and over, while 8 (8%) were 75 years and over. No overall differences in efficacy were observed between patients that were 65 years old and over and younger patients. The overall incidence and rate of all serious adverse events was higher in patients 65 years old and over. The clinical study did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects.

In GPA/MPA Study 2, 30 (26%) of the enrolled patients were at least 65 years old, of which 12 patients were exposed to non-U.S.-licensed rituximab and 18 were exposed to azathioprine. The clinical study did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Rituximab-pvvr is a genetically engineered chimeric murine/human monoclonal IgG_1 kappa antibody directed against the CD20 antigen. Rituximab-pvvr has an approximate molecular weight of 145 kD.

Rituximab-pvvr is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium.

RUXIENCE (rituximab-pvvr) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale brownish-yellow solution for intravenous infusion. RUXIENCE is supplied at a concentration of 10 mg/mL in either 100 mg/10 mL or 500 mg/50 mL single-dose vials. Each mL of solution contains 10 mg rituximab-pvvr, 0.056 mg of edetate disodium dihydrate, 1.2 mg of L-histidine, 2.57 mg of L-histidine hydrochloride monohydrate, 0.2 mg of polysorbate 80, 85 mg of sucrose, and Water for Injection, USP. The pH is 5.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rituximab-pvvr is a monoclonal antibody. Rituximab products target the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab products mediate B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC). B cells are believed to play a role in the pathogenesis of rheumatoid arthritis (RA) and associated chronic synovitis. In this setting, B cells may be acting at multiple sites in the autoimmune/inflammatory process, including through production of rheumatoid factor (RF) and other autoantibodies, antigen presentation, T-cell activation, and/or proinflammatory cytokine production.

12.2 Pharmacodynamics

Non-Hodgkin's Lymphoma (NHL)

In NHL patients, administration of rituximab resulted in depletion of circulating and tissue-based B cells. Among 166 patients in NHL Study 1 (NCT000168740), circulating CD19-positive B cells were depleted within the first three weeks with sustained depletion for up to 6 to 9 months post treatment in 83% of patients. B-cell recovery began at approximately 6 months and median B-cell levels returned to normal by 12 months following completion of treatment.

There were sustained and statistically significant reductions in both IgM and IgG serum levels observed from 5 through 11 months following rituximab administration; 14% of patients had IgM and/or IgG serum levels below the normal range.

Rheumatoid Arthritis

In RA patients, treatment with rituximab-induced depletion of peripheral B-lymphocytes, with the majority of patients demonstrating near complete depletion (CD19 counts below the lower limit of quantification, 20 cells/μL) within 2 weeks after receiving the first dose of rituximab. The majority of patients showed peripheral B-cell depletion for at least 6 months. A small proportion of patients (~4%) had prolonged peripheral B-cell depletion lasting more than 3 years after a single course of treatment.

Total serum immunoglobulin levels, IgM, IgG, and IgA were reduced at 6 months with the greatest change observed in IgM. At Week 24 of the first course of rituximab treatment, small proportions of patients experienced decreases in IgM (10%), IgG (2.8%), and IgA (0.8%) levels below the lower limit of normal (LLN). In the experience with rituximab in RA patients during repeated rituximab treatment, 23.3%, 5.5%, and 0.5% of patients experienced decreases in IgM, IgG, and IgA concentrations below LLN at any time after receiving rituximab, respectively. The clinical consequences of decreases in immunoglobulin levels in RA patients treated with rituximab are unclear.

Treatment with rituximab in patients with RA was associated with reduction of certain biologic markers of inflammation such as interleukin-6 (IL-6), C-reactive protein (CRP), serum amyloid protein (SAA), S100 A8/S100 A9 heterodimer complex (S100 A8/9), anti-citrullinated peptide (anti-CCP), and RF.

Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis

In GPA and MPA patients in GPA/MPA Study 1, peripheral blood CD19 B-cells depleted to less than 10 cells/μL following the first two infusions of rituximab, and remained at that level in most (84%) patients through Month 6. By Month 12, the majority of patients (81%) showed signs of B-cell return with counts greater than 10 cells/μL. By Month 18, most patients (87%) had counts greater than 10 cells/μL.

In GPA/MPA Study 2 where patients received non-U.S.-licensed rituximab as two 500 mg intravenous infusions separated by two weeks, followed by a 500 mg intravenous infusion at Month 6, 12, and 18, 70% (30 out of 43) of the rituximab-treated patients with CD19+ peripheral B cells evaluated post-baseline had undetectable CD19+ peripheral B cells at Month 24. At Month 24, all 37 patients with evaluable baseline CD19+ peripheral B cells and Month 24 measurements had lower CD19+ B cells relative to baseline.

12.3 Pharmacokinetics

Non-Hodgkin's Lymphoma (NHL)

Pharmacokinetics were characterized in 203 NHL patients receiving 375 mg/m^2 rituximab weekly by intravenous infusion for 4 doses. Rituximab was detectable in the serum of patients 3 to 6 months after completion of treatment.

The pharmacokinetic profile of rituximab when administered as 6 infusions of 375 mg/m^2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone.

Based on a population pharmacokinetic analysis of data from 298 NHL patients who received rituximab once weekly or once every three weeks, the estimated median terminal elimination half-life was 22 days (range, 6.1 to 52 days). Patients with higher CD19-positive cell counts or larger measurable tumor lesions at pretreatment had a higher clearance. However, dose adjustment for pretreatment CD19 count or size of tumor lesion is not necessary. Age and gender had no effect on the pharmacokinetics of rituximab.

Pharmacokinetics were characterized in 21 patients with CLL receiving rituximab according to the recommended dose and schedule. The estimated median terminal half-life of rituximab was 32 days (range, 14 to 62 days).

Rheumatoid Arthritis

Following administration of 2 doses of rituximab in patients with RA, the mean (±S.D.; % CV) concentrations after the first infusion (C_{max} first) and second infusion (C_{max} second) were 157 (±46; 29%) and 183 (±55; 30%) mcg/mL, and 318 (±86; 27%) and 381 (±98; 26%) mcg/mL for the 2 × 500 mg and 2 × 1,000 mg doses, respectively.

Based on a population pharmacokinetic analysis of data from 2,005 RA patients who received rituximab, the estimated clearance of rituximab was 0.335 L/day; volume of distribution was 3.1 L and mean terminal elimination half-life was 18.0 days (range, 5.17 to 77.5 days). Age, weight and gender had no effect on the pharmacokinetics of rituximab in RA patients.

Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis

The pharmacokinetic parameters in adult patients with GPA/MPA receiving 375 mg/m^2 intravenous rituximab or non-U.S.-licensed rituximab once weekly for four doses are summarized in Table 4.

Table 4 Population PK in Adult Patients with GPA/MPA

Parameter	Statistic	GPA/MPA Study 1
N	Number of Patients	97
Terminal Half-life (days)	Median (Range)	25 (11 to 52)
$AUC_{0–180d}$ (µg/mL*day)	Median (Range)	10302 (3653 to 21874)
Clearance (L/day)	Median (Range)	0.279 (0.113 to 0.653)
Volume of Distribution (L)	Median (Range)	3.12 (2.42 to 3.91)

The population PK analysis in adults with GPA and MPA showed that male patients and patients with higher BSA or positive anti-rituximab antibody levels have higher clearance. However, further dose adjustment based on gender or anti-drug antibody status is not necessary.

Specific Populations

The clearance and volume of distribution of rituximab increased with increasing body surface area (BSA).

No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of rituximab products.

Drug Interaction Studies

Formal drug interaction studies have not been performed with rituximab products.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

14.1 Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL

The safety and effectiveness of rituximab in relapsed, refractory CD20+ NHL were demonstrated in 3 single-arm studies enrolling 296 patients.

NHL Study 1

A multicenter, open-label, single-arm study was conducted in 166 patients with relapsed or refractory, low-grade or follicular, B-cell NHL who received 375 mg/m^2 of rituximab given as an intravenous infusion weekly for 4 doses. Patients with tumor masses greater than 10 cm or with greater than 5,000 lymphocytes/µL in the peripheral blood were excluded from the study.

Results are summarized in Table 5. The median time to onset of response was 50 days. Disease-related signs and symptoms (including B symptoms) resolved in 64% (25/39) of those patients with such symptoms at study entry.

NHL Study 2

In a multicenter, single-arm study, 37 patients with relapsed or refractory, low-grade NHL received 375 mg/m^2 of rituximab weekly for 8 doses. Results are summarized in Table 5.

NHL Study 3

In a multicenter, single-arm study, 60 patients received 375 mg/m^2 of rituximab weekly for 4 doses. All patients had relapsed or refractory, low-grade or follicular, B-cell NHL and had achieved an objective clinical response to rituximab administered 3.8–35.6 months (median 14.5 months) prior to retreatment with rituximab. Of these 60 patients, 5 received more than one additional course of rituximab. Results are summarized in Table 5.

Bulky Disease

In pooled data from studies 1 and 3, 39 patients with bulky (single lesion greater than 10 cm in diameter) and relapsed or refractory, low-grade NHL received rituximab 375 mg/m^2 weekly for 4 doses. Results are summarized in Table 5.

Table 5 Summary of Rituximab NHL Efficacy Data by Schedule and Clinical Setting

	NHL Study 1 Weekly × 4 N=166	**NHL Study 2 Weekly × 8 N=37**	**NHL Study 1 and NHL Study 3 Bulky disease, Weekly × 4 N=39***	**NHL Study 3 Retreatment, Weekly × 4 N=60**
Overall Response Rate	48%	57%	36%	38%
Complete Response Rate	6%	14%	3%	10%
Median Duration of Response†,‡,§ (Months) [Range]	11.2 [1.9 to 42.1+]	13.4 [2.5 to 36.5+]	6.9 [2.8 to 25.0+]	15.0 [3.0 to 25.1+]

* Six of these patients are included in the first column. Thus, data from 296 intent-to-treat patients are provided in this table.

† Kaplan-Meier projected with observed range.

‡ "+" indicates an ongoing response.

§ Duration of response: interval from the onset of response to disease progression.

14.2 Previously Untreated, Low-Grade or Follicular, CD20-Positive, B-Cell NHL

The safety and effectiveness of rituximab in previously untreated, low-grade or follicular, CD20+ NHL were demonstrated in 3 randomized, controlled trials enrolling 1,662 patients.

NHL Study 4

A total of 322 patients with previously untreated follicular NHL were randomized (1:1) to receive up to eight 3-week cycles of CVP chemotherapy alone (CVP) or in combination with rituximab 375 mg/m^2 on Day 1 of each cycle (R-CVP) in an open-label, multicenter study. The main outcome measure of the study was progression-free survival (PFS) defined as the time from randomization to the first of progression, relapse, or death.

Twenty-six percent of the study population was greater than 60 years of age, 99% had Stage III or IV disease, and 50% had an International Prognostic Index (IPI) score greater than or equal to 2. The results for PFS as determined by a blinded, independent assessment of progression are presented in Table 6. The point estimates may be influenced by the presence of informative censoring. The PFS results based on investigator assessment of progression were similar to those obtained by the independent review assessment.

Table 6 Efficacy Results in NHL Study 4

	Study Arm	
	R-CVP N=162	**CVP N=160**

	Study Arm	
	R-CVP N=162	**CVP N=160**
Median PFS (years)*	2.4	1.4
Hazard ratio (95% CI)†	0.44 (0.29, 0.65)	

* p <0.0001, two-sided stratified log-rank test.

† Estimates of Cox regression stratified by center.

NHL Study 5

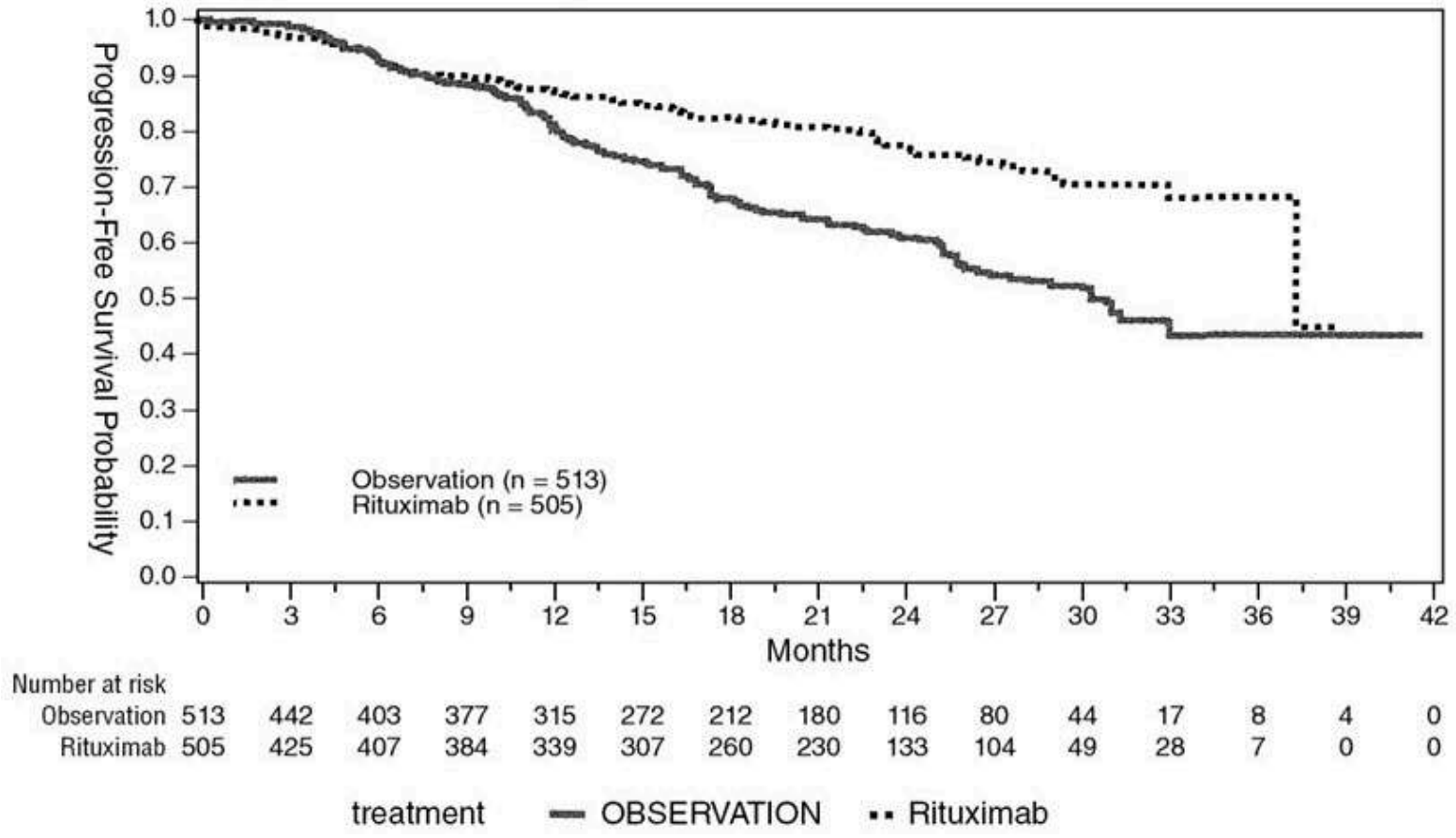
An open-label, multicenter, randomized (1:1) study was conducted in 1,018 patients with previously untreated follicular NHL who achieved a response (CR or PR) to rituximab in combination with chemotherapy. Patients were randomized to rituximab as single-agent maintenance therapy, 375 mg/m^2 every 8 weeks for up to 12 doses or to observation. Rituximab was initiated at 8 weeks following completion of chemotherapy. The main outcome measure of the study was progression-free survival (PFS), defined as the time from randomization in the maintenance/observation phase to progression, relapse, or death, as determined by independent review.

Of the randomized patients, 40% were greater than or equal to 60 years of age, 70% had Stage IV disease, 96% had ECOG performance status (PS) 0–1, and 42% had FLIPI scores of 3–5. Prior to randomization to maintenance therapy, patients had received R-CHOP (75%), R-CVP (22%), or R-FCM (3%); 71% had a complete or unconfirmed complete response and 28% had a partial response.

PFS was longer in patients randomized to rituximab as single-agent maintenance therapy (HR: 0.54, 95% CI: 0.42, 0.70). The PFS results based on investigator assessment of progression were similar to those obtained by the independent review assessment.

Figure 1

Kaplan-Meier Plot of IRC Assessed PFS in NHL Study 5



NHL Study 6

A total of 322 patients with previously untreated low-grade, B-cell NHL who did not progress after 6 or 8 cycles of CVP chemotherapy were enrolled in an open-label, multicenter, randomized trial. Patients were randomized (1:1) to receive rituximab, 375 mg/m^2 intravenous infusion, once weekly for 4 doses every 6 months for up to 16 doses or no further therapeutic intervention. The main outcome measure of the study was progression-free survival defined as the time from randomization to progression, relapse, or death. Thirty-seven percent of the study population was greater than 60 years of age, 99% had Stage III or IV disease, and 63% had an IPI score greater than or equal to 2.

There was a reduction in the risk of progression, relapse, or death (hazard ratio estimate in the range of 0.36 to 0.49) for patients randomized to rituximab as compared to those who received no additional treatment.

14.3 Diffuse Large B-Cell NHL (DLBCL)

The safety and effectiveness of rituximab were evaluated in three randomized, active-controlled, open-label, multicenter studies with a collective enrollment of 1,854 patients. Patients with previously untreated diffuse large B-cell NHL received rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens.

NHL Study 7

A total of 632 patients age greater than or equal to 60 years with DLBCL (including primary mediastinal B-cell lymphoma) were randomized in a 1:1 ratio to treatment with CHOP or R-CHOP. Patients received 6 or 8 cycles of CHOP, each cycle lasting 21 days. All patients in the R-CHOP arm received 4 doses of rituximab 375 mg/m^2 on Days –7 and –3 (prior to Cycle 1) and 48–72 hours prior to Cycles 3 and 5. Patients who received 8 cycles of CHOP also received rituximab prior to Cycle 7. The main outcome measure of the study was progression-free survival, defined as the time from randomization to the first of progression, relapse, or death. Responding patients underwent a second randomization to receive rituximab or no further therapy.

Among all enrolled patients, 62% had centrally confirmed DLBCL histology, 73% had Stage III–IV disease, 56% had IPI scores greater than or equal to 2, 86% had ECOG performance status of less than 2, 57% had elevated LDH levels, and 30% had two or more extranodal disease sites involved. Efficacy results are presented in Table 7. These results reflect a statistical approach which allows for an evaluation of rituximab administered in the induction setting that excludes any potential impact of rituximab given after the second randomization.

Analysis of results after the second randomization in NHL Study 7 demonstrates that for patients randomized to R-CHOP, additional rituximab exposure beyond induction was not associated with further improvements in progression-free survival or overall survival.

NHL Study 8

A total of 399 patients with DLBCL, age greater than or equal to 60 years, were randomized in a 1:1 ratio to receive CHOP or R-CHOP. All patients received up to eight 3-week cycles of CHOP induction; patients in the R-CHOP arm received rituximab 375 mg/m^2 on Day 1 of each cycle. The main outcome measure of the study was event-free survival, defined as the time from randomization to relapse, progression, change in therapy, or death from any cause. Among all enrolled patients, 80% had Stage III or IV disease, 60% of patients had an age-adjusted IPI greater than or equal to 2, 80% had ECOG performance status scores less than 2, 66% had elevated LDH levels, and 52% had extranodal involvement in at least two sites. Efficacy results are presented in Table 7.

NHL Study 9

A total of 823 patients with DLBCL, aged 18–60 years, were randomized in a 1:1 ratio to receive an anthracycline-containing chemotherapy regimen alone or in combination with rituximab. The main outcome measure of the study was time to treatment failure, defined as time from randomization to the earliest of progressive disease, failure to achieve a complete response, relapse, or death. Among all enrolled patients, 28% had Stage III–IV disease, 100% had IPI scores of less than or equal to 1, 99% had ECOG performance status of less than 2, 29% had elevated LDH levels, 49% had bulky disease, and 34% had extranodal involvement. Efficacy results are presented in Table 7.

Table 7 Efficacy Results in NHL Studies 7, 8, and 9

	NHL Study 7 (n=632)		NHL Study 8 (n=399)		NHL Study 9 (n=823)	
	R-CHOP	CHOP	R-CHOP	CHOP	R-Chemo	Chemo
Main outcome	**Progression-free survival (years)**		**Event-free survival (years)**		**Time to treatment failure (years)**	
Median of main outcome measure	3.1	1.6	2.9	1.1	NE*	NE*
Hazard ratio†	0.69‡		0.60‡		0.45‡	
Overall survival at 2 years§	74%	63%	69%	58%	95%	86%
Hazard ratio†	0.72‡		0.68‡		0.40‡	

* NE=Not reliably estimable.

† R-CHOP vs. CHOP.

‡ Significant at $p < 0.05$, 2-sided.

§ Kaplan-Meier estimates.

In NHL Study 8, overall survival estimates at 5 years were 58% vs. 46% for R-CHOP and CHOP, respectively.

14.4 Ninety-Minute Infusions in Previously Untreated Follicular NHL and DLBCL

In NHL Study 10, a total of 363 patients with previously untreated follicular NHL (n=113) or DLBCL (n=250) were evaluated in a prospective, open-label, multicenter, single-arm trial for the safety of 90-minute rituximab infusions. Patients with follicular NHL received rituximab 375 mg/m^2 plus CVP chemotherapy. Patients with DLBCL received rituximab 375 mg/m^2 plus CHOP chemotherapy. Patients with clinically significant cardiovascular disease were excluded from the study. Patients were eligible for a 90-minute infusion at Cycle 2 if they did not experience a Grade 3–4 infusion-related adverse event with Cycle 1 and had a circulating lymphocyte count less than or equal to 5,000/mm^3 before Cycle 2. All patients were pre-medicated with acetaminophen and an antihistamine and received the glucocorticoid component of their chemotherapy prior to rituximab infusion. The main outcome measure was the development of Grade 3–4 infusion-related reactions on the day of, or day after, the 90-minute infusion at Cycle 2 *[see Adverse Reactions (6.1)]*.

Eligible patients received their Cycle 2 rituximab infusion over 90 minutes as follows: 20% of the total dose given in the first 30 minutes and the remaining 80% of the total dose given over the next 60 minutes *[see Dosage and Administration (2.1)]*. Patients who tolerated the 90-minute rituximab infusion at Cycle 2 continued to receive subsequent rituximab infusions at the 90-minute infusion rate for the remainder of the treatment regimen (through Cycle 6 or Cycle 8).

The incidence of Grade 3–4 infusion-related reactions at Cycle 2 was 1.1% (95% CI [0.3%, 2.8%]) among all patients, 3.5% (95% CI [1.0%, 8.8%]) for those patients treated with R-CVP, and 0.0% (95% CI [0.0%, 1.5%]) for those patients treated with R-CHOP. For Cycles 2–8, the incidence of Grade 3–4 infusion-related reactions was 2.8% (95% CI [1.3%, 5.0%]). No acute fatal infusion-related reactions were observed.

14.5 Chronic Lymphocytic Leukemia (CLL)

The safety and effectiveness of rituximab were evaluated in two randomized (1:1) multicenter open-label studies comparing FC alone or in combination with rituximab for up to 6 cycles in patients with previously untreated CLL [CLL Study 1 (n=817)] or previously treated CLL [CLL Study 2 (n=552)]. Patients received fludarabine 25 mg/m^2/day and cyclophosphamide 250 mg/m^2/day on days 1, 2, and 3 of each cycle, with or without rituximab. In both studies, seventy-one percent of CLL patients received 6 cycles and 90% received at least 3 cycles of rituximab-based therapy.

In CLL Study 1, 30% of patients were 65 years or older, 31% were Binet stage C, 45% had B symptoms, more than 99% had ECOG performance status (PS) 0–1, 74% were male, and 100% were White. In CLL Study 2, 44% of patients were 65 years or older, 28% had B symptoms, 82% received a prior alkylating drug, 18% received prior fludarabine, 100% had ECOG PS 0–1, 67% were male, and 98% were White.

The main outcome measure in both studies was progression-free survival (PFS), defined as the time from randomization to progression, relapse, or death, as determined by investigators (CLL Study 1) or an independent review committee (CLL Study 2). The investigator assessed results in CLL Study 2 were supportive of those obtained by the independent review committee. Efficacy results are presented in Table 8.

Table 8 Efficacy Results in CLL Studies 1 and 2

	CLL Study 1* (Previously untreated)		CLL Study 2* (Previously treated)	
	R-FC N=408	FC N=409	R-FC N=276	FC N=276
Median PFS (months)	39.8	31.5	26.7	21.7
Hazard ratio (95% CI)	0.56 (0.43, 0.71)		0.76 (0.6, 0.96)	
P value (Log-Rank test)	<0.01		0.02	
Response rate (95% CI)	86% (82, 89)	73% (68, 77)	54% (48, 60)	45% (37, 51)

* As defined in 1996 National Cancer Institute Working Group guidelines.

Across both studies, 243 of 676 rituximab-treated patients (36%) were 65 years of age or older and 100 rituximab-treated patients (15%) were 70 years of age or older. The results of exploratory subset analyses in elderly patients are presented in Table 9.

Table 9 Efficacy Results in CLL Studies 1 and 2 in Subgroups Defined by Age*

	CLL Study 1		CLL Study 2	
Age subgroup	Number of Patients	Hazard Ratio for PFS (95% CI)	Number of Patients	Hazard Ratio for PFS (95% CI)

	CLL Study 1			CLL Study 2
Age subgroup	**Number of Patients**	**Hazard Ratio for PFS (95% CI)**	**Number of Patients**	**Hazard Ratio for PFS (95% CI)**
Age less than 65 yrs	572	0.52 (0.39, 0.70)	313	0.61 (0.45, 0.84)
Age greater than or equal to 65 yrs	245	0.62 (0.39, 0.99)	233	0.99 (0.70, 1.40)
Age less than 70 yrs	736	0.51 (0.39, 0.67)	438	0.67 (0.51, 0.87)
Age greater than or equal to 70 yrs	81	1.17 (0.51, 2.66)	108	1.22 (0.73, 2.04)

* From exploratory analyses.

14.6 Rheumatoid Arthritis (RA)

Reducing the Signs and Symptoms: Initial and Retreatment Courses

The efficacy and safety of rituximab were evaluated in two randomized, double-blind, placebo-controlled studies of adult patients with moderately- to severely-active RA who had a prior inadequate response to at least one TNF inhibitor. Patients were 18 years of age or older, diagnosed with active RA according to American College of Rheumatology (ACR) criteria, and had at least 8 swollen and 8 tender joints.

In RA Study 1 (NCT00468546), patients were randomized to receive either rituximab 2 × 1,000 mg + MTX or placebo + MTX for 24 weeks. Further courses of rituximab 2 × 1,000 mg + MTX were administered in an open-label extension study at a frequency determined by clinical evaluation, but no sooner than 16 weeks after the preceding course of rituximab. In addition to the intravenous premedication, glucocorticoids were administered orally on a tapering schedule from baseline through Day 14. The proportions of patients achieving ACR 20, 50, and 70 responses at Week 24 of the placebo-controlled period are shown in Table 10.

In RA Study 2 (NCT00266227), all patients received the first course of rituximab 2 × 1,000 mg + MTX. Patients who experienced ongoing disease activity were randomized to receive a second course of either rituximab 2 × 1,000 mg + MTX or placebo + MTX, the majority between Weeks 24–28. The proportions of patients achieving ACR 20, 50, and 70 responses at Week 24, before the retreatment course, and at Week 48, after retreatment, are shown in Table 10.

Table 10 ACR Responses in RA Study 1 and RA Study 2 (Percent of Patients) (Modified Intent-to-Treat Population)

Inadequate Response to TNF Antagonists							
RA Study 1 24 Week Placebo-Controlled (Week 24)				**RA Study 2 Placebo-Controlled Retreatment (Week 24 and Week 48)**			
Response	**Placebo + MTX n=201**	**Rituximab + MTX n=298**	**Treatment Difference (Rituximab – Placebo) (95% CI)**	**Response**	**Placebo + MTX Retreatment n=157**	**Rituximab + MTX Retreatment n=318**	**Treatment Difference (Rituximab – Placebo)*†‡ (95% CI)**
ACR20				ACR20			
Week 24	18%	51%	33% (26%, 41%)	Week 24	48%	45%	NA
				Week 48	45%	54%	11% (2%, 20%)
ACR50				ACR50			
Week 24	5%	27%	21% (15%, 27%)	Week 24	27%	21%	NA
				Week 48	26%	29%	4% (-4%, 13%)
ACR70				ACR70			

* In RA Study 2, all patients received a first course of rituximab 2 × 1,000 mg. Patients who experienced ongoing disease activity were randomized to receive a second course of either rituximab 2 × 1,000 mg + MTX or Placebo + MTX at or after Week 24.

† Since all patients received a first course of rituximab, no comparison between Placebo + MTX and rituximab + MTX is made at Week 24.

‡ For RA Study 1, weighted difference stratified by region (US, rest of the world) and Rheumatoid Factor (RF) status (positive greater than 20 IU/mL, negative less than 20 IU/mL) at baseline; For RA Study 2, weighted difference stratified by RF status at baseline and greater than or equal to 20% improvement from baseline in both SJC and TJC at Week 24 (Yes/No).

Inadequate Response to TNF Antagonists							
RA Study 1 24 Week Placebo-Controlled (Week 24)				RA Study 2 Placebo-Controlled Retreatment (Week 24 and Week 48)			
Response	Placebo + MTX n=201	Rituximab + MTX n=298	Treatment Difference (Rituximab – Placebo) (95% CI)	Response	Placebo + MTX Retreatment n=157	Rituximab + MTX Retreatment n=318	Treatment Difference (Rituximab – Placebo)*†‡ (95% CI)
Week 24	1%	12%	11% (7%, 15%)	Week 24	11%	8%	NA
				Week 48	13%	14%	1% (-5%, 8%)

* In RA Study 2, all patients received a first course of rituximab 2 × 1,000 mg. Patients who experienced ongoing disease activity were randomized to receive a second course of either rituximab 2 × 1,000 mg + MTX or Placebo + MTX at or after Week 24.

† Since all patients received a first course of rituximab, no comparison between Placebo + MTX and rituximab + MTX is made at Week 24.

‡ For RA Study 1, weighted difference stratified by region (US, rest of the world) and Rheumatoid Factor (RF) status (positive greater than 20 IU/mL, negative less than 20 IU/mL) at baseline; For RA Study 2, weighted difference stratified by RF status at baseline and greater than or equal to 20% improvement from baseline in both SJC and TJC at Week 24 (Yes/No).

Improvement was also noted for all components of ACR response following treatment with rituximab, as shown in Table 11.

Table 11 Components of ACR Response at Week 24 in RA Study 1 (Modified Intent-to-Treat Population)

Inadequate Response to TNF Antagonists				
	Placebo + MTX (n=201)		Rituximab + MTX (n=298)	
Parameter (median)	Baseline	Wk 24	Baseline	Wk 24
Tender Joint Count	31.0	27.0	33.0	13.0
Swollen Joint Count	20.0	19.0	21.0	9.5
Physician Global Assessment*	71.0	69.0	71.0	36.0
Patient Global Assessment*	73.0	68.0	71.0	41.0
Pain*	68.0	68.0	67.0	38.5
Disability Index (HAQ)†	2.0	1.9	1.9	1.5
CRP (mg/dL)	2.4	2.5	2.6	0.9

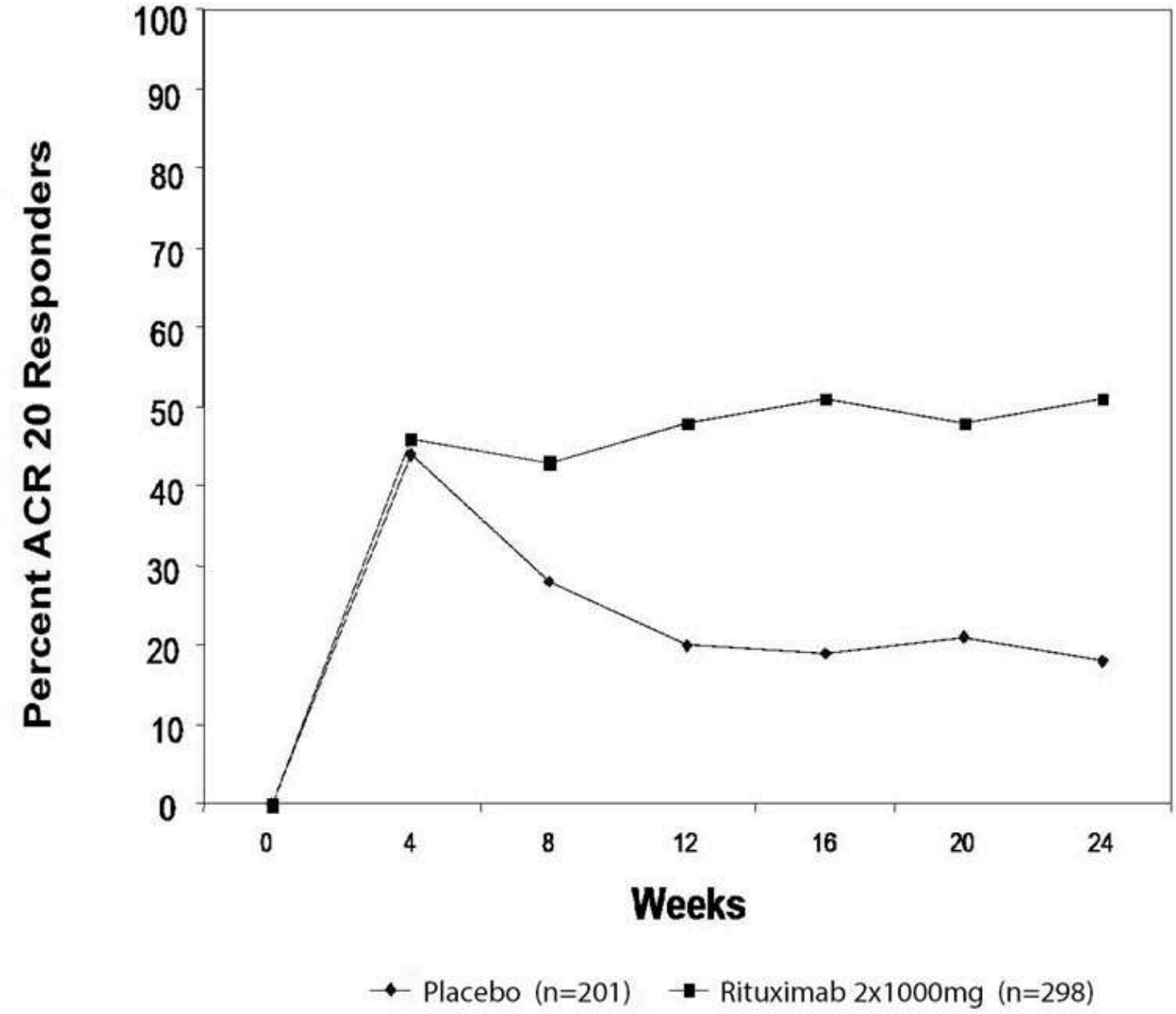
* Visual Analog Scale: 0=best, 100=worst.

† Disability Index of the Health Assessment Questionnaire: 0=best, 3=worst.

The time course of ACR 20 response for RA Study 1 is shown in Figure 2. Although both treatment groups received a brief course of intravenous and oral glucocorticoids, resulting in similar benefits at Week 4, higher ACR 20 responses were observed for the rituximab group by Week 8. A similar proportion of patients achieved these responses through Week 24 after a single course of treatment (2 infusions) with rituximab. Similar patterns were demonstrated for ACR 50 and 70 responses.

Figure 2
Percent of Patients Achieving ACR 20 Response by Visit*
RA Study 1 (Inadequate Response to TNF Antagonists)

* The same patients may not have responded at each time point.



* The same patients may not have responded at each time point.

Radiographic Response

In RA Study 1, structural joint damage was assessed radiographically and expressed as changes in Genant-modified Total Sharp Score (TSS) and its components, the erosion score (ES) and the joint space narrowing (JSN) score. Rituximab + MTX slowed the progression of structural damage compared to placebo + MTX after 1 year as shown in Table 12.

Table 12 Mean Radiographic Change from Baseline to 104 Weeks in RA Study 1

Inadequate Response to TNF Antagonists				
Parameter	**Rituximab 2 × 1,000 mg + MTX***	**Placebo + MTX†**	**Treatment Difference (Placebo – Rituximab)**	**95% CI**
Change during First Year				
TSS	0.66	1.77	1.11	(0.47, 1.75)
ES	0.44	1.19	0.75	(0.32, 1.19)
JSN Score	0.22	0.58	0.36	(0.10, 0.62)
Change during Second Year‡				

* Patients received up to 2 years of treatment with rituximab + MTX.

† Patients receiving Placebo + MTX. Patients receiving Placebo + MTX could have received retreatment with rituximab + MTX from Week 16 onward.

‡ Based on radiographic scoring following 104 weeks of observation.

Inadequate Response to TNF Antagonists				
Parameter	**Rituximab 2 × 1,000 mg + MTX***	**Placebo + MTX†**	**Treatment Difference (Placebo – Rituximab)**	**95% CI**
TSS	0.48	1.04	—	—
ES	0.28	0.62	—	—
JSN Score	0.20	0.42	—	—

* Patients received up to 2 years of treatment with rituximab + MTX.

† Patients receiving Placebo + MTX. Patients receiving Placebo + MTX could have received retreatment with rituximab + MTX from Week 16 onward.

‡ Based on radiographic scoring following 104 weeks of observation.

In RA Study 1 and its open-label extension, 70% of patients initially randomized to rituximab + MTX and 72% of patients initially randomized to placebo + MTX were evaluated radiographically at Year 2. As shown in Table 12, progression of structural damage in rituximab + MTX patients was further reduced in the second year of treatment.

Following 2 years of treatment with rituximab + MTX, 57% of patients had no progression of structural damage. During the first year, 60% of rituximab + MTX treated patients had no progression, defined as a change in TSS of zero or less compared to baseline, compared to 46% of placebo + MTX treated patients. In their second year of treatment with rituximab + MTX, more patients had no progression than in the first year (68% vs. 60%), and 87% of the rituximab + MTX treated patients who had no progression in the first year also had no progression in the second year.

Lesser Efficacy of 500 vs. 1,000 mg Treatment Courses for Radiographic Outcomes

RA Study 3 (NCT00299104) is a randomized, double-blind, placebo-controlled study which evaluated the effect of placebo + MTX compared to rituximab 2 × 500 mg + MTX and rituximab 2 × 1,000 mg + MTX treatment courses in MTX-naïve RA patients with moderately-to severely-active disease. Patients received a first course of two infusions of rituximab or placebo on Days 1 and 15. MTX was initiated at 7.5 mg/week and escalated up to 20 mg/week by Week 8 in all three treatment arms. After a minimum of 24 weeks, patients with ongoing disease activity were eligible to receive retreatment with additional courses of their assigned treatment. After one year of treatment, the proportion of patients achieving ACR 20/50/70 responses were similar in both rituximab dose groups and were higher than in the placebo group. However, with respect to radiographic scores, only the rituximab 1,000 mg treatment group demonstrated a statistically significant reduction in TSS: a change of 0.36 units compared to 1.08 units for the placebo group, a 67% reduction.

Physical Function Response

RA Study 4 (NCT00299130) is a randomized, double-blind, placebo-controlled study in adult RA patients with moderately-to severely-active disease with inadequate response to MTX. Patients were randomized to receive an initial course of rituximab 500 mg, rituximab 1,000 mg, or placebo in addition to background MTX.

Physical function was assessed at Weeks 24 and 48 using the Health Assessment Questionnaire Disability Index (HAQ-DI). From baseline to Week 24, a greater proportion of rituximab-treated patients had an improvement in HAQ-DI of at least 0.22 (a minimal clinically important difference) and a greater mean HAQ-DI improvement compared to placebo, as shown in Table 13. HAQ-DI results for the rituximab 500 mg treatment group were similar to the rituximab 1,000 mg treatment group; however radiographic responses were not assessed (see Dosing Precaution in the Radiographic Responses section above). These improvements were maintained at 48 weeks.

Table 13 Improvement from Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 24 in RA Study 4

	Placebo + MTX n=172	**Rituximab 2 × 1,000 mg + MTX n=170**	**Treatment Difference (Rituximab - Placebo)* (95% CI)**
Mean Improvement from Baseline	0.19	0.42	0.23 (0.11, 0.34)
Percent of patients with "Improved" score	48%	58%	11% (0%, 21%)

* Adjusted difference stratified by region (US, rest of the world) and Rheumatoid Factor (RF) status (positive greater than or equal to 20 IU/mL, negative less than 20 IU/mL) at baseline.

† Minimal Clinically Important Difference: MCID for HAQ=0.22.

	Placebo + MTX n=172	Rituximab 2 × 1,000 mg + MTX n=170	Treatment Difference (Rituximab - Placebo)* (95% CI)
(Change from Baseline greater than or equal to MCID)†			

* Adjusted difference stratified by region (US, rest of the world) and Rheumatoid Factor (RF) status (positive greater than or equal to 20 IU/mL, negative less than 20 IU/mL) at baseline.

† Minimal Clinically Important Difference: MCID for HAQ=0.22.

14.7 Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)

Induction Treatment of Adult Patients with Active Disease (GPA/MPA Study 1)

A total of 197 patients with active, severe GPA and MPA (two forms of ANCA-Associated Vasculitides) were treated in a randomized, double-blind, active-controlled multicenter, non-inferiority study, conducted in two phases – a 6 month remission induction phase and a 12 month remission maintenance phase. Patients were 15 years of age or older, diagnosed with GPA (75% of patients) or MPA (24% of patients) according to the Chapel Hill Consensus conference criteria (1% of the patients had unknown vasculitis type). All patients had active disease, with a Birmingham Vasculitis Activity Score for Granulomatosis with Polyangiitis (BVAS/GPA) greater than or equal to 3, and their disease was severe, with at least one major item on the BVAS/GPA. Ninety-six (49%) of patients had new disease and 101 (51%) of patients had relapsing disease.

Patients in both arms received 1,000 mg of pulse intravenous methylprednisolone per day for 1 to 3 days within 14 days prior to initial infusion. Patients were randomized in a 1:1 ratio to receive either rituximab 375 mg/m^2 once weekly for 4 weeks or oral cyclophosphamide 2 mg/kg daily for 3 to 6 months in the remission induction phase. Patients were pre-medicated with antihistamine and acetaminophen prior to rituximab infusion. Following intravenous corticosteroid administration, all patients received oral prednisone (1 mg/kg/day, not exceeding 80 mg/day) with pre-specified tapering. Once remission was achieved or at the end of the 6 month remission induction period, the cyclophosphamide group received azathioprine to maintain remission. The rituximab group did not receive additional therapy to maintain remission. The main outcome measure for both GPA and MPA patients was achievement of complete remission at 6 months defined as a BVAS/GPA of 0, and off glucocorticoid therapy. The pre-specified non-inferiority margin was a treatment difference of 20%. As shown in Table 14, the study demonstrated non-inferiority of rituximab to cyclophosphamide for complete remission at 6 months.

Table 14 Percentage of Patients with GPA/MPA Who Achieved Complete Remission at 6 Months (Intent-to-Treat Population)

	Rituximab (n=99)	Cyclophosphamide (n=98)	Treatment Difference (Rituximab – Cyclophosphamide)
Rate	64%	53%	11%
95.1%* CI	(54%, 73%)	(43%, 63%)	(-3%, 24%)†

* The 95.1% confidence level reflects an additional 0.001 alpha to account for an interim efficacy analysis.

† Non-inferiority was demonstrated because the lower bound was higher than the prespecified non-inferiority margin (-3% greater than -20%).

Complete Remission (CR) at 12 and 18 Months

In the rituximab group, 44% of patients achieved CR at 6 and 12 months, and 38% of patients achieved CR at 6, 12, and 18 months. In patients treated with cyclophosphamide (followed by azathioprine for maintenance of CR), 38% of patients achieved CR at 6 and 12 months, and 31% of patients achieved CR at 6, 12, and 18 months.

Retreatment of Flares with Rituximab

Based upon investigator judgment, 15 patients received a second course of rituximab therapy for treatment of relapse of disease activity which occurred between 8 and 17 months after the induction treatment course of rituximab.

Follow up Treatment of Adult Patients with GPA/MPA who have achieved disease control with other Immunosuppressant (GPA/MPA Study 2)

A total of 115 patients (86 with GPA, 24 with MPA, and 5 with renal-limited ANCA-associated vasculitis) in disease remission were randomized to receive azathioprine (58 patients) or non-U.S.-licensed rituximab (57 patients) in this open-label, prospective, multicenter, randomized, active-controlled study. Eligible patients were 21 years and older and had either newly diagnosed (80%) or relapsing disease (20%). A majority of the patients were ANCA-positive. Remission of active disease was achieved using a combination of glucocorticoids and cyclophosphamide. Within a maximum of 1 month after the last cyclophosphamide dose, eligible patients (based on BVAS of 0), were randomized in a 1:1 ratio to receive either non-U.S.-licensed rituximab or azathioprine.

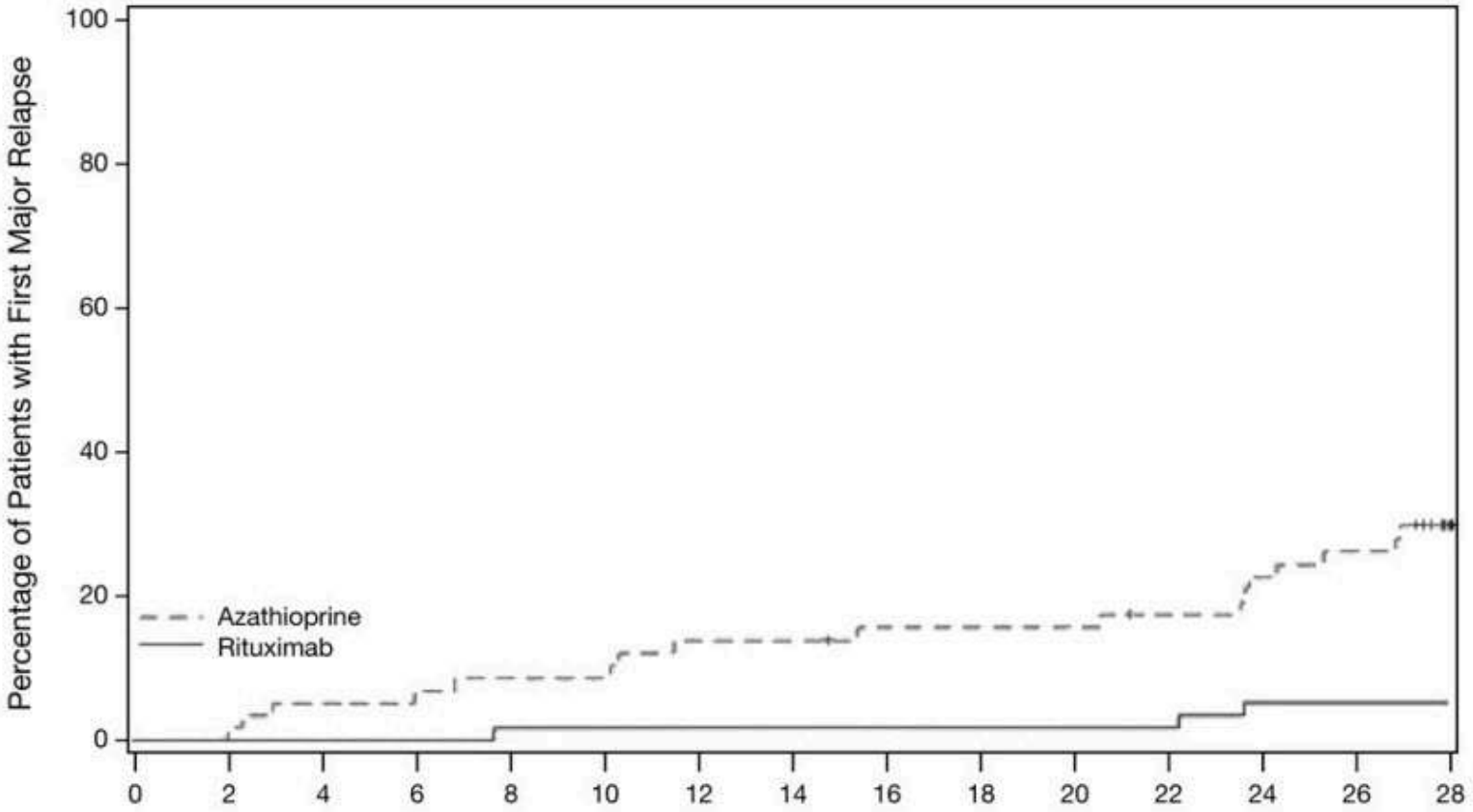
The non-U.S.-licensed rituximab was administered as two 500 mg intravenous infusions separated by two weeks (on Day 1 and Day 15) followed by a 500 mg intravenous infusion every 6 months for 18 months. Azathioprine was administered orally at a dose of 2 mg/kg/day for 12 months, then 1.5 mg/kg/day for 6 months, and finally 1 mg/kg/day for 4 months; treatment was discontinued after 22 months. Prednisone treatment was tapered and then kept at a low dose (approximately 5 mg per day) for at least 18 months after randomization. Prednisone dose tapering and the decision to stop prednisone treatment after month 18 were left at the investigator's discretion.

Planned follow-up was until month 28 (10 or 6 months, respectively, after the last non-U.S.-licensed rituximab infusion or azathioprine dose). The primary endpoint was the occurrence of major relapse (defined by the reappearance of clinical and/or laboratory signs of vasculitis activity that could lead to organ failure or damage, or could be life-threatening) through month 28.

By month 28, major relapse occurred in 3 patients (5%) in the non-U.S.-licensed rituximab group and 17 patients (29%) in the azathioprine group.

The observed cumulative incidence rate of first major relapse during the 28 months was lower in patients on non-U.S.-licensed rituximab relative to azathioprine (Figure 3).

Figure 3
Cumulative Incidence Over Time of First Major Relapse in Patients with GPA/MPA



No. of Subjects with Major Relapse														
Azathioprine	0	0	3	3	5	5	8	8	9	9	9	10	13	15	17
Rituximab	0	0	0	0	1	1	1	1	1	1	1	1	3	3	3
No. of Subjects at Risk															
Azathioprine	58	58	55	55	53	53	50	50	48	48	48	46	43	41	34
Rituximab	57	57	57	57	56	56	56	56	56	56	56	56	54	52	40

Patients were censored at the last follow up dates if they had no event.

16 HOW SUPPLIED/STORAGE AND HANDLING

RUXIENCE (rituximab-pvvr) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale brownish-yellow solution for intravenous infusion supplied as follows:

Carton contents	NDC number
One 100 mg/10 mL (10 mg/mL) single-dose vial	NDC 0069-0238-01
One 500 mg/50 mL (10 mg/mL) single-dose vial	NDC 0069-0249-01

Store RUXIENCE vials refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton. RUXIENCE vials should be protected from direct sunlight. Do not freeze or shake.

17 PATIENT COUNSELING INFORMATION

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

Infusion-Related Reactions

Inform patients about the signs and symptoms of infusion-related reactions. Advise patients to contact their healthcare provider immediately to report symptoms of infusion-related reactions including urticaria, hypotension, angioedema, sudden cough, breathing problems, weakness, dizziness, palpitations, or chest pain *[see Warnings and Precautions (5.1)]*.

Severe Mucocutaneous Reactions

Advise patients to contact their healthcare provider immediately for symptoms of severe mucocutaneous reactions, including painful sores or ulcers on the mouth, blisters, peeling skin, rash, and pustules *[see Warnings and Precautions (5.2)]*.

Hepatitis B Virus Reactivation

Advise patients to contact their healthcare provider immediately for symptoms of hepatitis including worsening fatigue or yellow discoloration of skin or eyes *[see Warnings and Precautions (5.3)]*.

Progressive Multifocal Leukoencephalopathy (PML)

Advise patients to contact their healthcare provider immediately for signs and symptoms of PML, including new or changes in neurological symptoms such as confusion, dizziness or loss of balance, difficulty talking or walking, decreased strength or weakness on one side of the body, or vision problems *[see Warnings and Precautions (5.4)]*.

Tumor Lysis Syndrome (TLS)

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

Infections

Advise patients to contact their healthcare provider immediately for signs and symptoms of infections including fever, cold symptoms (e.g., rhinorrhea or laryngitis), flu symptoms (e.g., cough, fatigue, body aches), earache or headache, dysuria, oral herpes simplex infection, and painful wounds with erythema and advise patients of the increased risk of infections during and after treatment with RUXIENCE *[see Warnings and Precautions (5.6)]*.

Cardiovascular Adverse Reactions

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

Renal Toxicity

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

Bowel Obstruction and Perforation

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

Embryo-Fetal Toxicity

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

Advise females of reproductive potential to use effective contraception during treatment with RUXIENCE and for 12 months after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

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

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Cork, Ireland, P43 X336
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LAB-1273-4.0

MEDICATION GUIDE

RUXIENCE® (RUKSee-ents)

(rituximab-pvvr)

injection

What is the most important information I should know about RUXIENCE?

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

- **Infusion-related reactions.** Infusion-related reactions are very common side effects of RUXIENCE treatment. Serious infusion-related reactions can happen during your infusion or within 24 hours after your infusion of RUXIENCE. Your healthcare provider should give you medicines before your infusion of RUXIENCE to decrease your chance of having a severe infusion-related reaction.

  Tell your healthcare provider or get medical help right away if you get any of these symptoms during or after an infusion of RUXIENCE:

  - hives (red itchy welts) or rash
  - itching
  - swelling of your lips, tongue, throat or face
  - sudden cough
  - shortness of breath, difficulty breathing, or wheezing
  - weakness
  - dizziness or feel faint
  - palpitations (feel like your heart is racing or fluttering)
  - chest pain

This Medication Guide has been approved by the U.S. Food and Drug Administration

Revised: 10/2023

- **Severe skin and mouth reactions.** Tell your healthcare provider or get medical help right away if you get any of these symptoms at any time during your treatment with RUXIENCE:

    - painful sores or ulcers on your skin, lips or in your mouth
    - blisters
    - peeling skin
    - rash
    - pustules

- **Hepatitis B virus (HBV) reactivation.** Before you receive your RUXIENCE treatment, your healthcare provider will do blood tests to check for HBV infection. If you have had hepatitis B or are a carrier of hepatitis B virus, receiving RUXIENCE could cause the virus to become an active infection again. Hepatitis B reactivation may cause serious liver problems including liver failure, and death. You should not receive RUXIENCE if you have active hepatitis B liver disease. Your healthcare provider will monitor you for hepatitis B infection during and for several months after you stop receiving RUXIENCE.
  Tell your healthcare provider right away if you get worsening tiredness, or yellowing of your skin or white part of your eyes, during treatment with RUXIENCE.
- **Progressive Multifocal Leukoencephalopathy (PML).** PML is a rare, serious brain infection caused by a virus that can happen in people who receive RUXIENCE. People with weakened immune systems can get PML. PML can result in death or severe disability. There is no known treatment, prevention, or cure for PML.
  Tell your healthcare provider right away if you have any new or worsening symptoms or if anyone close to you notices these symptoms:

    - confusion
    - dizziness or loss of balance
    - difficulty walking or talking
    - decreased strength or weakness on one side of your body
    - vision problems

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

What is RUXIENCE?

RUXIENCE is a prescription medicine used to treat:

- Adults with Non-Hodgkin's Lymphoma (NHL): alone or with other chemotherapy medicines.
- Adults with Chronic Lymphocytic Leukemia (CLL): with the chemotherapy medicines fludarabine and cyclophosphamide.
- Adults with Rheumatoid Arthritis (RA): with another prescription medicine called methotrexate, to reduce the signs and symptoms of moderate to severe active RA in adults, after treatment with at least one other medicine called a Tumor Necrosis Factor (TNF) antagonist has been used and did not work well.
- Adults with Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA): with glucocorticoids, to treat GPA and MPA.

RUXIENCE is not indicated for treatment of children.

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

- have had a severe reaction to RUXIENCE or another rituximab product
- have a history of heart problems, irregular heart beat or chest pain
- have lung or kidney problems
- have an infection or weakened immune system
- have or have had any severe infections including:

    - Hepatitis B virus (HBV)
    - Hepatitis C virus (HCV)
    - Cytomegalovirus (CMV)
    - Herpes simplex virus (HSV)
    - Parvovirus B19
    - Varicella zoster virus (chickenpox or shingles)
    - West Nile Virus

-

have had a recent vaccination or are scheduled to receive vaccinations. You should not receive certain vaccines before or during treatment with RUXIENCE.

- are pregnant or plan to become pregnant. Talk to your healthcare provider about the risks to your unborn baby if you receive RUXIENCE during pregnancy.
  Females who are able to become pregnant:
  - Your healthcare provider should do a pregnancy test to see if you are pregnant before starting RUXIENCE.
  - You should use effective birth control (contraception) during treatment with RUXIENCE and for **12 months** after your last dose of RUXIENCE. Talk to your healthcare provider about effective birth control.
  - Tell your healthcare provider right away if you become pregnant or think that you are pregnant during treatment with RUXIENCE.
- are breastfeeding or plan to breastfeed. RUXIENCE may pass into your breast milk. Do not breastfeed during treatment and for **6 months** after your last dose of RUXIENCE.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you take or have taken:

- a Tumor Necrosis Factor (TNF) inhibitor medicine
- a Disease Modifying Anti-Rheumatic Drug (DMARD)

If you are not sure if your medicine is one listed above, ask your healthcare provider.

How will I receive RUXIENCE?

- RUXIENCE is given by infusion through your central catheter or through a needle placed in a vein (intravenous infusion), in your arm. Talk to your healthcare provider about how you will receive RUXIENCE.
- Your healthcare provider may prescribe medicines before each infusion of RUXIENCE to reduce infusion side effects such as fever and chills.
- Your healthcare provider should do blood tests regularly to check for side effects to RUXIENCE.
- Before each RUXIENCE treatment, your healthcare provider or nurse will ask you questions about your general health. Tell your healthcare provider or nurse about any new symptoms.

What are the possible side effects of RUXIENCE?
RUXIENCE can cause serious side effects, including:

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

  TLS can happen within 12 to 24 hours after an infusion of RUXIENCE. Your healthcare provider may do blood tests to check you for TLS. Your healthcare provider may give you medicine to help prevent TLS.
  Tell your healthcare provider right away if you have any of the following signs or symptoms of TLS:
  - nausea
  - vomiting
  - diarrhea
  - lack of energy
- **Serious infections.** Serious infections can happen during and after treatment with RUXIENCE, and can lead to death. RUXIENCE can increase your risk of getting infections and can lower the ability of your immune system to fight infections. Types of serious infections that can happen with RUXIENCE include bacterial, fungal, and viral infections. After receiving RUXIENCE, some people have developed low levels of certain antibodies in their blood for a long period of time (longer than 11 months). Some of these people with low antibody levels developed infections. People with serious infections should not receive RUXIENCE. Tell your healthcare provider right away if you have any symptoms of infection:
  - fever
  - cold symptoms, such as runny nose or sore throat that do not go away

- flu symptoms, such as cough, tiredness, and body aches
- earache or headache
- pain during urination
- cold sores in the mouth or throat
- cuts, scrapes or incisions that are red, warm, swollen or painful

- **Heart problems.** RUXIENCE may cause chest pain, irregular heartbeats, and heart attack. Your healthcare provider may monitor your heart during and after treatment with RUXIENCE if you have symptoms or heart problems or have a history of heart problems. Tell your healthcare provider right away if you have chest pain or irregular heartbeats during treatment with RUXIENCE.
- **Kidney problems**, especially if you are receiving RUXIENCE for NHL. RUXIENCE can cause severe kidney problems that lead to death. Your healthcare provider should do blood tests to check how well your kidneys are working.
- **Stomach and Serious bowel problems that can sometimes lead to death.** Bowel problems, including blockage or tears in the bowel can happen if you receive RUXIENCE with chemotherapy medicines. Tell your healthcare provider right away if you have any severe stomach-area (abdomen) pain or repeated vomiting during treatment with RUXIENCE.

Your healthcare provider will stop treatment with RUXIENCE if you have severe, serious or life-threatening side effects.
The most common side effects of RUXIENCE include:

- infusion-related reactions (see "**What is the most important information I should know about RUXIENCE?**")
- infections (may include fever, chills)
- body aches
- tiredness
- nausea

In adults with GPA or MPA the most common side effects of RUXIENCE also include:

- low white and red blood cells
- swelling
- diarrhea
- muscle spasms

Other side effects with RUXIENCE include:

- aching joints during or within hours of receiving an infusion
- more frequent upper respiratory tract infection

These are not all of the possible side effects with RUXIENCE.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of RUXIENCE.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about RUXIENCE that is written for healthcare providers.

What are the ingredients in RUXIENCE?
Active ingredient: rituximab-pvvr
Inactive ingredients: edetate disodium dihydrate, L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sucrose, and Water for Injection.
Manufactured by Pfizer Ireland Pharmaceuticals, Cork, Ireland, P43 X336
U.S. License No. 2060
Distributed by Pfizer Labs Division of Pfizer Inc. New York, NY 10001
LAB-1274-4.0

For more information, go to www.pfizer.com or call 1-800-438-1985.

This Medication Guide has been approved by the U.S. Food and Drug Administration

Revised: 10/2023

Revised: 11/2021

Pfizer Laboratories Div Pfizer Inc