pyrexia, increased weight, herpes zoster, influenza, fatigue, neutropenia, myalgia, and influenza like illness. (6.1)
- Ulcerative colitis: Adverse reactions (≥ 5%) reported during induction or maintenance are: upper respiratory tract infections, increased blood creatine phosphokinase, acne, neutropenia, elevated liver enzymes, and rash. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**DRUG INTERACTIONS**
- Strong CYP3A4 Inhibitors: See the Full Prescribing Information for dosage modification for patients with atopic dermatitis and ulcerative colitis. (2.8, 7.1)
- Strong CYP3A4 Inducers: Coadministration of RINVOQ with strong CYP3A4 inducers is not recommended. (7.2)

**USE IN SPECIFIC POPULATIONS**
- Lactation: Advise not to breastfeed. (8.2)
- Hepatic Impairment: RINVOQ is not recommended in patients with severe hepatic impairment. (8.7)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: 3/2022**

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**FULL PRESCRIBING INFORMATION: CONTENTS***



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

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# FULL PRESCRIBING INFORMATION

**WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, AND THROMBOSIS**

**SERIOUS INFECTIONS**

**Patients treated with RINVOQ 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.**

**If a serious infection develops, interrupt RINVOQ until the infection is controlled.**

**Reported infections include:**

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before RINVOQ use and during therapy. Treatment for latent infection should be considered prior to RINVOQ use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

**The risks and benefits of treatment with RINVOQ 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 RINVOQ, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy *[see Warnings and Precautions (5.1)]*.**

**MORTALITY**

**In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing another Janus kinase (JAK) inhibitor to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with the JAK inhibitor *[see Warnings and Precautions (5.2)]*.**

**MALIGNANCIES**

**Lymphoma and other malignancies have been observed in patients treated with RINVOQ. In RA patients treated with another JAK inhibitor, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk *[see Warnings and Precautions (5.3)]*.**

**MAJOR ADVERSE CARDIOVASCULAR EVENTS**

**In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), was observed when compared with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue RINVOQ in patients that have experienced a myocardial infarction or stroke *[see Warnings and Precautions (5.4)]*.**

**THROMBOSIS**

**Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated with JAK inhibitors used to treat inflammatory conditions. Many of these adverse events were serious and some resulted in death. In RA patients 50 years of age and older with at least one cardiovascular risk factor treated with another JAK inhibitor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid RINVOQ in patients at risk. Patients with symptoms of thrombosis should discontinue RINVOQ and be promptly evaluated *[see Warnings and Precautions (5.5)]*.**

## 1 INDICATIONS AND USAGE

### 1.1 Rheumatoid Arthritis

RINVOQ® is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: Use of RINVOQ in combination with other JAK inhibitors, biologic disease-modifying antirheumatic drugs (DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine, is not recommended.

### 1.2 Psoriatic Arthritis

RINVOQ is indicated for the treatment of adults with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: Use of RINVOQ in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine, is not recommended.

### 1.3 Atopic Dermatitis

RINVOQ is indicated for the treatment of adults and pediatric patients 12 years of age and older with refractory, moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies are inadvisable.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with other immunosuppressants.

### 1.4 Ulcerative Colitis

RINVOQ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response or intolerance to one or more TNF blockers.

- Limitations of Use: RINVOQ is not recommended for use in combination with other JAK inhibitors, biological therapies for ulcerative colitis, or with potent immunosuppressants such as azathioprine and cyclosporine.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Evaluations and Immunizations Prior to Treatment Initiation

Prior to RINVOQ treatment initiation, consider performing the following evaluations:

- Active and latent tuberculosis (TB) infection evaluation - If positive, treat for TB prior to RINVOQ use *[see Warnings and Precautions (5.1)]*.
- Viral hepatitis screening in accordance with clinical guidelines - RINVOQ initiation is not recommended in patients with active hepatitis B or hepatitis C *[see Warnings and Precautions (5.1)]*.
- A complete blood count - RINVOQ initiation is not recommended in patients with an absolute lymphocyte count less than 500 cells/$mm^3$, absolute neutrophil count less than 1000 cells/$mm^3$, or hemoglobin level less than 8 g/dL *[see Dosage and Administration (2.8) and Warnings and Precautions (5.8)]*.
- Baseline hepatic function: RINVOQ initiation is not recommended for patients with severe hepatic impairment (Child-Pugh C) *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.
- Pregnancy Status: Verify the pregnancy status of females of reproductive potential prior to starting treatment *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.1, 8.3)]*.

Update immunizations according to current immunization guidelines *[see Warnings and Precautions (5.10)]*.

### 2.2 Important Administration Instructions

- RINVOQ tablets should be taken orally with or without food *[see Clinical Pharmacology (12.3)]*.
- RINVOQ tablets should be swallowed whole. RINVOQ should not be split, crushed, or chewed.

### 2.3 Recommended Dosage in Rheumatoid Arthritis

The recommended dosage of RINVOQ is 15 mg once daily.

### 2.4 Recommended Dosage in Psoriatic Arthritis

The recommended dosage of RINVOQ is 15 mg once daily.

### 2.5 Recommended Dosage in Atopic Dermatitis

Pediatric Patients 12 Years of Age and Older Weighing at Least 40 kg and Adults Less Than 65 Years of Age

Initiate treatment with 15 mg once daily. If an adequate response is not achieved, consider increasing the dosage to 30 mg once daily. Discontinue RINVOQ if an adequate response is not achieved with the 30 mg dose. Use the lowest effective dose needed to maintain response.

Adults 65 Years of Age and Older

The recommended dosage is 15 mg once daily.

### 2.6 Recommended Dosage in Ulcerative Colitis

Adult Patients: Induction

The recommended induction dose of RINVOQ is 45 mg once daily for 8 weeks.

Adult Patients: Maintenance

The recommended dose of RINVOQ for maintenance treatment is 15 mg once daily. A dosage of 30 mg once daily may be considered for patients with refractory, severe or extensive disease. Discontinue RINVOQ if an adequate therapeutic response is not achieved with the 30 mg dosage. Use the lowest effective dosage needed to maintain response.

### 2.7 Recommended Dosage in Patients with Renal Impairment or Hepatic Impairment

Renal Impairment

*Rheumatoid Arthritis and Psoriatic Arthritis*:

- No dosage adjustment is needed for patients with mild, moderate, or severe renal impairment.

*Atopic Dermatitis:*

- For patients with severe renal impairment [estimated glomerular filtration rate (eGFR) 15 to < 30 mL/min/1.73m$^2$] the recommended dosage is 15 mg once daily *[see Use in Specific Populations (8.6)]*.
- No dosage adjustment is needed for patients with mild or moderate renal impairment (eGFR ≥ 30 mL/min/1.73m$^2$).
- RINVOQ is not recommended for use in patients with end stage renal disease (eGFR < 15 mL/min/1.73m$^2$) *[see Use in Specific Populations (8.6)]*.

*Ulcerative Colitis:*

- For patients with severe renal impairment (eGFR 15 to < 30 mL/min/1.73m$^2$), the recommended dosage is:
    - *Induction:* 30 mg once daily for 8 weeks

- *Maintenance:* 15 mg once daily

- No dosage adjustment is needed for patients with mild or moderate renal impairment (eGFR ≥ 30 mL/min/1.73m$^2$).
- RINVOQ is not recommended for use in patients with end stage renal disease (eGFR < 15 mL/min/1.73m$^2$) *[see Use in Specific Populations (8.6)]*.

Hepatic Impairment

RINVOQ is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) *[see Use in Specific Populations (8.7)]*.

*Rheumatoid Arthritis, Psoriatic Arthritis, and Atopic Dermatitis*:
No dosage adjustment is needed for patients with mild or moderate hepatic impairment (Child-Pugh A or B).

*Ulcerative Colitis:*
For patients with mild to moderate hepatic impairment (Child-Pugh A or B) the recommended dosage is:

- *Induction:* 30 mg once daily for 8 weeks
- *Maintenance:* 15 mg once daily

**2.8 Dosage Modifications Due to Drug Interactions**

Rheumatoid Arthritis, Psoriatic Arthritis, Atopic Dermatitis
The recommended dosage in patients receiving strong CYP3A4 inhibitors is 15 mg once daily *[see Drug Interactions (7.1)]*.

Ulcerative Colitis
The recommended dosage in patients with ulcerative colitis receiving strong CYP3A4 inhibitors *[see Drug Interactions (7.1)]:*

- *Induction:* 30 mg once daily for 8 weeks
- *Maintenance:* 15 mg once daily

**2.9 Dosage Interruption**

Infections
If a patient develops a serious infection, including serious opportunistic infection, interrupt RINVOQ treatment until the infection is controlled *[see Warnings and Precautions (5.1)]*.

Laboratory Abnormalities
Interruption of dosing may be needed for management of laboratory abnormalities as described in Table 1 *[see Warnings and Precautions (5.8)]*.

**Table 1: Recommended Dosage Interruptions for Laboratory Abnormalities**

| Laboratory Measure | Action |
|---|---|
| Absolute Neutrophil Count (ANC) | Interrupt treatment if ANC is less than 1000 cells/mm$^3$; treatment may be restarted once ANC returns above this value |
| Absolute Lymphocyte Count (ALC) | Interrupt treatment if ALC is less than 500 cells/mm$^3$; treatment may be restarted once ALC returns above this value |
| Hemoglobin (Hb) | Interrupt treatment if Hb is less than 8 g/dL; treatment may be restarted once Hb returns above this value |
| Hepatic transaminases | Interrupt treatment if drug-induced liver injury is suspected, until this diagnosis is excluded. |

## 3 DOSAGE FORMS AND STRENGTHS

Extended-release tablets:

- 15 mg: purple, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with ‘a15’ on one side.
- 30 mg: red, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with ‘a30’ on one side.
- 45 mg: yellow to mottled yellow, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with ‘a45’ on one side.

## 4 CONTRAINDICATIONS

RINVOQ is contraindicated in patients with known hypersensitivity to upadacitinib or any of its excipients *[see Warnings and Precautions (5.6)]*.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Serious Infections

Serious and sometimes fatal infections have been reported in patients receiving RINVOQ. The most frequent serious infections reported with RINVOQ included pneumonia and cellulitis *[see Adverse Reactions (6.1)]*. Among opportunistic infections, tuberculosis, multidermatomal herpes zoster, oral/esophageal candidiasis, and cryptococcosis, were reported with RINVOQ.

Avoid use of RINVOQ in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating RINVOQ in patients:

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

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with RINVOQ. Interrupt RINVOQ if a patient develops a serious or opportunistic infection.

A patient who develops a new infection during treatment with RINVOQ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and RINVOQ should be interrupted if the patient is not responding to antimicrobial therapy. RINVOQ may be resumed once the infection is controlled.

Tuberculosis

Evaluate and test patients for latent and active tuberculosis (TB) infection prior to administration of RINVOQ. Patients with latent TB should be treated with standard antimycobacterial therapy before initiating RINVOQ. RINVOQ should not be given to patients with active TB. Consider anti-TB therapy prior to initiation of RINVOQ in patients with previously untreated latent TB or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but who have risk factors for TB infection.

Consultation with a physician with expertise in the treatment of TB is recommended to aid in the decision about whether initiating anti-TB therapy is appropriate for an individual patient.

During RINVOQ use, monitor patients for the development of signs and symptoms of TB, including patients who tested negative for latent TB infection prior to initiating therapy.

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster) and hepatitis B virus reactivation, were reported in clinical trials with RINVOQ *[see Adverse Reactions (6.1)]*. The risk of herpes zoster appears to be higher in patients treated with RINVOQ in Japan. If a patient develops herpes zoster, consider temporarily interrupting RINVOQ until the episode resolves.

Screening for viral hepatitis and monitoring for reactivation should be performed in accordance with clinical guidelines before starting and during therapy with RINVOQ. Patients who were positive for hepatitis C antibody and hepatitis C virus RNA, were excluded from clinical trials. Patients who were positive for hepatitis B surface antigen or hepatitis B virus DNA were excluded from clinical trials. However, cases of hepatitis B reactivation were still reported in patients enrolled in the Phase 3 trials of RINVOQ. If hepatitis B virus DNA is detected while receiving RINVOQ, a liver specialist should be consulted.

**5.2 Mortality**

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed in patients treated with the JAK inhibitor compared with TNF blockers.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ.

### 5.3 Malignancy and Lymphoproliferative Disorders

Malignancies, including lymphomas, were observed in clinical trials of RINVOQ *[see Adverse Reactions (6.1)]*.

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lymphomas was observed in patients treated with the JAK inhibitor compared to those treated with TNF blockers. A higher rate of lung cancers was observed in current or past smokers treated with the JAK inhibitor compared to those treated with TNF blockers. In this study, current or past smokers had an additional increased risk of overall malignancies.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy when on treatment, and patients who are current or past smokers.

Non-Melanoma Skin Cancer

NMSCs have been reported in patients treated with RINVOQ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Exposure to sunlight and UV light should be limited by wearing protective clothing and using a broad-spectrum sunscreen.

### 5.4 Major Adverse Cardiovascular Events

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke was observed with the JAK inhibitor compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with RINVOQ, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Discontinue RINVOQ in patients that have experienced a myocardial infarction or stroke.

### 5.5 Thrombosis

Thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis, have occurred in patients treated for inflammatory conditions with JAK inhibitors, including RINVOQ. Many of these adverse events were serious and some resulted in death.

In a large, randomized, postmarketing safety study of another JAK inhibitor in RA patients 50 years of age and older with at least one cardiovascular risk factor, higher rates of overall thrombosis, DVT, and PE were observed compared to those treated with TNF blockers.

If symptoms of thrombosis occur, patients should discontinue RINVOQ and be evaluated promptly and treated appropriately. Avoid RINVOQ in patients that may be at increased risk of thrombosis.

### 5.6 Hypersensitivity Reactions

Serious hypersensitivity reactions such as anaphylaxis and angioedema were reported in patients receiving RINVOQ in clinical trials. If a clinically significant hypersensitivity reaction occurs, discontinue RINVOQ and institute appropriate therapy *[see Adverse Reactions (6.1)]*.

### 5.7 Gastrointestinal Perforations

Gastrointestinal perforations have been reported in clinical trials with RINVOQ.

Monitor RINVOQ-treated patients who may be at risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis or taking NSAIDs). Evaluate promptly patients presenting with new onset abdominal pain for early identification of gastrointestinal perforation.

### 5.8 Laboratory Abnormalities

Neutropenia

Treatment with RINVOQ was associated with an increased incidence of neutropenia (ANC less than 1000 cells/$mm^3$).

Evaluate neutrophil counts at baseline and thereafter according to routine patient management. Avoid RINVOQ initiation and interrupt RINVOQ treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/$mm^3$) *[see Dosage and Administration (2.1, 2.8)]*.

Lymphopenia

ALC less than 500 cells/$mm^3$ were reported in RINVOQ-treated patients in clinical trials.

Evaluate lymphocyte counts at baseline and thereafter according to routine patient management. Avoid RINVOQ initiation or interrupt RINVOQ treatment in patients with a low lymphocyte count (i.e., less than 500 cells/$mm^3$) *[see Dosage and Administration (2.1, 2.8)]*.

Anemia

Decreases in hemoglobin levels to less than 8 g/dL were reported in RINVOQ-treated patients in clinical trials.

Evaluate hemoglobin at baseline and thereafter according to routine patient management. Avoid RINVOQ initiation or interrupt RINVOQ treatment in patients with a low hemoglobin level (i.e., less than 8 g/dL) *[see Dosage and Administration (2.1, 2.8)]*.

Lipids

Treatment with RINVOQ was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol *[see Adverse Reactions (6.1)]*. Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Assess lipid parameters approximately 12 weeks after initiation of treatment, and thereafter according to the clinical guidelines for hyperlipidemia. Manage patients according to clinical guidelines for the management of hyperlipidemia.

Liver Enzyme Elevations

Treatment with RINVOQ was associated with increased incidence of liver enzyme elevations compared to treatment with placebo.

Evaluate liver enzymes at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury.

If increases in ALT or AST are observed during routine patient management and drug-induced liver injury is suspected, RINVOQ should be interrupted until this diagnosis is excluded.

### 5.9 Embryo-Fetal Toxicity

Based on findings in animal studies, RINVOQ may cause fetal harm when administered to a pregnant woman. Administration of upadacitinib to rats and rabbits during organogenesis caused increases in fetal malformations. Verify the pregnancy status of patients of reproductive potential prior to starting treatment. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception during treatment with RINVOQ and for 4 weeks following completion of therapy *[see Use in Specific Populations (8.1, 8.3)]*.

### 5.10 Vaccinations

Avoid use of live vaccines during, or immediately prior to, RINVOQ therapy. Prior to initiating RINVOQ, it is recommended that patients be brought up to date with all immunizations, including varicella zoster or prophylactic herpes zoster vaccinations, in agreement with current immunization guidelines.

## 6 ADVERSE REACTIONS

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

- Serious Infections *[see Warnings and Precautions (5.1)]*
- Mortality *[see Warnings and Precautions (5.2)]*
- Malignancy and Lymphoproliferative Disorders *[see Warnings and Precautions (5.3)]*
- Major Adverse Cardiovascular Events *[see Warnings and Precautions (5.4)]*
- Thrombosis *[see Warnings and Precautions (5.5)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.6)]*
- Gastrointestinal Perforations *[see Warnings and Precautions (5.7)]*
- Laboratory Abnormalities *[see Warnings and Precautions (5.8)]*

### 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.

*Opportunistic Infections (excluding tuberculosis)*

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, opportunistic infections were reported in 3 patients (1.2 per 100 patient-years) treated with placebo, and 5 patients (1.9 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, opportunistic infections were reported in 1 patient (1.2 per 100 patient-years) treated with placebo, 2 patients (2.3 per 100 patient-years) treated with RINVOQ 15 mg, and 6 patients (7.1 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Opportunistic infections were reported in 1 patient (0.8 per 100 patient-years) treated with MTX monotherapy, 0 patients treated with RINVOQ 15 mg monotherapy, and 4 patients (3.2 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Opportunistic infections were reported in 7 patients (0.6 per 100 patient-years) treated with RINVOQ 15 mg and 15 patients (1.4 per 100 patient-years) treated with upadacitinib 30 mg.

*Malignancies*

Placebo-controlled Trials: In RA-III, RA-IV, and RA-V, malignancies excluding NMSC were reported in 1 patient (0.4 per 100 patient-years) treated with placebo, and 1 patient (0.4 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, malignancies excluding NMSC were reported in 0 patients treated with placebo, 1 patient (1.1 per 100 patient-years) treated with RINVOQ 15 mg, and 3 patients (3.5 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Trials: Malignancies excluding NMSC were reported in 1 patient (0.8 per 100 patient-years) treated with MTX monotherapy, 3 patients (2.4 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 0 patients treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Malignancies excluding NMSC were reported in 13 patients (1.2 per 100 patient-years) treated with RINVOQ 15 mg and 14 patients (1.3 per 100 patient-years) treated with upadacitinib 30 mg.

*Gastrointestinal Perforations*

Placebo-controlled Trials: There were no gastrointestinal perforations (based on medical review) reported in patients treated with placebo, RINVOQ 15 mg, and upadacitinib 30 mg.

MTX-controlled Trials: There were no cases of gastrointestinal perforations reported in the MTX and RINVOQ 15 mg group through 12/14 weeks. Two cases of gastrointestinal perforations were observed in the upadacitinib 30 mg group.

12-Month Exposure Dataset: Gastrointestinal perforations were reported in 1 patient treated with RINVOQ 15 mg and 4 patients treated with upadacitinib 30 mg.

*Thrombosis*

Placebo-controlled Trials: In RA-IV, venous thrombosis (pulmonary embolism or deep vein thrombosis) was observed in 1 patient treated with placebo and 1 patient treated with RINVOQ 15 mg. In RA-V, venous thrombosis was observed in 1 patient treated with RINVOQ 15 mg.

There were no observed cases of venous thrombosis reported in RA-III. No cases of arterial thrombosis were observed through 12/14 weeks.

MTX-controlled Trials: In RA-II, venous thrombosis was observed in 0 patients treated with MTX monotherapy, 1 patient treated with RINVOQ 15 mg monotherapy and 0 patients treated with upadacitinib 30 mg monotherapy through Week 14. In RA-II, no cases of arterial thrombosis were observed through 12/14 weeks. In RA-I, venous thrombosis was observed in 1 patient treated with MTX, 0 patients treated with RINVOQ 15 mg and 1 patient treated with upadacitinib 30 mg through Week 24. In RA-I, arterial thrombosis was observed in 1 patient treated with upadacitinib 30 mg through Week 24.

12-Month Exposure Dataset: Venous thrombosis events were reported in 5 patients (0.5 per 100 patient-years) treated with RINVOQ 15 mg and 4 patients (0.4 per 100 patient-years) treated with upadacitinib 30 mg. Arterial thrombosis events were reported in 0 patients treated with RINVOQ 15 mg and 2 patients (0.2 per 100 patient-years) treated with upadacitinib 30 mg.

*Laboratory Abnormalities*

*Hepatic Transaminase Elevations*

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, alanine transaminase (ALT) and aspartate transaminase (AST) elevations ≥ 3 x upper limit of normal (ULN) in at least one measurement were observed in 2.1% and 1.5% of patients treated with RINVOQ 15 mg, and in 1.5% and 0.7% of patients treated with placebo, respectively. In RA-III and RA-V, ALT and AST elevations ≥ 3 x ULN in at least one measurement were observed in 0.8% and 1.0% of patients treated with RINVOQ 15 mg, 1.0% and 0% of patients treated with upadacitinib 30 mg and in 1.3% and 1.0% of patients treated with placebo, respectively.

In MTX-controlled trials, for up to 12/14 weeks, ALT and AST elevations ≥ 3 x ULN in at least one measurement were observed in 0.8% and 0.4% of patients treated with RINVOQ 15 mg, 1.7% and 1.3% of patients treated with upadacitinib 30 mg and in 1.9% and 0.9% of patients treated with MTX, respectively.

*Lipid Elevations*

Upadacitinib treatment was associated with dose-related increases in total cholesterol, triglycerides and LDL cholesterol. Upadacitinib was also associated with increases in HDL cholesterol. Elevations in LDL and HDL cholesterol peaked by Week 8 and remained stable thereafter. In controlled trials, for up to 12/14 weeks, changes from baseline in lipid parameters in patients treated with RINVOQ 15 mg and upadacitinib 30 mg, respectively, are summarized below:

- Mean LDL cholesterol increased by 14.81 mg/dL and 17.17 mg/dL.
- Mean HDL cholesterol increased by 8.16 mg/dL and 9.01 mg/dL.
- The mean LDL/HDL ratio remained stable.
- Mean triglycerides increased by 13.55 mg/dL and 14.44 mg/dL.

*Creatine Phosphokinase Elevations*

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related increases in creatine phosphokinase (CPK) values were observed.

CPK elevations > 5 x ULN were reported in 1.0%, and 0.3% of patients over 12/14 weeks in the RINVOQ 15 mg and placebo groups, respectively. Most elevations >5 x ULN were transient and did not require treatment discontinuation. In RA-III and RA-V, CPK elevations > 5 x ULN were observed in 0.3% of patients treated with placebo, 1.6% of patients treated with RINVOQ 15 mg, and none in patients treated with upadacitinib 30 mg.

*Neutropenia*

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related decreases in neutrophil counts, below 1000 cells/$mm^3$ in at least one measurement occurred in 1.1% and <0.1% of patients in the RINVOQ 15 mg and placebo groups, respectively. In RA-III and RA-V, decreases in neutrophil counts below 1000 cells/$mm^3$ in at least one measurement occurred in 0.3% of patients treated with placebo, 1.3% of patients treated with RINVOQ 15 mg, and 2.4% of patients treated with upadacitinib 30 mg. In clinical trials, treatment was interrupted in response to ANC less than 1000 cells/$mm^3$.

*Lymphopenia*

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related decreases in lymphocyte counts below 500 cells/$mm^3$ in at least one measurement occurred in 0.9% and 0.7% of patients in the RINVOQ 15 mg and placebo groups, respectively. In RA-III and RA-V, decreases in lymphocyte counts below 500 cells/$mm^3$ in at least one measurement occurred in 0.5% of patients treated with placebo, 0.5% of patients treated with RINVOQ 15 mg, and 2.4% of patients treated with upadacitinib 30 mg.

*Anemia*

In placebo-controlled trials (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, hemoglobin decreases below 8 g/dL in at least one measurement occurred in <0.1% of patients in both the RINVOQ 15 mg and placebo groups. In RA-III and RA-V, hemoglobin decreases below 8 g/dL in at least one measurement were observed in 0.3% of patients treated with placebo, and none in patients treated with RINVOQ 15 mg and upadacitinib 30 mg.

Adverse Reactions in Patients with Psoriatic Arthritis

A total of 1827 patients with psoriatic arthritis were treated with upadacitinib in clinical studies representing 1639.2 patient-years of exposure, of whom 722 were exposed to upadacitinib for at least one year. In the two Phase 3 studies, 907 patients received at least 1 dose of RINVOQ 15 mg, of whom 359 were exposed for at least one year.

Two placebo-controlled studies were integrated (640 patients on RINVOQ 15 mg once daily and 635 patients on placebo) to evaluate the safety of RINVOQ 15 mg in comparison to placebo for up to 24 weeks after treatment initiation.

Overall, the safety profile observed in patients with active psoriatic arthritis treated with RINVOQ 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis. During the 24-week placebo-controlled period, the frequencies of herpes zoster and herpes simplex were >1% (1.1% and 1.4%, respectively) with RINVOQ 15 mg and 0.8% and 1.3%, respectively with placebo. A higher incidence of acne and bronchitis was also observed in patients treated with RINVOQ 15 mg (1.3% and 3.9%, respectively) compared to placebo (0.3% and 2.7%, respectively).

Adverse Reactions in Patients with Atopic Dermatitis

Three Phase 3 (AD-1, AD-2, and AD-3) and one Phase 2b (AD-4) randomized, double-blind, placebo-controlled, multicenter trials evaluated the safety of RINVOQ in patients with moderate-to-severe atopic dermatitis. The majority of patients were White (68%) and male (57%). The mean age was 34 years (ranged from 12 to 75 years) and 13% of the patients were 12 to less than 18 years. In these 4 trials, 2612 patients were treated with RINVOQ 15 mg or 30 mg orally once daily, with or without concomitant topical corticosteroids (TCS).

In the Phase 3 clinical trials (AD-1, AD-2, and AD-3), a total of 1239 patients received RINVOQ 15 mg, of whom 791 were exposed for at least one year and 1246 patients received RINVOQ 30 mg, of whom 826 were exposed for at least one year.

Trials AD-1, AD-2, and AD-4 compared the safety of RINVOQ monotherapy to placebo through Week 16. Trial AD-3 compared the safety of RINVOQ + TCS to placebo + TCS through Week 16.

*Weeks 0 to 16 (Trials AD-1 to AD-4)*

In RINVOQ trials with and without TCS (Trials AD-1, 2, 3 and 4) through Week 16, the proportion of patients who discontinued treatment because of adverse reactions in the RINVOQ 15 mg, 30 mg and placebo groups were 2.3%, 2.9% and 3.8%, respectively. Table 3 summarizes the adverse reactions that occurred at a rate of at least 1% in the RINVOQ 15 mg or 30 mg groups during the first 16 weeks of treatment.

**Table 3: Adverse Reactions Reported in ≥ 1% of Patients with Atopic Dermatitis Treated with RINVOQ 15 mg or 30 mg**

| **Adverse Reaction** | **Placebo** | **RINVOQ 15 mg** | **RINVOQ 30 mg** |
|---|---|---|---|
| | n=902 (%) | n=899 (%) | n=906 (%) |
| Upper respiratory tract infection (URTI)* | 17 | 23 | 25 |
| Acne** | 2 | 10 | 16 |
| Herpes simplex*** | 2 | 4 | 8 |
| Headache | 4 | 6 | 6 |
| Increased blood creatine phosphokinase | 2 | 5 | 6 |
| Cough | 1 | 3 | 3 |
| Hypersensitivity**** | 2 | 2 | 3 |
| Folliculitis | 1 | 2 | 3 |
| Nausea | 1 | 3 | 3 |
| Abdominal pain***** | 1 | 3 | 2 |
| Pyrexia | 1 | 2 | 2 |

| | | | |
|---|---|---|---|
| Increased Weight | 1 | 2 | 2 |
| Herpes zoster****** | 1 | 2 | 2 |
| Influenza | <1 | 2 | 2 |
| Fatigue | 1 | 1 | 2 |
| Neutropenia | <1 | 1 | 2 |
| Myalgia | 1 | 1 | 2 |
| Influenza like illness | 1 | 1 | 2 |

* Includes: laryngitis, laryngitis viral, nasopharyngitis, oropharyngeal pain, pharyngeal abscess, pharyngitis, pharyngitis streptococcal, pharyngotonsillitis, respiratory tract infection, respiratory tract infection viral, rhinitis, rhinolaryngitis, sinusitis, tonsillitis, tonsillitis bacterial, upper respiratory tract infection, viral pharyngitis, viral upper respiratory tract infection
** Includes: acne and dermatitis acneiform
*** Includes: genital herpes, genital herpes simplex, herpes dermatitis, herpes ophthalmic, herpes simplex, nasal herpes, ophthalmic herpes simplex, herpes virus infection, oral herpes
**** Includes anaphylactic reaction, anaphylactic shock, angioedema, dermatitis exfoliative generalized, drug hypersensitivity, eyelid oedema, face oedema, hypersensitivity, periorbital swelling, pharyngeal swelling, swelling face, toxic skin eruption, type I hypersensitivity, urticaria
***** Includes abdominal pain and abdominal pain upper
****** Includes herpes zoster and varicella

Other adverse reactions reported in less than 1% of patients in the RINVOQ 15 mg and/or 30 mg group and at a higher rate than in the placebo group through Week 16 included anemia, oral candidiasis, pneumonia, and the adverse event of retinal detachment.

The safety profile of RINVOQ through Week 52 was generally consistent with the safety profile observed at Week 16.

Overall, the safety profile observed in patients with AD treated with RINVOQ was similar to the safety profile in patients with RA. Other specific adverse reactions that were reported in patients with AD included eczema herpeticum/Kaposi's varicelliform eruption.

*Eczema Herpeticum/Kaposi's Varicelliform Eruption*

Placebo-controlled Period (16 weeks): Eczema herpeticum was reported in 4 patients (1.6 per 100 patient-years) treated with placebo, 6 patients (2.2 per 100 patient-years) treated with RINVOQ 15 mg and 7 patients (2.6 per 100 patient-years) treated with RINVOQ 30 mg.

12-Month Exposure (Weeks 0 to 52): Eczema herpeticum was reported in 18 patients (1.6 per 100 patient-years) treated with RINVOQ 15 mg and 17 patients (1.5 per 100 patient-years) treated with RINVOQ 30 mg.

Adverse Reactions in Patients with Ulcerative Colitis

RINVOQ was studied up to 8 weeks in patients with moderately to severely active ulcerative colitis in two randomized, double-blind, placebo-controlled induction studies (UC-1, UC-2) and a randomized, double-blind, placebo controlled, dose-finding study (UC-4; NCT02819635). Long term safety up to 52-weeks was evaluated in patients who responded to induction therapy in a randomized, double-blind, placebo-controlled maintenance study (UC-3) and a long-term extension study *[see Clinical Studies (14.4)]*.

In the two induction studies (UC-1, UC-2) and a dose finding study (UC-4), 1097 patients were enrolled of whom 719 patients received RINVOQ 45 mg once daily.

In the maintenance study (UC-3), 746 patients were enrolled of whom 250 patients received RINVOQ 15 mg once daily and 251 patients received RINVOQ 30 mg once daily.

Adverse reactions reported in ≥2% of patients in any treatment arm in the induction and maintenance studies are shown in Tables 4 and 5, respectively.

**Table 4. Adverse Reactions Reported in ≥2% of Patients with Ulcerative Colitis Treated with RINVOQ 45 mg in Placebo-Controlled Induction Studies (UC-1, UC-2 and UC-4)**

| **Adverse Reaction** | **Placebo** | **RINVOQ 45 mg Once Daily** |
|---|---|---|
| | N= 378 (%) | N = 719 (%) |
| Upper respiratory tract infection* | 7 | 9 |
| Acne* | 1 | 6 |
| Increased blood creatine phosphokinase | 1 | 5 |
| Neutropenia* | <1 | 5 |
| Rash* | 1 | 4 |
| Elevated liver enzymes** | 2 | 3 |
| Lymphopenia* | 1 | 3 |
| Folliculitis | 1 | 2 |
| Herpes simplex* | <1 | 2 |
| * Composed of several similar terms<br>** Elevated liver enzymes composed of elevated ALT, AST, GGT, ALP, liver transaminases, hepatic enzymes, bilirubin, drug-induced liver injury and cholestasis. | | |

Other adverse reactions reported in less than 2% of patients in the RINVOQ 45 mg group and at a higher rate than in the placebo group through Week 8 included herpes zoster and pneumonia.

**Table 5. Adverse Reactions Reported in ≥2% of Patients with Ulcerative Colitis Treated with RINVOQ 15 mg or 30 mg in the Placebo-Controlled Maintenance Study (UC-3)[1]**

| **Adverse Reaction** | **Placebo** | **RINVOQ 15 mg Once Daily** | **RINVOQ 30 mg Once Daily** |
|---|---|---|---|
| | n = 245 (%) | n = 250 (%) | n = 251 (%) |
| Upper respiratory tract infection* | 18 | 16 | 20 |
| Increased blood creatine phosphokinase | 2 | 6 | 8 |
| Neutropenia* | 2 | 3 | 6 |
| Elevated liver enzymes** | 1 | 6 | 4 |

| Adverse Reaction | Placebo | RINVOQ 15 mg Once Daily | RINVOQ 30 mg Once Daily |
|---|---|---|---|
| | n = 245 (%) | n = 250 (%) | n = 251 (%) |
| Rash* | 4 | 5 | 5 |
| Herpes zoster | 0 | 4 | 4 |
| Folliculitis | 2 | 2 | 4 |
| Hypercholesterolemia* | 1 | 2 | 4 |
| Influenza | 1 | 3 | 3 |
| Herpes simplex* | 1 | 2 | 3 |
| Lymphopenia* | 2 | 3 | 2 |
| Hyperlipidemia* | 0 | 2 | 2 |
| [1] Patients who were responders to 8 weeks induction therapy with RINVOQ 45 mg once daily<br>* Composed of several similar terms<br>** Elevated liver enzymes composed of elevated ALT, AST, GGT, ALP, liver transaminases, hepatic enzymes, bilirubin, drug-induced liver injury, and cholestasis. | | | |

The safety profile of RINVOQ in the long-term extension study was similar to the safety profile observed in the placebo-controlled induction and maintenance periods.

Overall, the safety profile observed in patients with ulcerative colitis treated with RINVOQ was generally similar to the safety profile in patients with RA and AD.

*Specific Adverse Reactions*

*Serious Infections*

Induction Studies: In UC-1, UC-2, and UC-4, serious infections were reported in 5 patients (8.4 per 100 patient-years) treated with placebo and 9 patients (8.4 per 100 patient-years) treated with RINVOQ 45 mg through 8 weeks.

Placebo-controlled Maintenance Study: In UC-3, serious infections were reported in 8 patients (6.3 per 100 patient-years) treated with placebo, 8 patients (4.5 per 100 patient-years) treated with RINVOQ 15 mg, and 6 patients (3.1 per 100 patient-years) treated with RINVOQ 30 mg through 52 weeks.

*Laboratory Abnormalities*

*Hepatic Transaminase Elevations*

In studies UC-1, UC-2, and UC-4, elevations of ALT to ≥ 3 x ULN in at least one measurement were observed in 1.5% of patients treated with RINVOQ 45 mg, and 0% of patients treated with placebo for 8 weeks. AST elevations to ≥ 3 x ULN occurred in 1.5% of patients treated with RINVOQ 45 mg, and 0.3% of patients treated with placebo. Elevations of ALT to ≥ 5 x ULN occurred in 0.4% of patients treated with RINVOQ 45 mg and 0% of patients treated with placebo.

In UC-3, elevations of ALT to ≥ 3 x ULN in at least one measurement were observed in 4% of patients treated with RINVOQ 30 mg, 2% of patients treated with RINVOQ 15 mg, and 0.8% of patients treated with placebo for 52 weeks. Elevations of AST to ≥ 3 x ULN in at least one measurement were observed in 2% of patients treated with RINVOQ 30 mg, 1.6% of patients treated with RINVOQ 15 mg and 0.4% of patients treated with placebo. Elevations of ALT to ≥ 5 x ULN were observed in 0.8% of patients treated with 30 mg, 0.4% of patients treated with 15 mg, and 0.4% of patients treated with placebo.

Overall, laboratory abnormalities observed in patients with ulcerative colitis treated with RINVOQ were similar to those described in patients with RA.

## 7 DRUG INTERACTIONS

### 7.1 Strong CYP3A4 Inhibitors

Upadacitinib exposure is increased when RINVOQ is co-administered with a strong CYP3A4 inhibitor (such as ketoconazole and clarithromycin), which may increase the risk of RINVOQ adverse reactions *[see Clinical Pharmacology (12.3)]*. Monitor patients closely for adverse reactions when co-administering RINVOQ 15 mg once daily with strong CYP3A4 inhibitors.

For patients with atopic dermatitis, coadministration of RINVOQ 30 mg once daily with strong CYP3A4 inhibitors is not recommended.

For patients with ulcerative colitis taking strong CYP3A4 inhibitors, reduce the RINVOQ induction dosage to 30 mg once daily. The recommended maintenance dosage is 15 mg once daily *[see Dosage and Administration (2.8)]*.

### 7.2 Strong CYP3A4 Inducers

Upadacitinib exposure is decreased when RINVOQ is co-administered with strong CYP3A4 inducers (such as rifampin), which may lead to reduced therapeutic effect of RINVOQ *[see Clinical Pharmacology (12.3)]*. Coadministration of RINVOQ with strong CYP3A4 inducers is not recommended.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

Available data from the pharmacovigilance safety database and postmarketing case reports on use of RINVOQ in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects or miscarriage. Based on animal studies, RINVOQ has the potential to adversely affect a developing fetus. Advise patients of reproductive potential and pregnant patients of the potential risk to the fetus.

In animal embryo-fetal development studies, oral upadacitinib administration to pregnant rats and rabbits at exposures equal to or greater than approximately 1.6 and 15 times the 15 mg dose,

0.8 and 7.6 times the 30 mg dose, and 0.6 and 5.6 times the maximum recommended human dose (MRHD) of 45 mg (on an AUC basis) resulted in dose-related increases in skeletal malformations (rats only), an increased incidence of cardiovascular malformations (rabbits only), increased post-implantation loss (rabbits only), and decreased fetal body weights in both rats and rabbits. No developmental toxicity was observed in pregnant rats and rabbits treated with oral upadacitinib during organogenesis at exposures approximately 0.29 and 2.2 times the 15 mg dose, 0.15 times and 1.1 times the 30 mg dose, and at 0.11 and 0.82 times the MHRD (on an AUC basis). In a pre- and post-natal development study in pregnant female rats, oral upadacitinib administration at exposures approximately 3 times the 15 mg dose, 1.4 times the 30 mg dose, and the same as the MRHD (on an AUC basis) resulted in no maternal or developmental toxicity (*see Data)*.

The background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages are 2-4% and 15-20%, respectively.

Report pregnancies to the AbbVie Inc.'s Adverse Event reporting line at 1-888-633-9110, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Clinical Considerations

*Disease-Associated Maternal and/or Embryo/Fetal Risk*

Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis or ulcerative colitis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Data

*Animal Data*

In an oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 5, 25, and 75 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that consisted of misshapen humerus and bent scapula) at exposures equal to or greater than approximately 1.7 times the 15 mg dose, 0.9 times the 30 mg dose, and 0.6 times the MRHD (on an AUC basis at maternal oral doses of 5 mg/kg/day and higher). Additional skeletal malformations (bent forelimbs/hindlimbs and rib/vertebral defects) and decreased fetal body weights were observed in the absence of maternal toxicity at an exposure approximately 84 times the 15 mg dose, 43 times the 30 mg dose, and 31 times the MRHD (on an AUC basis at a maternal oral dose of 75 mg/kg/day).

In a second oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 1.5 and 4 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that included bent humerus and scapula) at exposures approximately 1.6 times the 15 mg dose, 0.8 times the 30 mg dose, and 0.6 times the MRHD (on an AUC basis at maternal oral doses of 4 mg/kg/day). No developmental toxicity was observed in rats at an exposure approximately 0.29 times the 15 mg dose, 0.15 times the 30 mg dose, and 0.11 times the MRHD (on an AUC basis at a maternal oral dose of 1.5 mg/kg/day).

In an oral embryo-fetal developmental study, pregnant rabbits received upadacitinib at doses of 2.5, 10, and 25 mg/kg/day during the period of organogenesis from gestation day 7 to 19. Embryolethality, decreased fetal body weights, and cardiovascular malformations were observed in the presence of maternal toxicity at an exposure approximately 15 times the 15 mg dose, 7.6 times the 30 mg dose, and 5.6 times the MRHD (on an AUC basis at a maternal oral dose of 25 mg/kg/day). Embryolethality consisted of increased post-implantation loss that was due to elevated incidences of both total and early resorptions. No developmental toxicity was observed in rabbits at an exposure approximately 2.2 times the 15 mg dose, 1.1 times the 30 mg dose, and 0.82 times the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

In an oral pre- and post-natal development study, pregnant female rats received upadacitinib at doses of 2.5, 5, and 10 mg/kg/day from gestation day 6 through lactation day 20. No maternal or developmental toxicity was observed in either mothers or offspring, respectively, at an exposure approximately 3 times the 15 mg dose, 1.4 times the 30 mg dose, and at approximately the same exposure as the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

### 8.2 Lactation

Risk Summary

There are no data on the presence of upadacitinib in human milk, the effects on the breastfed infant, or the effects on milk production. Available pharmacodynamic/toxicological data in animals have shown excretion of upadacitinib in milk *(see Data).* When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious adverse reactions in the breastfed infant, advise patients that breastfeeding is not recommended during treatment with RINVOQ, and for 6 days (approximately 10 half-lives) after the last dose.

Data

A single oral dose of 10 mg/kg radiolabeled upadacitinib was administered to lactating female Sprague-Dawley rats on post-partum days 7-8. Drug exposure was approximately 30-fold greater in milk than in maternal plasma based on $AUC_{0-t}$ values. Approximately 97% of drug-related material in milk was parent drug.

### 8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to starting treatment with RINVOQ *[see Use in Specific Populations (8.1)]*.

Contraception

*Females*

Based on animal studies, upadacitinib may cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to use effective contraception during treatment with RINVOQ and for 4 weeks after the final dose.

### 8.4 Pediatric Use

Juvenile Idiopathic Arthritis and Psoriatic Arthritis

The safety and effectiveness of RINVOQ in pediatric patients with juvenile idiopathic arthritis and psoriatic arthritis have not been established.

Atopic Dermatitis

The safety and effectiveness of RINVOQ in pediatric patients 12 years of age and older weighing at least 40 kg with atopic dermatitis have been established. A total of 344 pediatric patients aged 12 to 17 years with moderate to severe atopic dermatitis were randomized across three trials (AD-1, AD-2 and AD-3) to receive either RINVOQ 15 mg (N=114) or 30 mg (N=114) or matching placebo (N=116) in monotherapy or combination with topical corticosteroids. Efficacy was consistent between the pediatric patients and adults *[see Clinical Studies (14.3)]*. The adverse reaction profile in the pediatric patients was similar to the adults *[see Adverse Reactions (6.1)]*.

The safety and effectiveness of RINVOQ in pediatric patients less than 12 years of age with atopic dermatitis have not been established.

Ulcerative Colitis

The safety and effectiveness of RINVOQ in pediatric patients with ulcerative colitis have not been established.

### 8.5 Geriatric Use

Rheumatoid Arthritis and Psoriatic Arthritis

Of the 4381 patients treated in the five clinical studies, a total of 906 rheumatoid arthritis patients were 65 years of age or older, including 146 patients 75 years and older. Of the 1827 patients treated in the two psoriatic arthritis Phase 3 clinical studies, a total of 274 patients were 65 years of age or older, including 34 patients 75 years and older. No differences in effectiveness were observed between these patients and younger patients; however, there was a higher rate of overall adverse events, including serious infections, in patients 65 years of age and older.

Atopic Dermatitis

Of the 2583 patients treated in the three Phase 3 clinical trials, a total of 120 patients with atopic dermatitis were 65 years of age or older, including 6 patients 75 years of age. No differences in effectiveness were observed between these patients and younger patients; however, there was a higher rate of serious infections and malignancies in those patients 65 years of age or older in the 30 mg dosing group in the long-term trials.

Ulcerative Colitis

Of the 1097 patients treated in the controlled clinical trials, a total of 95 patients with ulcerative colitis were 65 years and older. Clinical studies of RINVOQ did not include sufficient numbers of patients 65 years of age and older with ulcerative colitis to determine whether they respond differently from younger adult patients.

### 8.6 Renal Impairment

For patients with rheumatoid arthritis and psoriatic arthritis, no dosage adjustment is needed in patients with mild (eGFR 60 to < 90 mL/min/1.73 $m^2$), moderate (eGFR 30 to < 60 mL/min/1.73 $m^2$), or severe renal impairment (eGFR 15 to < 30 mL/min/1.73 $m^2$).

For patients with atopic dermatitis, the maximum recommended dosage is 15 mg once daily for patients with severe renal impairment. No dosage adjustment is needed in patients with mild or moderate renal impairment.

For patients with ulcerative colitis, the recommended dosage for severe renal impairment is 30 mg once daily for induction and 15 mg once daily for maintenance. No dosage adjustment is needed in patients with mild or moderate renal impairment *[see Dosage and Administration (2.7)]*.

RINVOQ has not been studied in patients with end stage renal disease (eGFR <15 mL/min/1.73$m^2$). Use in patients with atopic dermatitis or ulcerative colitis with end stage renal disease is not recommended *[see Clinical Pharmacology (12.3)]*.

### 8.7 Hepatic Impairment

The use of RINVOQ has not been studied in patients with severe hepatic impairment (Child Pugh C), and therefore not recommended for use in patients with rheumatoid arthritis, psoriatic arthritis, atopic dermatitis or ulcerative colitis *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*.

For patients with rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, no dosage adjustment is needed in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment.

For patients with ulcerative colitis, the recommended dosage for mild to moderate hepatic impairment is 30 mg once daily for induction and 15 mg once daily for maintenance *[see Dosage and Administration (2.6)]*.

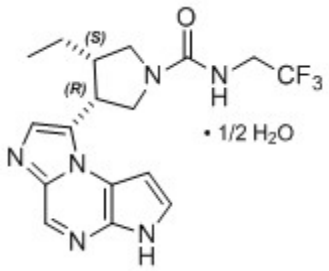
## 11 DESCRIPTION

RINVOQ is formulated with upadacitinib, a JAK inhibitor.

Upadacitinib has the following chemical name: (3*S*,4*R*)-3-Ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-*N*-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrate (2:1).

The strength of upadacitinib is based on anhydrous upadacitinib. The solubility of upadacitinib in water is 38 to less than 0.2 mg/mL across a pH range of 2 to 9 at 37 ºC.

Upadacitinib has a molecular weight of 389.38 g/mol and a molecular formula of $C_{17}H_{19}F_3N_6O$ • ½ $H_2O$. The chemical structure of upadacitinib is:




RINVOQ 15 mg extended-release tablets for oral administration are purple, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with ‘a15’ on one side. Each tablet contains the following inactive ingredients: colloidal silicon dioxide, ferrosoferric oxide, hypromellose, iron oxide red, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl alcohol, polyethylene glycol, talc, tartaric acid and titanium dioxide.

RINVOQ 30 mg extended-release tablets for oral administration are red, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with ‘a30’ on one side. Each tablet contains the following inactive ingredients: colloidal silicon dioxide, hypromellose, iron oxide red, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl alcohol, polyethylene glycol, talc, tartaric acid and titanium dioxide.

RINVOQ 45 mg extended-release tablets for oral administration are yellow to mottled yellow, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with ‘a45’ on one side. Each tablet contains the following inactive ingredients: colloidal silicon dioxide, hypromellose, iron oxide yellow, iron oxide red, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl alcohol, polyethylene glycol, talc, tartaric acid and titanium dioxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Upadacitinib is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs) which modulate intracellular activity including gene expression. Upadacitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs.

JAK enzymes transmit cytokine signaling through their pairing (e.g., JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, JAK2/JAK2, JAK2/TYK2). In a cell-free isolated enzyme assay, upadacitinib had greater inhibitory potency at JAK1 and JAK2 relative to JAK3 and TYK2. In human leukocyte cellular assays, upadacitinib inhibited cytokine-induced STAT phosphorylation mediated by JAK1 and JAK1/JAK3 more potently than JAK2/JAK2 mediated STAT phosphorylation. The relevance of inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known.

## 12.2 Pharmacodynamics

Inhibition of IL-6 Induced STAT3 and IL-7 Induced STAT5 Phosphorylation

In healthy volunteers, the administration of upadacitinib (immediate release formulation) resulted in a dose- and concentration-dependent inhibition of IL-6 (JAK1/JAK2)-induced STAT3 and IL-7 (JAK1/JAK3)-induced STAT5 phosphorylation in whole blood. The maximal inhibition was observed 1 hour after dosing which returned to near baseline by the end of dosing interval.

Lymphocytes

In patients with rheumatoid arthritis, treatment with upadacitinib was associated with a small, transient increase in mean ALC from baseline up to Week 36 which gradually returned to, at or near baseline levels with continued treatment.

Immunoglobulins

In patients with rheumatoid arthritis, small decreases from baseline in mean IgG and IgM levels were observed with upadacitinib treatment in the controlled period; however, the mean values at baseline and at all visits were within the normal reference range.

Cardiac Electrophysiology

At 2.5 times the mean exposure of the maximum therapeutic dose, 45 mg once daily dose, there was no clinically relevant effect on the QTc interval.

## 12.3 Pharmacokinetics

Upadacitinib plasma exposures are proportional to dose over the therapeutic dose range. After a single dose administration of RINVOQ 15 mg, 30 mg, and 45 mg under fasting condition in healthy subjects, mean $C_{max}$ was 31.6 ng/mL, 71.8 ng/mL, and 90.7 ng/mL, respectively, and mean $AUC_{inf}$ was 265 ng·h/mL, 543 ng·h/mL, and 752 ng·h/mL, respectively. Steady-state plasma concentrations are achieved within 4 days with minimal accumulation after once daily administration. Upadacitinib pharmacokinetics are comparable between rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, and ulcerative colitis patients.

Absorption

Following oral administration of upadacitinib extended-release formulation, upadacitinib is absorbed with a median $T_{max}$ of 2 to 4 hours.

Coadministration of upadacitinib with a high-fat/ high-calorie meal had no clinically relevant effect on upadacitinib exposures (increased $AUC_{inf}$ by 29% and $C_{max}$ by 39% to 60%). In clinical trials, upadacitinib was administered without regard to meals *[see Dosage and Administration (2.2)]*.

Distribution

Upadacitinib is 52% bound to plasma proteins. Upadacitinib partitions similarly between plasma and blood cellular components with a blood to plasma ratio of 1.0.

Elimination

*Metabolism*

Upadacitinib metabolism is mediated by mainly CYP3A4 with a potential minor contribution from CYP2D6. The pharmacologic activity of upadacitinib is attributed to the parent molecule. In a human radiolabeled study, unchanged upadacitinib accounted for 79% of the total radioactivity in plasma while the main metabolite detected (product of monooxidation followed by glucuronidation) accounted for 13% of the total plasma radioactivity. No active metabolites have been identified for upadacitinib.

*Excretion*

Following single dose administration of [$^{14}$C]-upadacitinib immediate-release solution, upadacitinib was eliminated predominantly as the unchanged parent drug in urine (24%) and feces (38%). Approximately 34% of upadacitinib dose was excreted as metabolites. Upadacitinib mean terminal elimination half-life ranged from 8 to 14 hours.

Specific Populations

*Body Weight, Gender, and Race*

Body weight, gender, race, and ethnicity did not have a clinically meaningful effect on upadacitinib exposure *[see Use in Specific Populations (8.5)]*.

*Pediatric Patients*

No meaningful difference in the systemic exposure of upadacitinib was observed in pediatric patients with atopic dermatitis 12 years of age and older weighing at least 40 kg compared to adults.

*Geriatric Patients*

No clinically meaningful differences in the pharmacokinetics of upadacitinib were observed in geriatric patients (≥ 65 years of age) compared to younger adult patients.

*Patients with Renal Impairment*

Upadacitinib mean $AUC_{inf}$ after a single dose administration of 15 mg upadacitinib was 18%, 33%, and 44% higher in patients with mild (eGFR 60 to < 90 mL/min/1.73 $m^2$), moderate (eGFR 30 to < 60 mL/min/1.73 $m^2$), and severe renal impairment (eGFR 15 to < 30 mL/min/1.73 $m^2$), respectively, compared to subjects with normal renal function (eGFR ≥ 90 mL/min/1.73 $m^2$). Upadacitinib mean $C_{max}$ was similar among subjects with normal and impaired renal function. In patients receiving 15 mg, 30 mg, or 45 mg once daily upadacitinib, mild and moderate renal impairment is not expected to have a clinically relevant effect on upadacitinib exposure *[see Dosage and Administration (2.7) and Use in Specific Populations (8.6)]*.

*Patients with Hepatic Impairment*

Upadacitinib mean $AUC_{inf}$ after a single dose administration of 15 mg upadacitinib was 28% and 24% higher in patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment, respectively, compared to subjects with normal liver function. Upadacitinib mean $C_{max}$ was unchanged in patients with mild hepatic impairment and 43% higher in patients with moderate hepatic impairment compared to subjects with normal liver function. Upadacitinib was

not studied in patients with severe hepatic impairment (Child-Pugh C) *[see Dosage and Administration (2.7) and Use in Specific Populations (8.7)]*.

Drug Interaction Studies

*Potential for Other Drugs to Influence the Pharmacokinetics of Upadacitinib*

Upadacitinib is metabolized *in vitro* by CYP3A4 with a minor contribution from CYP2D6. The effect of co-administered drugs on upadacitinib plasma exposures is provided in Table 6 *[see Drug Interactions (7)]*.

**Table 6: Change in Pharmacokinetics of Upadacitinib in the Presence of Co-administered Drugs**

| Co-administered Drug | Regimen of Co-administered Drug | Ratio (90% CI)[a] | |
|---|---|---|---|
| | | $C_{max}$ | AUC |
| Methotrexate | 10 to 25 mg/week | 0.97 (0.86-1.09) | 0.99 (0.93- 1.06) |
| Strong CYP3A4 inhibitor: Ketoconazole | 400 mg once daily x 6 days | 1.70 (1.55-1.89) | 1.75 (1.62-1.88) |
| Strong CYP3A4 inducer: Rifampin | 600 mg once daily x 9 days | 0.49 (0.44-0.55) | 0.39 (0.37-0.42) |
| OATP1B inhibitor: Rifampin | 600 mg single dose | 1.14 (1.02-1.28) | 1.07 (1.01-1.14) |

CI: Confidence interval
[a] Ratios for $C_{max}$ and AUC compare co-administration of the medication with upadacitinib vs. administration of upadacitinib alone.

pH modifying medications (e.g., antacids or proton pump inhibitors) are not expected to affect upadacitinib plasma exposures based on *in vitro* assessments and population pharmacokinetic analyses. CYP2D6 metabolic phenotype had no effect on upadacitinib pharmacokinetics (based on population pharmacokinetic analyses), indicating that inhibitors of CYP2D6 have no clinically relevant effect on upadacitinib exposures.

*Potential for Upadacitinib to Influence the Pharmacokinetics of Other Drugs*

*In vitro* studies indicate that upadacitinib does not inhibit the activity of cytochrome P450 (CYP) enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at clinically relevant concentrations. *In vitro* studies indicate that upadacitinib induces CYP3A4 but does not induce CYP2B6 or CYP1A2 at clinically relevant concentrations. *In vitro* studies indicate that upadacitinib does not inhibit the transporters P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, and MATE2K at clinically relevant concentrations.

Clinical studies indicate that upadacitinib has no clinically relevant effects on the pharmacokinetics of co-administered drugs. Following upadacitinib 30 mg and 45 mg once daily, the effects on each CYP enzymes (CYP1A2, CYP3A, CYP2C9, and CYP2C19) were similar between two doses except for the effect on CYP2D6. Following upadacitinib 30 mg and 45 mg once daily, a weak induction of CYP3A4 was observed. A weak inhibition of CYP2D6 was

observed at upadacitinib 45 mg but not at 30 mg. Summary of results from clinical studies which evaluated the effect of upadacitinib on other drugs is provided in Table 7.

**Table 7: Change in Pharmacokinetics of Co-administered Drugs or In Vivo Markers of CYP Activity in the Presence of Upadacitinib**

| Co-administered Drug or CYP Activity Marker | Multiple-Dose Regimen of Upadacitinib | Ratio (90% CI)[a] | |
|---|---|---|---|
| | | $C_{max}$ | AUC |
| Methotrexate | 6 mg to 24 mg BID[b] | 1.03 (0.86-1.23) | 1.14 (0.91-1.43) |
| Sensitive CYP1A2 Substrate: Caffeine | 45 mg QD[c] | 1.05 (0.97-1.14) | 1.04 (0.95-1.13) |
| Sensitive CYP3A Substrate: Midazolam | 30 mg QD[c] | 0.74 (0.68-0.80) | 0.74 (0.68-0.80) |
| Sensitive CYP3A Substrate: Midazolam | 45 mg QD[c] | 0.75 (0.69 -0.83) | 0.76 (0.69 -0.83) |
| Sensitive CYP2D6 Substrate: Dextromethorphan | 30 mg QD[c] | 1.09 (0.98-1.21) | 1.07 (0.95-1.22) |
| Sensitive CYP2D6 Substrate: Dextromethorphan | 45 mg QD[c] | 1.30 (1.13-1.50) | 1.35 (1.18-1.54) |
| Sensitive CYP2C9 Substrate: S-Warfarin | 45 mg QD[c] | 1.18 (1.05-1.33) | 1.12 (1.05-1.20) |
| Sensitive CYP2C19 Marker: 5-OH Omeprazole to Omeprazole metabolic ratio | 45 mg QD[c] | -- | 0.96 (0.90-1.02) |
| CYP2B6 Substrate: Bupropion | 30 mg QD[c] | 0.87 (0.79-0.96) | 0.92 (0.87-0.98) |
| Rosuvastatin | 30 mg QD[c] | 0.77 (0.63-0.94) | 0.67 (0.56-0.82) |
| Atorvastatin | 30 mg QD[c] | 0.88 (0.79-0.97) | 0.77 (0.70-0.85) |
| Ethinylestradiol | 30 mg QD[c] | 0.96 (0.89-1.02) | 1.11 (1.04-1.19) |
| Levonorgestrel | 30 mg QD[c] | 0.96 (0.87-1.06) | 0.96 (0.85-1.07) |

CYP: cytochrome P450; CI: Confidence interval; BID: twice daily; QD: once daily
[a] Ratios for $C_{max}$ and AUC compare co-administration of the medication with upadacitinib vs. administration of medication alone.
[b] Immediate-release formulation
[c] Extended-release formulation

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of upadacitinib was evaluated in Sprague-Dawley rats and Tg.rasH2 mice. No evidence of tumorigenicity was observed in male or female rats that received upadacitinib for up to 101 weeks at oral doses up to 15 or 20 mg/kg/day, respectively (approximately 4 and 10 times the 15 mg dose, 2 and 5 times the 30 mg dose, and 1.6 and 4 times the maximum recommended human dose (MRHD) of 45 mg on an AUC basis, respectively). No evidence of tumorigenicity was observed in male or female Tg.rasH2 mice that received upadacitinib for 26 weeks at oral doses up to 20 mg/kg/day.

Mutagenesis

Upadacitinib tested negatively in the following genotoxicity assays: the *in vitro* bacterial mutagenicity assay (Ames assay), *in vitro* chromosome aberration assay in human peripheral blood lymphocytes, and *in vivo* rat bone marrow micronucleus assay.

Impairment of Fertility

Upadacitinib had no effect on fertility in male or female rats at oral doses up to 50 mg/kg/day in males and 75 mg/kg/day in females (approximately 42 and 84 times the 15 mg dose, 22 and 43 times the 30 mg dose, and 16 and 31 times the MRHD, respectively, on an AUC basis). However, maintenance of pregnancy was adversely affected at oral doses of 25 mg/kg/day and 75 mg/kg/day based upon dose-related findings of increased post-implantation losses (increased resorptions) and decreased numbers of mean viable embryos per litter (approximately 22 and 84 times the 15 mg dose, 11 and 43 times the 30 mg dose, and 8 and 31 times the MHRD on an AUC basis, respectively). The number of viable embryos was unaffected in female rats that received upadacitinib at an oral dose of 5 mg/kg/day and were mated to males that received the same dose (approximately 2 times the 15 mg dose, 0.9 times the 30 mg dose, and at 0.6 times the MRHD on an AUC basis).

## 14 CLINICAL STUDIES

### 14.1 Rheumatoid Arthritis

The efficacy and safety of RINVOQ 15 mg once daily were assessed in five Phase 3 randomized, double-blind, multicenter trials in patients with moderately to severely active rheumatoid arthritis and fulfilling the ACR/EULAR 2010 classification criteria. Patients 18 years of age and older were eligible to participate. The presence of at least 6 tender and 6 swollen joints and evidence of systemic inflammation based on elevation of hsCRP was required at baseline. Although other doses have been studied, the recommended dosage of RINVOQ is 15 mg once daily.

Trial RA-I (NCT02706873) was a 24-week monotherapy trial in 947 patients with moderately to severely active rheumatoid arthritis who were naïve to methotrexate (MTX). Patients received RINVOQ 15 mg or upadacitinib 30 mg orally once daily or MTX as monotherapy. At Week 26, non-responding patients on upadacitinib could be rescued with the addition of MTX, while patients on MTX could be rescued with the addition of blinded RINVOQ 15 mg or upadacitinib

30 mg once daily. The primary endpoint was the proportion of patients who achieved an ACR50 response at Week 12. Key secondary endpoints included disease activity score (DAS28-CRP) ≤3.2 at Week 12, DAS28-CRP <2.6 at Week 24, change from baseline in HAQ-DI at Week 12, and change from baseline in van der Heijde-modified total Sharp Score (mTSS) at Week 24.

Trial RA-II (NCT02706951) was a 14-week monotherapy trial in 648 patients with moderately to severely active rheumatoid arthritis who had an inadequate response to MTX. Patients received RINVOQ 15 mg or upadacitinib 30 mg once daily monotherapy or continued their stable dose of MTX monotherapy. At Week 14, patients who were randomized to MTX were advanced to RINVOQ 15 mg or upadacitinib 30 mg once daily monotherapy in a blinded manner based on pre-determined assignment at baseline. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 14. Key secondary endpoints included DAS28-CRP ≤3.2, DAS28-CRP <2.6, and change from baseline in HAQ-DI at Week 14.

Trial RA-III (NCT02675426) was a 12-week trial in 661 patients with moderately to severely active rheumatoid arthritis who had an inadequate response to conventional disease modifying anti-rheumatic drugs (cDMARDs). Patients received RINVOQ 15 mg or upadacitinib 30 mg once daily or placebo added to background cDMARD therapy. At Week 12, patients who were randomized to placebo were advanced to RINVOQ 15 mg or upadacitinib 30 mg once daily in a blinded manner based on pre-determined assignment at baseline. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12. Key secondary endpoints included DAS28-CRP ≤3.2, DAS28-CRP<2.6, and change from baseline in HAQ-DI at Week 12.

Trial RA-IV (NCT02629159) was a 48-week trial in 1629 patients with moderately to severely active rheumatoid arthritis who had an inadequate response to MTX. Patients received RINVOQ 15 mg once daily, active comparator, or placebo added to background MTX. From Week 14, non-responding patients on RINVOQ 15 mg could be rescued to active comparator in a blinded manner, and non-responding patients on active comparator or placebo could be rescued to RINVOQ 15 mg in a blinded manner. At Week 26, all patients randomized to placebo were switched to RINVOQ 15 mg once daily in a blinded manner. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12 versus placebo. Key secondary endpoints versus placebo included DAS28-CRP ≤3.2, DAS28-CRP <2.6, change from baseline in HAQ-DI at Week 12, and change from baseline in mTSS at Week 26.

Trial RA-V (NCT02706847) was a 12-week trial in 499 patients with moderately to severely active rheumatoid arthritis who had an inadequate response or intolerance to biologic DMARDs. Patients received RINVOQ 15 mg or upadacitinib 30 mg once daily or placebo added to background cDMARD therapy. At Week 12, patients who were randomized to placebo were advanced to RINVOQ 15 mg or upadacitinib 30 mg once daily in a blinded manner based on pre-determined assignment at baseline. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12. Key secondary endpoints included DAS28-CRP ≤3.2 and change from baseline in HAQ-DI at Week 12.

Clinical Response

The percentages of RINVOQ-treated patients achieving ACR20, ACR50, and ACR70 responses, and DAS28(CRP) < 2.6 in all trials are shown in Table 8.

Patients treated with RINVOQ 15 mg, alone or in combination with cDMARDs, achieved higher ACR response rates compared to MTX monotherapy or placebo, respectively, at the primary efficacy timepoint (Table 8).

In Trial IV, the percent of patients achieving ACR20 response by visit is shown in Figure 1.

In Trials RA-III and RA-V, higher ACR20 response rates were observed at 1 week with RINVOQ 15 mg versus placebo.

Treatment with RINVOQ 15 mg, alone or in combination with cDMARDs, resulted in greater improvements in the ACR components compared to MTX or placebo at the primary efficacy timepoint (Table 9).

**Table 8: Clinical Response in RA Patients in Trials RA-I, RA-II, RA-III, RA-IV and RA V**

| | **Trial RA-I MTX-Naïve** | | **Trial RA-II MTX-IR** | | **Trial RA-III cDMARD-IR** | | **Trial RA-IV MTX-IR** | | **Trial RA-V bDMARD-IR** | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Monotherapy | | Monotherapy | | Background cDMARDs | | Background MTX | | Background cDMARDs | |
| | MTX | RINVOQ 15 mg % Δ (95% CI) | MTX | RINVOQ 15 mg % Δ (95% CI) | PBO | RINVOQ 15 mg % Δ (95% CI) | PBO | RINVOQ 15 mg % Δ (95% CI) | PBO | RINVOQ 15 mg % Δ (95% CI) |
| N | 314 | 317 | 216 | 217 | 221 | 221 | 651 | 651 | 169 | 164 |
| Week | | | | | | | | | | |
| **ACR20** | | | | | | | | | | |
| 12[a]/14[b] | 54 | 76<br>22 (14, 29) | 41 | 68<br>26 (17, 36) | 36 | 64<br>28 (19, 37) | 36 | 71<br>34 (29, 39) | 28 | 65<br>36 (26, 46) |
| 24[c]/26[d] | 59 | 79<br>20 (13, 27) | | | | | 36 | 67<br>32 (27, 37) | | |
| **ACR50** | | | | | | | | | | |
| 12[a]/14[b] | 28 | 52<br>24 (16, 31) | 15 | 42<br>27 (18, 35) | 15 | 38<br>23 (15, 31) | 15 | 45<br>30 (26, 35) | 12 | 34<br>22 (14, 31) |
| 24[c]/26[d] | 33 | 60<br>27 (19, 34) | | | | | 21 | 54<br>33 (28, 38) | | |
| **ACR70** | | | | | | | | | | |
| 12[a]/14[b] | 14 | 32<br>18 (12, 25) | 3 | 23<br>20 (14, 26) | 6 | 21<br>15 (9, 21) | 5 | 25<br>20 (16, 24) | 7 | 12<br>5 (-1, 11) |
| 24[c]/26[d] | 18 | 44<br>26 (19, 33) | | | | | 10 | 35<br>25 (21, 29) | | |
| **DAS28-CRP <2.6** | | | | | | | | | | |
| 12[a]/14[b] | 14 | 36<br>22 (15, 28) | 8 | 28<br>20 (13, 27) | 10 | 31<br>21 (14, 28) | 6 | 29<br>23 (19, 27) | 9 | 29<br>19 (11, 27) |
| 24[c]/26[d] | 18 | 48<br>30 (23, 37) | | | | | 9 | 41<br>32 (27, 36) | | |

Abbreviations: ACR20 (or 50 or 70) = American College of Rheumatology ≥20% (or ≥50% or ≥70%) improvement; bDMARD = biologic disease-modifying anti-rheumatic drug; CRP = c-

Serious Infections

Inform patients that they may be more likely to develop infections when taking RINVOQ. Instruct patients to contact their healthcare provider immediately during treatment if they develop any signs or symptoms of an infection *[see Warnings and Precautions (5.1)]*.

Advise patients that the risk of herpes zoster is increased in patients taking RINVOQ and in some cases can be serious *[see Warnings and Precautions (5.1)]*.

Malignancies

Inform patients that RINVOQ may increase their risk of certain cancers and that periodic skin examinations should be performed while using RINVOQ.

Advise patients that exposure to sunlight and UV light should be limited by wearing protective clothing and using a broad-spectrum sunscreen *[see Warnings and Precautions (5.3)]*.

Major Adverse Cardiovascular Events

Inform patients that RINVOQ may increase their risk of major adverse cardiovascular events (MACE) including myocardial infarction, stroke, and cardiovascular death. Instruct all patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events *[see Warnings and Precautions (5.4)]*.

Thrombosis

Inform patients that events of deep venous thrombosis and pulmonary embolism have been reported in clinical trials with RINVOQ. Instruct patients to seek immediate medical attention if they develop any signs or symptoms of a DVT or PE *[see Warnings and Precautions (5.5)]*.

Hypersensitivity Reactions

Advise patients to discontinue RINVOQ and seek immediate medical attention if they develop any signs and symptoms of allergic reactions *[see Warnings and Precautions (5.6)]*.

Gastrointestinal Perforations

Inform patients that gastrointestinal perforations have been reported in clinical trials with RINVOQ and that risk factors include the use of NSAIDS or history of diverticulitis. Instruct patients to seek medical care immediately if they experience new onset of abdominal pain, fever, chills, nausea, or vomiting *[see Warnings and Precautions (5.7)]*.

Retinal Detachment

Inform patients that retinal detachment has been reported in clinical trials with RINVOQ. Advise patients to immediately inform their healthcare provider if they develop any sudden changes in vision while receiving RINVOQ *[see Adverse Reactions (6.1)]*.

Laboratory Abnormalities

Inform patients that RINVOQ may affect certain lab tests, and that blood tests are required before and during RINVOQ treatment *[see Warnings and Precautions (5.8)]*.

Vaccinations

Advise patients to avoid use of live vaccines with RINVOQ. Instruct patients to inform their healthcare practitioner that they are taking RINVOQ prior to a potential vaccination *[see Warnings and Precautions (5.10)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential that exposure to RINVOQ during pregnancy may result in fetal harm. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.1)]*.

Advise females of reproductive potential that effective contraception should be used during treatment and for 4 weeks following the final dose of upadacitinib *[see Use in Specific Populations (8.3)]*.

Advise females patients who are exposed to RINVOQ during pregnancy to contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Lactation

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

Administration

Advise patients not to chew, crush, or split RINVOQ tablets *[see Dosage and Administration (2.2)]*.

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