PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrRINVOQ®

Upadacitinib extended-release tablets

Extended-release tablets, 15 mg upadacitinib, oral

Selective immunosuppressant

AbbVie Corporation

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RECENT MAJOR LABEL CHANGES

1 Indications	06/2021
1.2 Indications, Geriatrics	06/2021
4.1 Dosage and Administration, Dosing Considerations	06/2021
4.2 Dosage and Administration, Recommended Dose and Dosage Adjustment	06/2021
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Rheumatoid Arthritis

RINVOQ (upadacitinib) is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate.

RINVOQ may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).

Psoriatic Arthritis

RINVOQ is indicated for the treatment of adults with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other DMARDs.

RINVOQ may be used as monotherapy or in combination with methotrexate.

Limitations of Use: RINVOQ should not be used in combination with other Janus kinase (JAK) inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine (see **7 WARNINGS AND PRECAUTIONS**).

1.1 Pediatrics

The safety and efficacy of RINVOQ in children and adolescents aged 0 to less than 18 years have not been established. No data are available, therefore, RINVOQ should not be used in this pediatric patient population (see **4.2 Recommended Dose and Dosage Adjustment**, **7.1.3 Pediatrics**, and **10.3 Pharmacokinetics**).

1.2 Geriatrics

Caution should be used when treating geriatric patients with RINVOQ. There are limited data in patients 75 years of age and older. In clinical studies of patients treated with RINVOQ, there was an increased incidence of adverse events, including serious infections, in patients 65 years of age and older (see **4.2 Recommended Dose and Dosage Adjustment**, **7.1.4 Geriatrics**, and **10.3 Pharmacokinetics**).

2 CONTRAINDICATIONS

RINVOQ is contraindicated in patients who are hypersensitive to upadacitinib or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see the **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** section.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

SERIOUS INFECTIONS

Patients treated with RINVOQ are at increased risk for developing serious infections that may lead to hospitalization or death (see **7 WARNINGS AND PRECAUTIONS** and **8.2 Clinical Trial Adverse Reactions**). 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.

Treatment with RINVOQ should not be initiated in patients with active infections including chronic or localized infections.

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 **7 WARNINGS AND PRECAUTIONS**).

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with RINVOQ (see **7 WARNINGS AND PRECAUTIONS**).

THROMBOSIS

Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated with Janus kinase inhibitors, including RINVOQ, for inflammatory conditions. Many of these adverse events were serious and some resulted in death. Consider the risks and benefits prior to treating patients who may be at increased risk. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately (see **7 WARNINGS AND PRECAUTIONS**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- RINVOQ should not be initiated in patients with active infections including chronic or localized infections (see **7 WARNINGS AND PRECAUTIONS**).

- RINVOQ should not be initiated in patients with an absolute lymphocyte count (ALC) less than 500 cells/mm^3, absolute neutrophil count (ANC) less than 1000 cells/mm^3, or hemoglobin level less than 8 g/dL (see **7 WARNINGS AND PRECAUTIONS**).

- RINVOQ should not be initiated in patients with severe hepatic impairment (Child-Pugh C) (see **10.3 Pharmacokinetics**).

- RINVOQ should not be used concomitantly with other potent immunosuppressants. Concomitant use of RINVOQ with other potent immunosuppressants (such as azathioprine, cyclosporine, tacrolimus), biologic DMARDs, or other JAK inhibitors has not been evaluated in clinical studies. There is a risk of additive immunosuppression when RINVOQ is co-administered with potent immunosuppressant drugs (see **7 WARNINGS AND PRECAUTIONS** and **9.4 Drug-Drug Interactions**).

- RINVOQ should be used with caution in patients receiving chronic treatment with strong CYP3A inhibitors. Upadacitinib exposure is increased when co-administered with strong CYP3A inhibitors (such as ketoconazole) (see **9.2 Drug interactions Overview**).

- Co-administration of RINVOQ with strong CYP3A4 inducers is not recommended. Upadacitinib exposure is decreased when co-administered with strong CYP3A inducers (such as rifampin), which may lead to reduced therapeutic effect of RINVOQ (see **7 WARNINGS AND PRECAUTIONS** and **9.2 Drug interactions Overview**).

4.2 Recommended Dose and Dosage Adjustment

The recommended oral dose of RINVOQ is 15 mg once daily.

Dose Interruption

RINVOQ treatment should be interrupted if a patient develops a serious infection until the infection is controlled (see **7 WARNINGS AND PRECAUTIONS**).

RINVOQ treatment should be interrupted for management of laboratory abnormalities as described in Table 1.

Table 1. Recommended Dose Interruptions for Laboratory Abnormalities

Laboratory measure	Action
Absolute Neutrophil Count (ANC)	Treatment should be interrupted if ANC is less than 1000 cells/mm^3 and may be restarted once ANC returns above this value
Absolute Lymphocyte Count (ALC)	Treatment should be interrupted if ALC is less than 500 cells/mm^3 and may be restarted once ALC returns above this value
Hemoglobin (Hb)	Treatment should be interrupted if Hb is less than 8 g/dL and may be restarted once Hb returns above this value
Hepatic transaminases	Treatment should be temporarily interrupted if drug-induced liver injury is suspected

Dosing in special populations

Pediatrics (<18 years of age): Health Canada has not authorized an indication for pediatric use of RINVOQ. No data are available regarding the safety and efficacy of RINVOQ in children and adolescents aged 0 to less than 18 years. Therefore, RINVOQ should not be used in this pediatric patient population (see **1.1 Pediatrics**, **7.1.3 Pediatrics**, and **10.3 Pharmacokinetics**).

Geriatric (≥65 years of age): No dose adjustment is required in patients aged 65 years and older (see **7.1.4 Geriatrics** and **10.3 Pharmacokinetics**).

Hepatic Impairment: RINVOQ should not be used in patients with severe hepatic impairment (Child Pugh C). The use of RINVOQ has not been studied in patients with severe hepatic impairment. No dose adjustment is required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment (see **10.3 Pharmacokinetics**).

Renal Impairment: No dose adjustment is required in patients with mild, moderate, or severe renal impairment. The use of RINVOQ has not been studied in subjects with end stage renal disease (see **10.3 Pharmacokinetics**).

4.3 Reconstitution

No reconstitution required.

4.4 Administration

RINVOQ is to be taken orally once daily with or without food and may be taken at any time of the day. RINVOQ tablets should be swallowed whole. RINVOQ should not be split, crushed, or chewed.

Rheumatoid Arthritis

RINVOQ may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).

Psoriatic Arthritis

RINVOQ may be used as monotherapy or in combination with methotrexate.

4.5 Missed Dose

If a dose of RINVOQ is missed, it should be taken as soon as possible. The subsequent dose should be taken at the regularly scheduled time.

5 OVERDOSAGE

Upadacitinib was administered in clinical trials up to doses equivalent in daily AUC (area under the curve) to 60 mg extended-release once daily. Adverse events were comparable to those seen at lower doses and no specific toxicities were identified. Approximately 90% of upadacitinib in the systemic circulation is eliminated within 24 hours of dosing (within the range of doses evaluated in clinical studies). In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	extended-release tablet/ 15 mg/upadacitinib	colloidal silicon dioxide, ferrosoferric oxide (E172), hypromellose, iron oxide red (E172), magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, tartaric acid, and titanium dioxide.

RINVOQ 15 mg extended-release tablets are purple, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with 'a15' on one side. The tablets are provided in bottles. Each bottle contains 30 tablets.

The tablets do not contain gluten.

7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

Carcinogenesis and Mutagenesis

Malignancies were observed in clinical studies of RINVOQ (see **8.2 Clinical Trial Adverse Reactions**). Consider the risks and benefits of RINVOQ treatment prior to initiating therapy in patients with a known

malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing RINVOQ in patients who develop a malignancy.

Non-Melanoma Skin Cancer (NMSC)

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

Cardiovascular

Thrombosis: Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated for inflammatory conditions with JAK inhibitors, including RINVOQ (see **8.2 Clinical Trial Adverse Reactions**). Many of these adverse events were serious and some resulted in death.

Consider the risks and benefits of RINVOQ treatment prior to treating patients who may be at increased risk of thrombosis. If symptoms of thrombosis occur, RINVOQ treatment should be discontinued and patients should be evaluated promptly and treated appropriately.

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 **8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**). 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.

Assessment of lipid parameters should be performed at baseline, 12 weeks after initiation of RINVOQ treatment and thereafter according to the clinical guidelines for hyperlipidemia. Manage patients according to clinical guidelines for the management of hyperlipidemia (see **7 WARNINGS AND PRECAUTIONS**).

Gastrointestinal

Gastrointestinal Perforations: Events of gastrointestinal perforation have been reported in clinical studies with RINVOQ (see **8.2 Clinical Trial Adverse Reactions**), although the role of JAK inhibition in these events is not known. In these studies, many patients with rheumatoid arthritis were receiving background therapy with nonsteroidal anti-inflammatory drugs (NSAIDs).

RINVOQ should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis or taking concomitant NSAIDs and/or corticosteroids). Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Hematologic

Anemia: Decreases in hemoglobin levels to less than 8 g/dL were reported in RINVOQ clinical studies (see **8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**). Evaluate hemoglobin prior to initiation of RINVOQ and thereafter according to routine patient management. Do not initiate RINVOQ treatment, and interrupt RINVOQ treatment in patients with a low hemoglobin level (i.e., less than 8 g/dL) (see **4.1 Dosing Consideration**, **4.2 Recommended Dose and Dosage Adjustment** and **7 WARNINGS AND PRECAUTIONS**).

Lymphopenia: Absolute Lymphocyte Counts (ALC) less than 500 cells/mm^3 were reported in RINVOQ clinical studies (see **8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**). Evaluate lymphocyte counts prior to initiation of RINVOQ and thereafter according to routine patient management. Do not initiate RINVOQ treatment, and interrupt RINVOQ treatment in patients with a low lymphocyte count (i.e., less than 500 cells/mm^3) (see **4.1 Dosing Consideration**, **4.2 Recommended Dose and Dosage Adjustment** and **7 WARNINGS AND PRECAUTIONS,**).

Neutropenia: Treatment with RINVOQ was associated with an increased incidence of neutropenia (ANC less than 1000 cells/mm^3) (see **8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**). Evaluate neutrophil counts prior to initiating RINVOQ and thereafter according to routine patient management. Do not initiate RINVOQ treatment, and interrupt RINVOQ treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/mm^3) (see **4.1 Dosing Consideration**, **4.2 Recommended Dose and Dosage Adjustment** and **7 WARNINGS AND PRECAUTIONS**).

Hepatic/Biliary/Pancreatic

Treatment with RINVOQ was associated with an increased incidence of liver enzyme elevation compared to placebo (see **8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**). Increases to ≥3X the upper limit of normal (ULN) for both alanine transaminase (ALT) and aspartate transaminase (AST) were the more frequently reported, but increases to ≥5X and ≥10X ULN were also observed in patients treated with RINVOQ in clinical trials. Unconfirmed drug induced liver injury (DILI) was observed in four patients receiving upadacitinib in clinical trials, including 2 patients receiving RINVOQ. Upadacitinib was discontinued in 3 cases and was continued without interruption in one patient receiving RINVOQ.

Liver enzymes should be evaluated before initiating RINVOQ treatment and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of DILI. If increases in ALT or AST are observed during routine patient management and DILI is suspected, RINVOQ should be interrupted until this diagnosis is excluded (see **4.2 Recommended Dose and Dosage Adjustment** and **7 WARNINGS AND PRECAUTIONS**).

Although patients with active hepatitis B or C infection were excluded from clinical trials, cases of hepatitis B virus reactivation were still reported in patients enrolled in the clinical studies of RINVOQ. Screening for viral hepatitis and monitoring for reactivation should be performed in accordance with clinical guidelines before starting and during therapy with RINVOQ. If hepatitis B virus DNA is detected while receiving RINVOQ, a liver specialist should be consulted (see **7 WARNINGS AND PRECAUTIONS**).

The use of RINVOQ has not been studied in patients with severe hepatic impairment and therefore, RINVOQ should not be used in these patients (see **4.2 Recommended Dose and Dosage Adjustment** and **10.3 Pharmacokinetics**).

Immune

RINVOQ should not be used concomitantly with other potent immunosuppressants. Concomitant use of RINVOQ with other potent immunosuppressants (such as azathioprine, cyclosporine, tacrolimus), biologic DMARDs, or other JAK inhibitors has not been evaluated in clinical studies. There is a risk of additive immunosuppression when RINVOQ is co-administered with potent immunosuppressant drugs (see **4.1 Dosing Consideration** and **9.2 Drug Interactions Overview**).

Immunizations

No data are available on the response to vaccination with live or inactivated vaccines in patients receiving RINVOQ. Live or attenuated vaccines should not be used immediately prior to or during RINVOQ therapy. Prior to initiating RINVOQ treatment, patients should be brought up to date with all immunizations, including prophylactic zoster vaccinations, in agreement with current immunization guidelines. The interval between live vaccinations and initiation of RINVOQ therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

Infections

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 **8.2 Clinical Trial Adverse Reactions**). Among opportunistic infections, tuberculosis, multidermatomal herpes zoster, oral/esophageal candidiasis, and cryptococcosis were reported with RINVOQ.

RINVOQ should not be initiated in patients with active infections including chronic or 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. Do not resume RINVOQ treatment until the infection is controlled.

Tuberculosis: Patients should be screened for tuberculosis (TB) before starting RINVOQ therapy. RINVOQ should not be given to patients with active TB. Anti-TB therapy should be considered 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.

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 studies with RINVOQ (see **8.2 Clinical Trial**

Adverse Reactions). 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 studies. Patients who were positive for hepatitis B surface antigen or hepatitis B virus DNA were excluded from clinical studies. However, cases of hepatitis B reactivation were still reported in patients enrolled in the clinical studies of RINVOQ. If hepatitis B virus DNA is detected while receiving RINVOQ, a liver specialist should be consulted.

Monitoring and Laboratory Tests

Hematology: Lymphocyte counts, neutrophil counts, and hemoglobin should be evaluated before initiating RINVOQ treatment and thereafter according to routine patient management. Treatment should not be initiated and should be interrupted in patients with low lymphocyte count (ALC less than 500 cells/mm^3), low neutrophil count (ANC less than 1000 cells/mm^3), or low hemoglobin level (less than 8 g/dL) (see **4.1 Dosing Consideration**, **4.2 Recommended Dose and Dosage Adjustment** and **7 WARNINGS AND PRECAUTIONS**).

Lipids: Assessment of lipid parameters should be performed at baseline, 12 weeks after initiation of RINVOQ treatment and thereafter according to the clinical guidelines for hyperlipidemia. Patients should be managed according to clinical guidelines for the management of hyperlipidemia (see **7 WARNINGS AND PRECAUTIONS**).

Liver Enzyme Elevations: Liver enzymes should be evaluated before initiating RINVOQ treatment 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 treatment should be interrupted until this diagnosis is excluded (see **4.2 Recommended Dose and Dosage Adjustment** and **7 WARNINGS AND PRECAUTIONS**).

Musculoskeletal

Treatment with RINVOQ was associated with dose-related increases in creatine phosphokinase (CPK) (see **8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**). CPK levels should be checked in patients with symptoms of muscle weakness and/or muscle pain to evaluate for evidence of rhabdomyolysis.

Reproductive Health: Female and Male Potential

Teratogenic Risk: 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 (see **16 NON-CLINICAL TOXICOLOGY**). Pregnant women should be advised of the potential risk to a fetus. Females of reproductive potential should be advised to use effective contraception during treatment with RINVOQ and for 4 weeks following completion of therapy (see**7.1.1 Pregnant Women**).

7.1 Special Populations

7.1.1 Pregnant Women

RINVOQ should not be used during pregnancy. There are limited human data on the use of upadacitinib in pregnant women. There are no adequate and well-controlled studies to assess the use of RINVOQ in pregnant women. Studies in animals have shown reproductive toxicity (see **16 NON-CLINICAL TOXICOLOGY**). In animal embryo-fetal developmental studies, upadacitinib was teratogenic in rats and rabbits with dose-related increases in skeletal malformations in rat fetuses and an increased incidence of cardiovascular malformations in rabbit fetuses when exposed in utero. Increased post-implantation loss was seen in rabbits and decreased fetal body weights were observed in both rats and rabbits. The effect of upadacitinib on human fertility has not been evaluated. Animal studies do not indicate effects with respect to fertility (see **16 NON-CLINICAL TOXICOLOGY**).

Based on animal studies, upadacitinib has the potential to adversely affect a developing fetus and may cause embryo-fetal harm when administered to pregnant women. Women of reproductive potential should be advised to use effective contraception during treatment and for 4 weeks following the final dose of RINVOQ. If the patient becomes pregnant while taking RINVOQ, inform the patient of the potential hazard to a fetus.

7.1.2 Breast-feeding

RINVOQ should not be used during breast-feeding. It is unknown if upadacitinib is excreted in human milk. Lactation studies have not been conducted to assess 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. Following administration of upadacitinib to lactating rats, upadacitinib exposure was approximately 30-fold greater in milk than in maternal plasma. Approximately 97% of drug-related material in milk was parent drug.

A risk to newborns/infants cannot be excluded. 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, patients should be advised not to breast-feed during treatment with RINVOQ, and for 6 days (approximately 10 half-lives) after the last dose.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see **1.1 Pediatrics**, **4.2 Recommended Dose and Dosage Adjustment**, and **10.3 Pharmacokinetics**).

7.1.4 Geriatrics

Caution should be used when treating geriatric patients with RINVOQ. There are limited data in patients 75 years of age and older. In five phase 3 clinical studies, 518 rheumatoid arthritis patients treated with RINVOQ were 65 years of age and older, including 78 patients 75 years of age and older. In two phase 3 clinical studies, 129 psoriatic arthritis patients treated with RINVOQ were 65 years of age or older, including 18 patients 75 years of age and older. Although no differences in effectiveness were observed between these patients and younger patients, there was an increased incidence of adverse events, including serious infections and adverse events leading to RINVOQ discontinuation in patients ≥65 years of age (see **1.2 Geriatrics**, **4.2 Recommended Dose and Dosage Adjustment**, and **10.3 Pharmacokinetics**).

7.1.5 Asian Patients

Asian patients have an increased risk of herpes zoster compared to other races. Therefore, RINVOQ should be used with caution in these patients (see **8 ADVERSE REACTIONS**).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most commonly reported adverse reactions occurring in ≥2% of patients treated with RINVOQ 15 mg were upper respiratory tract infection, nausea, bronchitis, blood creatine phosphokinase (CPK) increased, urinary tract infection, ALT increased, AST increased, headache, cough and back pain. There is increased incidence of opportunistic infections including herpes zoster in patients taking RINVOQ. A higher incidence of herpes zoster was observed in Asian patients. Therefore, RINVOQ should be used with caution in Asian patients.

In clinical trials, the most common SAEs in patients treated with upadacitinib (incidence rate of ≥0.5 per 100 patient-years) included pneumonia, osteoarthritis, and pulmonary embolism. Uncommon SAEs in patients treated with upadacitinib include deep vein thrombosis, arterial thrombosis, gastrointestinal perforation, anemia, malignancies, and cellulitis.

The most common causes of death in the upadacitinib clinical program were cardiovascular related.

The most common adverse reactions leading to discontinuation from treatment were infections. The most common infections (incidence rate of ≥0.5 per 100 patient-years) resulting in discontinuation of treatment were pneumonia and herpes zoster.

[see **7 WARNINGS AND PRECAUTIONS** and **8.2, 8.3, 8.4 ADVERSE REACTIONS]**

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Rheumatoid Arthritis

A total of 3833 patients with rheumatoid arthritis were treated with upadacitinib in the phase 3 clinical studies, of whom 2806 were exposed to upadacitinib for at least one year.

In five phase 3 studies, 2630 patients received at least 1 dose of RINVOQ 15 mg, of whom 1860 were exposed for at least one year. In Studies I, II, III and V, 1213 patients received at least 1 dose of RINVOQ 15 mg, of whom 986 patients were exposed for at least one year, and 1203 patients received at least 1 dose of upadacitinib 30 mg, of whom 946 were exposed for at least one year.

The following four safety datasets were integrated from the five phase 3 clinical studies and were used to evaluate the adverse drug reaction profile of RINVOQ 15 mg once daily (QD):

1) Placebo-controlled studies: Studies III, IV, and V were integrated to represent the safety of RINVOQ 15 mg (n = 1035) in comparison to placebo (n = 1042) for up to 12 to 14 weeks following treatment initiation.

2) Studies III and V were integrated to represent safety through 12 weeks for placebo (n = 390), RINVOQ 15 mg (n = 385), and upadacitinib 30 mg (n = 384). Study IV did not include the 30 mg dose and therefore, safety data for upadacitinib 30 mg can only be compared to placebo and RINVOQ 15 mg data from pooling Studies III and V.

3) Methotrexate (MTX)-controlled studies: Studies I and II were integrated to represent safety through 12 to 14 weeks for MTX (n = 530), RINVOQ 15 mg (n = 534), and upadacitinib 30 mg (n = 529).

4) 12-Month exposure dataset: Studies I, II, III, and V were integrated to represent the long-term safety of RINVOQ 15 mg (n = 1213) and upadacitinib 30 mg (n = 1203).

Exposure adjusted incidence rates were adjusted by study for all the adverse events (AEs) reported.

The adverse reactions occurring in ≥1% of patients treated with RINVOQ 15 mg once daily during the double-blind, placebo-controlled portion of the three placebo-controlled studies (Studies III, IV, and V) for up to 12 to 14 weeks are listed below in Table 3.

Table 3. Adverse Reactions Reported in ≥1% of Rheumatoid Arthritis Patients Treated with RINVOQ 15 mg in Placebo-controlled Studies

	Placebo N = 1042 (%)	RINVOQ 15 mg N = 1035 (%)	Adalimumab[a] N = 327 (%)
Upper respiratory tract infection (URTI)*	9.5	13.5	8.0
Nausea	2.2	3.5	2.4
Blood creatine phosphokinase (CPK) increased	0.9	2.5	0.3
Cough	1.0	2.2	1.2
Neutropenia	0.2	1.8	0.3
Pyrexia	0	1.2	0.3
Hypercholesterolemia	0.2	1.1	1.2
Weight increased	0.3	1.0	0.3

a. Study IV

*URTI includes: acute sinusitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, viral upper respiratory tract infection

The frequency of herpes zoster, lymphopenia, CPK elevations and ALT/AST elevations were higher with RINVOQ 15 mg compared to adalimumab.

Specific Adverse Reactions

The exposure-adjusted rates of specific adverse reactions are provided in Table 4.

Table 4. Specific Adverse Reactions Reported in Rheumatoid Arthritis Patients in Clinical Trials with RINVOQ

	Placebo-controlled Studies Week 12/14 (n/100 PY)			MTX-controlled Studies Week 12/14 (n/100 PY)			12-month exposure (n/100 PY)	
	Placebo N=1042	RINVOQ 15 mg N=1035	Upadacitinib 30 mg N=384	MTX N=530	RINVOQ 15 mg N=534	Upadacitinib 30 mg N=529	RINVOQ 15 mg N=1213	Upadacitinib 30 mg N=1203
Infections	218 (95.7)	284 (127.8)	126 (180.3)	127 (119.5)	104 (91.8)	128 (115.1)	615 (83.8)	674 (99.7)
Serious Infections[a]	6 (2.3)	12 (4.6)	7 (8.2)	2 (1.6)	3 (2.4)	8 (6.4)	38 (3.5)	59 (5.6)
TB[b]	0	0	0	0	0	0	2 (0.2)	1 (<0.1)
Opportunistic Infections (excluding TB)	3 (1.2)	5 (1.9)	6 (7.1)	1 (0.8)	0	4 (3.2)	7 (0.6)	15 (1.4)
Malignancy (excluding NMSC)	1 (0.4)	1 (0.4)	3 (3.5)	1 (0.8)	3 (2.4)	0	13 (1.2)	14 (1.3)
Gastrointestinal Perforations	0	0	0	0	0	2 (1.6)	1 (<0.1)	4 (0.4)
Venous Thrombosis[c]	1 (0.4)	1(0.4)	0	0[c]	1 (0.8)	1 (0.8)	5 (0.5)	4 (0.4)
Arterial Thrombosis[d]	0	0	0	0	0	0[d]	0	2 (0.2)

a. The most frequently reported serious infections were pneumonia and cellulitis.
b. Including extra-pulmonary tuberculosis.
c. One event of venous thrombosis was reported in MTX group between Week 12/14 and Week 24 (Study I).
d. One event of arterial thrombosis was reported in Upadacitinib 30 mg group between Week 12/14 and Week 24 (Study I).

Psoriatic Arthritis

A total of 1827 patients in the with psoriatic arthritis were treated with upadacitinib in clinical studies, of whom 722 were exposed to upadacitinib for at least one year. In the 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).

In patients treated with upadacitinib in combination with MTX therapy compared to patients treated with monotherapy, higher rates were observed for serious infections (1.1% vs 0.5%, respectively),

hepatic disorders (7.7% vs 4.2%, respectively), elevation of CPK (7.1% vs 5.2%, respectively), anemia (1.3% vs 0.5%, respectively), and lymphopenia (1.3% vs 1.1%, respectively).

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Not applicable

8.3 Less Common Clinical Trial Adverse Reactions

Rheumatoid Arthritis
Infections and Infestations: herpes zoster, herpes simplex, pneumonia, oral candidiasis.

Psoriatic Arthritis
The incidence rates of less common clinical trial adverse drug reactions (<1%) in the two controlled Phase 3 psoriatic arthritis clinical studies were generally similar to those reported in RA clinical studies with the exception of herpes zoster and herpes simplex.

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Not applicable

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Rheumatoid Arthritis

Clinically significant changes in hematology and chemistry laboratory findings during the clinical trials are presented in Table 5 and Table 6.

Table 5. Biochemical changes Reported in Rheumatoid Arthritis Patients in Clinical Trials with RINVOQ

	Placebo-controlled Studies Week 12/14 (%)			MTX-controlled Studies Week 12/14 (%)		
	Placebo[a] N= 1042	RINVOQ 15 mg[a] N= 1035	Upadacitinib 30 mg[a] N= 384	MTX N= 530	RINVOQ 15 mg N= 534	Upadacitinib 30 mg N= 529
ALT ≥3X ULN	1.5	2.1	1.0	1.9	0.8	1.7
AST ≥3X ULN	0.7	1.5	0	0.9	0.4	1.3
CPK ≥5X ULN[d]	0.3	1.0	0	0	0.8	1.1

ULN = Upper limit of normal in at least one measurement
a. Studies III, IV, V; subjects were permitted background DMARDs.
b. Most elevations >5X ULN were transient and did not require treatment discontinuation.

Table 6. Hematological changes Reported in Rheumatoid Arthritis Patients in Placebo-controlled Clinical Trials with RINVOQ

	Placebo-controlled Studies		
	Placebo[a] N= 1042 (%)	RINVOQ 15 mg[a] N= 1035 (%)	Upadacitinib 30 mg [a] N= 384 (%)
Neutropenia[b]	<0.1	1.1	2.4
Lymphopenia[c]	0.7	0.9	2.4
Anemia[d]	<0.1	<0.1	0

ULN = Upper limit of normal in at least one measurement

a. subjects were permitted background DMARDs.

b. Decrease in neutrophil counts, below 1000 cells/mm^3 in at least one measurement. In clinical studies, treatment was interrupted in response to ANC less than 1000 cells/mm^3.

c. Decrease in lymphocyte counts, below 500 cells/mm^3 in at least one measurement.

d. Decrease in hemoglobin, below 8g/dL in at least one measurement.

Lipid elevations

RINVOQ 15 mg 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 studies, 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 0.38 mmol/L and 0.44 mmol/L.
- Mean HDL cholesterol increased by 0.21 mmol/L and 0.23 mmol/L.
- The mean LDL/HDL ratio remained stable.
- Mean triglycerides increased by 0.15 mmol/L and 0.16 mmol/L.

Psoriatic Arthritis

In the controlled clinical trials in psoriatic arthritis, changes in hematologic and clinical chemistry findings observed with RINVOQ treatment were similar to the changes observed in clinical trials in RA.

8.5 Post-Market Adverse Reactions

Not applicable

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

In vitro assessment of interactions

In vitro metabolism studies indicated that upadacitinib metabolism is mediated by CYP3A4 with a potential minor contribution from CYP2D6.

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

In vitro, upadacitinib is a substrate for the efflux transporters P-gp and BCRP.

9.3 Drug-Behavioural Interactions

Not applicable

9.4 Drug-Drug Interactions

Potential for Other Drugs to Affect the Pharmacokinetics of Upadacitinib

Upadacitinib exposure is increased when co-administered with strong CYP3A4 inhibitors (such as ketoconazole). RINVOQ should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors (see **4.1 Dosing Considerations**).

Upadacitinib exposure is decreased when co-administered with strong CYP3A4 inducers (such as rifampin), which may lead to reduced therapeutic effect of RINVOQ. Coadministration of RINVOQ with strong CYP3A4 inducers is not recommended (see **4.1 Dosing Considerations**).

The effect of co-administered drugs on upadacitinib plasma exposures is provided in Table 7. The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 7. Change in Pharmacokinetics of Upadacitinib in the Presence of Co-administered Drugs

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Upadacitinib	N	Ratio (with/without co-administered drug) No effect = 1.0 (90% CI)[a]		Clinical Comment
				C_{max}	AUC	
Methotrexate	10 to 25 mg/week	6 to 24 mg BID[b]	11	0.97 (0.86-1.09)	0.99 (0.93- 1.06)	No dose adjustment of RINVOQ is required
Strong CYP3A4 inhibitor: Ketoconazole	400 mg QD x 6 days	3 mg single dose[b]	11	1.70 (1.55-1.89)	1.75 (1.62-1.88)	Use RINVOQ with caution if used chronically

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Upadacitinib	N	Ratio (with/without co-administered drug) No effect = 1.0 (90% CI)[a]		Clinical Comment
				C_{max}	AUC	
Strong CYP3A4 inducer: Rifampin	600 mg QD x 9 days	12 mg single dose[b]	12	0.49 (0.44-0.55)	0.39 (0.37-0.42)	Coadministration of RINVOQ with strong CYP3A4 inducers is not recommended
OATP1B inhibitor: Rifampin	600 mg single dose	12 mg single dose[b]	12	1.14 (1.02- 1.28)	1.07 (1.01- 1.14)	No dose adjustment of RINVOQ is required

a. Ratios for C_{max} and AUC compare co-administration of the medication with upadacitinib vs administration of upadacitinib alone. Data represent the point estimates and the corresponding 90% confidence intervals for the difference of the least square means obtained from the repeated measures analyses of the natural logarithms of C_{max} and AUC.

b. Upadacitinib was administered as an immediate-release formulation.

Methotrexate, inhibitors of organic anion transporting polypeptide 1B (OATP1B) transporters, and pH modifying medications (e.g., antacids or proton pump inhibitors) have no effect on 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 Affect the Pharmacokinetics of Other Drugs

The effect of upadacitinib on plasma exposures of other drugs is provided in Table 8. The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 8. Drug Interactions: Change in Pharmacokinetics of Co-administered Drugs in the Presence of Upadacitinib

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Upadacitinib	N	Ratio (with/without co-administered drug) No effect = 1.0 (90% CI)[a]		Clinical Comment
				C_{max}	AUC	
Methotrexate	10 to 25 mg/week	6 mg to 24 mg BID x 27 days	11	1.03 (0.86-1.23)	1.14 (0.91-1.43)	No dose adjustment of methotrexate is required
Sensitive CYP1A2 Substrate Caffeine	200 mg single dose	30 mg QD x 10 days	20	1.13 (1.05- 1.22)	1.22 (1.15- 1.29)	No dose adjustment of CYP1A2 drug substrates is required
Sensitive CYP3A Substrate Midazolam	5 mg single dose	30 mg QD x 10 days	20	0.74 (0.68-0.80)	0.74 (0.68-0.80)	No dose adjustment of CYP3A drug substrates is required
Sensitive CYP2D6 Substrate Dextromethorphan	30 mg single dose	30 mg QD x 10 days	20	1.09 (0.98- 1.21)	1.07 (0.95- 1.22)	No dose adjustment of CYP2D6 drug substrates is required
Sensitive CYP2C9 Substrate S-Warfarin	10 mg single dose	30 mg QD x 10 days	20	1.07 (1.02- 1.11)	1.11 (1.07- 1.15)	No dose adjustment of CYP2C9 drug substrates is required
Sensitive CYP2C19 Marker 5-OH Omeprazole to Omeprazole metabolic ratio	40 mg single dose omeprazole	30 mg QD x 10 days	20	--	1.09 (1.00- 1.19)	No dose adjustment of CYP2C19 drug substrates is required
CYP2B6 Substrate Bupropion	150 mg single dose	30 mg QD x 10 days	22	0.87 (0.79- 0.96)	0.92 (0.87- 0.98)	No dose adjustment of CYP2B6 drug substrates is required
Rosuvastatin	5 mg single dose	30 mg QD x 10 days	12	0.77 (0.63-0.94)	0.67 (0.56-0.82)	No dose adjustment of rosuvastatin is required
Atorvastatin	10 mg single dose	30 mg QD x 10 days	24	0.88 (0.79-0.97)	0.77 (0.70-0.85)	No dose adjustment of

Co-administered Drug	Regimen of Co-administered Drug	Regimen of Upadacitinib	N	Ratio (with/without co-administered drug) No effect = 1.0 (90% CI)[a]		Clinical Comment
				C_{max}	AUC	
						atorvastatin is required
Ethinylestradiol	0.03 mg single dose	30 mg QD x 11 days	22	0.96 (0.89- 1.02)	1.11 (1.04- 1.19)	No dose adjustment of ethinylestradiol is required
Levonorgestrel	0.15 mg single dose	30 mg QD x 11 days	22	0.96 (0.87- 1.06)	0.96 (0.85- 1.07)	No dose adjustment of levonorgestrel is required

a. Ratios for C_{max} and AUC compare co-administration of the medication with upadacitinib vs administration of medication alone. Data represent the point estimates and the corresponding 90% confidence intervals for the difference of the least square means obtained from the repeated measures analyses of the natural logarithms of C_{max} and AUC.

Immunosuppressants, Other JAK Inhibitors, or Biologic DMARDs

There is a risk of added immunosuppression when RINVOQ is co-administered with other potent immunosuppressive drugs (e.g., tacrolimus, cyclosporine, azathioprine). The combined use of RINVOQ with other potent immunosuppressants, other JAK inhibitors, or biologic DMARDs has not been evaluated in clinical studies and is not recommended (see **4.1 Dosing Considerations** and **7 WARNINGS AND PRECAUTIONS**).

9.5 Drug-Food Interactions

Grapefruit juice inhibits CYP3A-mediated metabolism. RINVOQ should be used with caution when administered concomitantly with grapefruit juice.

9.6 Drug-Herb Interactions

St John's Wort is a CYP3A inducer which may lead to reduced therapeutic effect of RINVOQ. Coadministration of RINVOQ with St John's Wort is not recommended.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Upadacitinib is a Janus Kinase (JAK) inhibitor. JAKs are intracellular enzymes that transduce signals from cell surface receptors for cytokines or growth factors involved in a broad range of cellular processes including inflammatory responses, hematopoiesis and immune surveillance. 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).

Upadacitinib inhibits JAKs with a high degree of selectivity against other kinases in the human genome. In cell-free isolated enzyme assays, upadacitinib had greater inhibitory potency at JAK1 relative to JAK2, JAK3 and TYK2 with IC50 values of 43, 120, 2300, and 4700 nM for JAK1, JAK2, JAK3, and TYK2, respectively. However, 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. Upadacitinib blocked IL-2 induced (JAK1/JAK3) and IL-6 induced (JAK1/JAK2) STAT phosphorylation at 9 to 13 nM and erythropoietin induced (JAK2/JAK2) STAT phosphorylation at 628 nM. The relevance of inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known.

10.2 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 of the clinical studies; however, the mean values at baseline and at all visits were within the normal reference range.

High-sensitivity C-reactive Protein (hsCRP)

In patients with rheumatoid arthritis, treatment with upadacitinib was associated with significant decreases from baseline in mean hsCRP levels as early as Week 1 which were maintained with continued treatment.

Cardiac Electrophysiology

The effect of upadacitinib on QTc interval was evaluated in subjects who received single and multiple doses of upadacitinib. Upadacitinib does not prolong QTc interval at therapeutic or supra therapeutic plasma concentrations.

10.3 Pharmacokinetics

Upadacitinib is absorbed following administration of the extended-release formulation with a median time to maximum observed plasma concentration (T_{max}) of approximately 2 to 3 hours under fasting conditions and 4 hours under non-fasting conditions. Upadacitinib plasma exposures are proportional to dose over the range of 7.5 mg to 45 mg using the extended-release formulation under fasting conditions. Steady-state plasma concentrations are achieved within 4 days with minimal accumulation after multiple once-daily administrations using the 15 mg extended-release formulation. The

pharmacokinetics of upadacitinib do not change over time.

Subjects with rheumatoid arthritis (RA) are estimated to have ~38% lower upadacitinib CL/F compared to healthy subjects. The pharmacokinetic properties of RINVOQ are provided in Table 9.

Table 9. Summary of RINVOQ's Pharmacokinetic Parameters in Humans

	$C_{max, ss}$ (ng/mL)	$t_{½}$ (h)	$AUC_{τ, ss}$ (ng*hr/mL)	Apparent Oral Clearance (L/h)
Healthy Volunteers	28.1 ± 9.29[a]	8.8 ± 5.4[c]	251 ± 69.8[a]	64.9 ± 18.77[a]
Rheumatoid Arthritis Patients	41.3 ± 7.2[b]	9-14[d]	396 ± 141[b]	40.5 (37)[e]

Abbreviations: $C_{max, ss}$ = maximum observed drug concentration; $t_{1/2}$ = terminal elimination half-life; $AUC_{τ, ss}$ = area under the concentration-time curve during one dosing interval at steady state. Values presented are mean ± standard deviation unless otherwise specified.

a. Summary of pharmacokinetic parameters across phase 1 studies for 15 mg QD regimen (fasting and non-fasting conditions).
b. Summary of upadacitinib model-estimated exposures in RA patients in phase 3 studies.
c. Harmonic mean ± pseudo-standard deviation across phase 1 studies for 15 mg QD regimen (fasting and non-fasting conditions).
d. Harmonic mean range for the extended-release formulation in healthy subjects in Study M14-680.
e. Apparent oral clearance in RA patients from population pharmacokinetic analysis represented as parameter estimate (percent inter-subject variability).

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 using the extended-release formulation 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%). In clinical trials, upadacitinib was administered without regard to meals (see **4.2 Recommended Dose and Dosage Adjustment**).

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.

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.

Elimination: Following single dose administration of (^{14}C)upadacitinib immediate-release solution, upadacitinib was eliminated predominantly as the unchanged parent substance in urine (24%) and feces (38%). Approximately 34% of upadacitinib dose was excreted as metabolites. Upadacitinib mean terminal elimination half-life ranged from 9 to 14 hours.

Special Populations and Conditions

- **Pediatrics**

  The pharmacokinetics of RINVOQ have not been investigated in the pediatric population.

- **Geriatrics**

No dose adjustment is required for patients aged >65 years (see **4.2 Recommended Dose and Dosage Adjustment**). Age did not have a clinically meaningful effect on upadacitinib exposure.

- **Other Intrinsic Factors**

  Sex, body weight, race and ethnicity did not have a clinically meaningful effect on upadacitinib exposure. Upadacitinib pharmacokinetics are consistent between rheumatoid arthritis and psoriatic arthritis patients.

- **Hepatic Impairment**

  Mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment has no clinically relevant effect on upadacitinib exposure. Upadacitinib AUC_{inf} was 28% and 24% higher in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal liver function. Upadacitinib C_{max} was unchanged in subjects with mild hepatic impairment and 43% higher in subjects with moderate hepatic impairment compared to subjects with normal liver function. Upadacitinib was not studied in patients with severe hepatic impairment (Child-Pugh C) and should not be intitated in this patient population (see **4.1 Dosing Considerations**).

- **Renal Impairment**

  Renal impairment has no clinically relevant effect on upadacitinib exposure. Upadacitinib AUCinf was 18, 33, and 44% higher in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function. Upadacitinib C_{max} was similar in subjects with normal and impaired renal function.

11 STORAGE, STABILITY AND DISPOSAL

Temperature:

Store between 2 and 25°C.

Moisture:

Store in the original bottle in order to protect from moisture.

Others:

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Upadacitinib (INN)

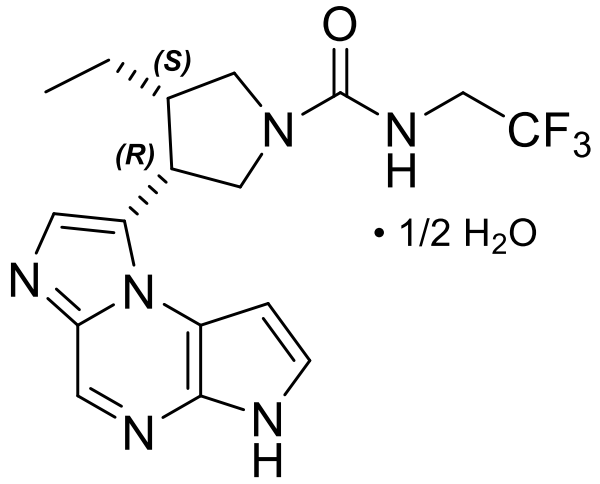
Chemical name: (3S,4R)-3-Ethyl-4-(3H-imidazo(1,2-a)pyrrolo(2,3-e)pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrate (2:1)

Molecular formula and molecular mass: $C_{17}H_{19}F_3N_6O \bullet ½\ H_2O$ (hemihydrate)

389.38 g/mol (hemihydrate)

380.38 g/mol (anhydrate)

Structural formula:



Physicochemical properties: Upadacitinib is a white to light brown powder. 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°C.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Rheumatoid Arthritis

The efficacy and safety of RINVOQ (upadacitinib) 15 mg once daily were assessed in five phase 3 randomized, double-blind, multicenter studies in patients with moderately to severely active rheumatoid arthritis and fulfilling the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 classification criteria (see Table 10**Error! Reference source not found.**). Patients over 18 years of age were eligible to participate. The presence of at least 6 tender and 6 swollen joints and evidence of systemic inflammation based on elevation of high-sensitivity C-reactive protein (hsCRP) was required at baseline. Although other doses have been studied, the recommended dose of RINVOQ is 15 mg once daily.

Baseline demographics were generally similar among the treatment groups in each study and comparable between the studies. Typical of the overall rheumatoid arthritis population, the majority of patients were female and white. The mean (standard deviation (SD)) age ranged from 53.4 (12.73) to 57.1 (11.42) years. The baseline demographics in each study are shown in Table 10**.**

Table 10. Summary of patient demographics for clinical trials in Rheumatoid Arthritis

Study #	Study design	Dosage, route of administration and duration	Study subjects, N	Mean age, years (SD)	Female, %	Mean Disease Duration, years (SD)[f]
STUDY I SELECT-EARLY (M13-545)	Randomized, double-blind, active-controlled, multicenter, in MTX-naïve[a] patients Monotherapy	RINVOQ 15 mg Upadacitinib 30 mg MTX Tablets, orally, once daily Main treatment period: 24 weeks	947	53.4 (12.73)	76.3	2.7 (5.38)
STUDY II SELECT-MONOTHERAPY (M15-555)	Randomized, double-blind, active-controlled, multicenter, in MTX-IR[b] patients Monotherapy	RINVOQ 15 mg Upadacitinib 30 mg MTX Tablets, orally, once daily Main treatment period: 14 weeks	648	54.3 (12.05)	80.7	6.6 (7.58)

Study #	Study design	Dosage, route of administration and duration	Study subjects, N	Mean age, years (SD)	Female, %	Mean Disease Duration, years (SD)[f]
STUDY III SELECT-NEXT (M13-549)	Randomized, double-blind, placebo-controlled, multicenter, in csDMARD-IR[c] patients On background csDMARDs	RINVOQ 15 mg Upadacitinib 30 mg Placebo Tablets, orally, once daily Main treatment period: 12 weeks	661	55.7 (11.65)	78.7	7.3 (7.72)
STUDY IV SELECT-COMPARE (M14-465)	Randomized, double-blind, placebo- and active-controlled, multicenter, in MTX-IR[d] patients On background MTX	RINVOQ 15 mg Placebo Tablets, orally, once daily Adalimumab 40 mg EOW Main treatment period: 26 weeks	1629	53.9 (12.07)	79.3	8.2 (7.97)
STUDY V SELECT-BEYOND (M13-542)	Randomized, double-blind, placebo-controlled, multicenter, in bDMARD-IR[e] patients On background csDMARDs	RINVOQ 15 mg Upadacitinib 30 mg Placebo Tablets, orally, once daily Main treatment period: 12 weeks	499	57.1 (11.42)	83.9	13.2 (9.45)

a. Patients were naïve to MTX or received no more than 3 weekly MTX doses

b. Patients had inadequate response to MTX

c. Patients who had an inadequate response to csDMARDs; patients with prior exposure to at most one bDMARD were eligible (up to 20% of total number of patients) if they had either limited exposure (<3 months) or had to discontinue the bDMARD due to intolerability

d. Patients who had an inadequate response to MTX; patients with prior exposure to at most one bDMARD (except adalimumab) were eligible (up to 20% of total study number of patients) if they had either limited exposure (<3 months) or had to discontinue the bDMARD due to intolerability

e. Patients who had an inadequate response or intolerance to at least one bDMARD

f. Years since RA diagnosis

Study I (M13-545) was a 48-week 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

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 Health Assessment Questionnaire – Disability Index (HAQ-DI) at Week 12, and change from baseline in van der Heijde-modified total Sharp Score (mTSS) at Week 24.

Study II (M15-555) 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.

Study III (M13-549) was a 12-week trial in 661 patients with moderately to severely active rheumatoid arthritis who had an inadequate response to conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs). Patients received RINVOQ 15 mg or upadacitinib 30 mg once daily or placebo added to background csDMARD 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.

Study IV (M14-465) 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, adalimumab, or placebo added to background MTX. From Week 14, non-responding patients on RINVOQ 15 mg could be rescued to adalimumab in a blinded manner, and non-responding patients on adalimumab 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.

Study V (M13-542) 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 csDMARD 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.

Study Results

The percentages of patients treated with RINVOQ 15 mg achieving ACR20, ACR50, and ACR70 responses, DAS28-CRP <2.6 in all studies are shown in Table 11.

In all studies, patients treated with RINVOQ 15 mg, alone or in combination with csDMARDs, achieved significantly higher ACR20, ACR50, and ACR70 response rates compared to MTX monotherapy or placebo, respectively, at the primary efficacy time point, except for ACR70 in Study V (Table 11).

In Study IV, the percentage of patients achieving ACR20 responses by visit is shown in Figure 1. In Studies III and V, significantly higher ACR20 response rates were observed as early as Week 1 with RINVOQ 15 mg versus placebo.

Treatment with RINVOQ 15 mg, alone or in combination with csDMARDs, resulted in significantly greater improvements in the individual ACR components compared to placebo or MTX at the primary efficacy time point (Table 12).

Table 11. Proportion of Patients Achieving ACR Responses and DAS28-CRP <2.6

Efficacy Measure	Study	Study I MTX-Naïve		Study II MTX-IR		Study III csDMARD-IR		Study IV[h] MTX-IR			Study V bDMARD-IR	
		Monotherapy		Monotherapy		Background csDMARDs		Background MTX			Background csDMARDs	
		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)	ADA 40 mg	PBO	RINVOQ 15 mg % Δ (95% CI)
	Week	**N = 314**	**317**	**216**	**217**	**221**	**221**	**651**	**651**	**327**	**169**	**164**
ACR 20[f]	12[a]/14[b]	54	76[e] 22 (14, 29)	41	68[e] 27 (18, 36)	36	64[e] 28 (19, 37)	36	71[e] 34 (29, 39)	63	28	65[e] 36 (26, 46)
	24[c]/26[d]	59	79[e] 20 (13, 27)					36	67[e] 32 (27, 37)	57		
ACR 50[f]	12[a]/14[b]	28	52[e] 24 (16, 31)	15	42[e] 27 (19, 35)	15	38[e] 23 (15, 31)	15	45[e] 30 (26, 35)	29	12	34[e] 22 (14, 31)
	24[c]/26[d]	33	60[e] 27 (19, 34)					21	54[e] 33 (28, 38)	42		
ACR 70[g]	12[a]/14[b]	14	33[e] 19 (12, 25)	3	23[e] 20 (14, 26)	6	21[e] 15 (9, 21)	5	25[e] 20 (6, 24)	14	7	12 5 (-1, 11)
	24[c]/26[d]	19	45[e] 26 (19, 33)					10	35[e] 25 (21, 29)	23		
DAS28-CRP <2.6[f]	12[a]/14[b]	14	36[e] 22 (16, 29)	8	28[e] 20 (13, 27)	10	31[e] 21 (14, 28)	6	29[e] 23 (19, 27)	18	10	29[e] 19 (11, 27)
	24[c]/26[d]	19	48[e] 30 (23, 37)					9	41[e] 32 (27, 36)	27		

Patients who discontinued randomized treatment, or had cross-over between randomized treatments, or were missing data at week of evaluation were imputed as non-responders in the analyses.

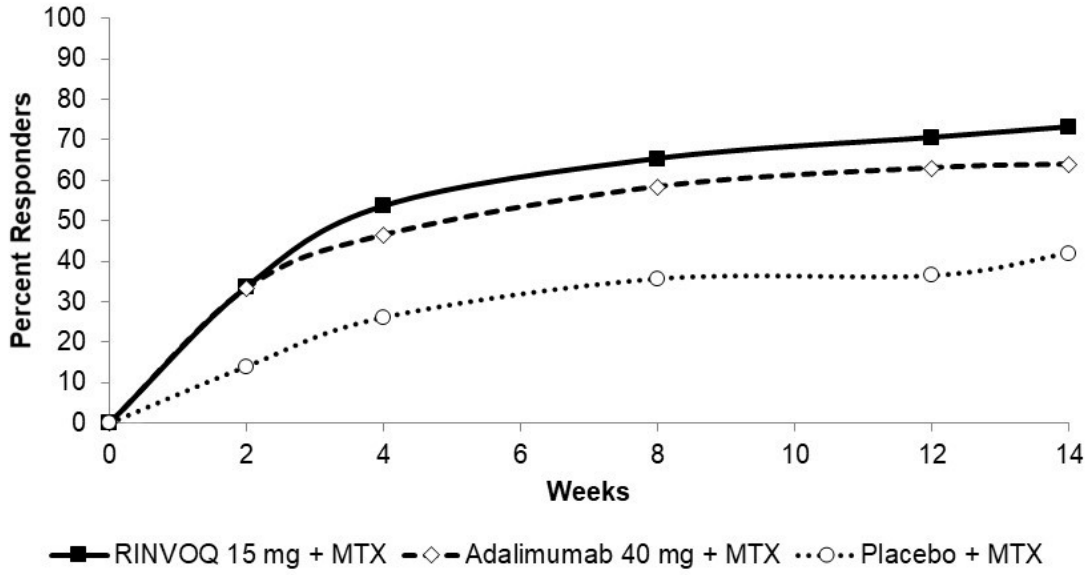
a. Study I, Study III, Study IV, Study V
b. Study II
c. Study I
d. Study IV
e. p≤0.001 RINVOQ 15 mg vs placebo or MTX comparison
f. The following comparisons for RINVOQ 15 mg vs placebo or MTX are included in multiplicity adjustment for overall type I error control: ACR20 at Week 12/14 in Study II, Study III, Study IV, and Study V; ACR50 at Week 12 in Study I; DAS28-CRP <2.6 at Week 24 in Study I, and at Week 12/14 for Study II, Study III, and Study IV.
g. Not included in multiplicity adjustment for overall type I error control.
h. No conclusions can be drawn regarding the superiority of upadacitinib + MTX versus adalimumab + MTX.

Table 12. Components of ACR Response (mean change from baseline)[a]

ACR Component	Study	Study I MTX-Naïve		Study II MTX-IR		Study III csDMARD-IR		Study IV MTX-IR			Study V bDMARD-IR	
		Monotherapy		Monotherapy		Background csDMARDs		Background MTX			Background csDMARDs	
		MTX	RINVOQ 15 mg	MTX	RINVOQ 15 mg	PBO	RINVOQ 15 mg	PBO	RINVOQ 15 mg	ADA 40 mg	PBO	RINVOQ 15 mg
	Week	N = 314	317	216	217	221	221	651	651	327	169	164
Number of tender joints (0-68)	12[b]/14[c]	-13	-17[h]	-11	-15[h]	-8	-14[h]	-10	-16[h]	-14	-8	-16[h]
	24[d]/26[e]	-16	-19[h]					-9	-18[h]	-15		
Number of swollen joints (0-66)	12[b]/14[c]	-10	-12[h]	-8	-11[h]	-6	-9[h]	-7	-11[h]	-10	-6	-11[h]
	24[d]/26[e]	-12	-14[h]					-6	-12[h]	-11		
Pain[f]	12[b]/14[c]	-25	-36[h]	-14	-26[h]	-10	-30[h]	-15	-32[h]	-25	-10	-26[h]
	24[d]/26[e]	-28	-40[h]					-19	-37[h]	-32		
Patient global assessment[f]	12[b]/14[c]	-25	-35[h]	-11	-23[h]	-10	-30[h]	-15	-30[h]	-24	-10	-26[h]
	24[d]/26[e]	-28	-39[h]					-18	-36[h]	-30		
Disability Index (HAQ-DI)[g]	12[b]/14[c]	-0.5	-0.8[h]	-0.3	-0.7[h]	-0.3	-0.6[h]	-0.3	-0.6[h]	-0.5	-0.2	-0.4[h]
	24[d]/26[e]	-0.6	-0.9[h]					-0.3	-0.7[h]	-0.6		
Physician global assessment[f]	12[b]/14[c]	-35	-46[h]	-26	-40[h]	-23	-38[h]	-25	-39[h]	-36	-26	-39[h]
	24[d]/26[e]	-45	-50[h]					-27	-45[h]	-41		
hsCRP (mg/L)	12[b]/14[c]	-10.6	-17.5[h]	-1.1	-10.2[h]	-0.4	-10.1[h]	-1.7	-12.5[h]	-9.2	-1.1	-11.0[h]
	24[d]/26[e]	-11.6	-18.4[h]					-1.5	-13.5[h]	-10.3		

a. Data shown are least square (LS) means of change from baseline
b. Study I, Study III, Study IV, Study V
c. Study II, primary efficacy time point is at Week 14
d. Study I
e. Study IV
f. Visual analog scale: 0 = best, 100 = worst
g. Health Assessment Questionnaire-Disability Index: 0=best, 3=worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. Data shown are the within group LS means of change from baseline.
h. p≤0.001 RINVOQ 15 mg vs placebo or MTX comparison

Figure 1. Percent of Patients Achieving ACR20 in Study IV



Patients who discontinued randomized treatment, or were missing ACR20 results, or were lost-to-follow-up or withdrawn from the study were imputed as non-responders.

In Study I and Study IV, a higher proportion of patients treated with RINVOQ 15 mg alone or in combination with MTX, achieved DAS28-CRP <2.6 compared to MTX or placebo at the primary efficacy time point (Table 13).

Table 13. Proportion of Patients with DAS28-CRP Less Than 2.6 with Number of Residual Active Joints at Primary Efficacy Time Point

	Study I MTX-Naïve		**Study IV MTX-IR**	
	Monotherapy		**Background MTX**	
DAS28-CRP Less Than 2.6	**MTX** N = 314	**RINVOQ 15 mg** N = 317	**MTX** N = 651	**RINVOQ 15 mg** N = 651
Proportion of responders at Week 12 (n)	14% (43)	36% (113)	6% (40)	29% (187)
Of responders, proportion with 0 active joints (n)	51% (22)	45% (51)	60% (24)	48% (89)
Of responders, proportion with 1 active joint (n)	35% (15)	23% (26)	20% (8)	23% (43)
Of responders, proportion with 2 active joints (n)	9% (4)	17% (19)	15% (6)	13% (25)
Of responders, proportion with 3 or more active joints (n)	5% (2)	15% (17)	5% (2)	16% (30)

Radiographic response

Inhibition of progression of structural joint damage was assessed using the modified Total Sharp Score (mTSS) and its components, the erosion score, and joint space narrowing score at Week 26 in Study IV and Week 24 in Study I. The proportion of patients with no radiographic progression (mTSS change from baseline ≤0) was also assessed.

In Study IV, treatment with RINVOQ 15 mg resulted in significantly greater inhibition of the progression of structural joint damage compared to placebo at Weeks 26 (

Table *17*). Analyses of erosion and joint space narrowing scores were consistent with overall results. In this study, 76% of patients in the placebo plus MTX group experienced no radiographic progression at Week 26 compared to 84% of patients treated with RINVOQ 15 mg.

In Study I, treatment with RINVOQ 15 mg monotherapy resulted in significantly greater inhibition of the progression of structural joint damage compared to MTX monotherapy at Week 24 (

Table *17*). Analyses of erosion and joint space narrowing scores were consistent with overall results. In this study, 78% of the patients in the MTX monotherapy group experienced no radiographic progression at Week 24 compared to 88% of the patients treated with RINVOQ 15 mg monotherapy.

Table 14. Radiographic Changes

Measurement tool	**Study**	**Study I MTX-Naïve**		**Study IV MTX-IR**		
		Monotherapy		**Background MTX**		
	Treatment Group	**MTX**	**RINVOQ 15 mg Δ (95% CI)**	**PBO[a]**	**RINVOQ 15 mg Δ (95% CI)**	**ADA 40 mg**

	Week					
Modified Total Sharp Score, mean change from baseline	24[b]/26[c]	0.7	0.1[f] -0.5 (-0.9, -0.2)	0.9	0.2[e] -0.7 (-1.0, -0.4)	0.1
Erosion Score, mean change from baseline	24[b]/26[c]	0.3	0.1[e] -0.3 (-0.4, -0.1)	0.4	0[e] -0.4 (-0.6, -0.2)	0
Joint Space Narrowing Score, mean change from baseline	24[b]/26[c]	0.3	0.1[g] -0.2 (-0.4, -0.0)	0.6	0.2[e] -0.4 (-0.6, -0.2)	0.1
Proportion of patients with no radiographic progression[d]	24[b]/26[c]	77.7	87.5[f] 9.8 (3.5, 16.2)	76.0	83.5[f] 7.5 (3, 12.1)	86.8

Analyses are based on linear extrapolation

a. Study I
b. Study IV
c. No progression defined as mTSS change ≤0
d. p≤0.001 RINVOQ 15 mg vs placebo or MTX comparison
e. p≤0.01 RINVOQ 15 mg vs placebo or MTX comparison
f. p≤0.05 RINVOQ 15 mg vs placebo or MTX comparison

Physical function response and health-related outcomes

Treatment with RINVOQ 15 mg, alone or in combination with csDMARDs, resulted in a significant improvement in physical function compared to all comparators (placebo, MTX, or adalimumab) as measured by HAQ-DI at Week 12/14 (Table 18).

In Studies II, III, and IV, treatment with RINVOQ 15 mg resulted in a significantly greater improvement in the mean duration of morning joint stiffness compared to placebo or MTX at Week 12/14.

Other health-related outcomes

Across all studies, patients receiving RINVOQ 15 mg experienced significantly greater improvement from baseline in physical component summary (PCS) score, mental component summary (MCS) scores, and in all 8 domains of the Short Form Health Survey (SF-36) compared to placebo in combination with csDMARDs or MTX monotherapy at Week 12/14.

Fatigue was assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F) in Studies I, III, and IV. Improvement in fatigue at Week 12 was observed in patients treated with RINVOQ 15 mg compared to patients on placebo in combination with csDMARDs MTX monotherapy.

Table 15. Physical Function Response HAQ-DI (MCID) at Week 12[b]/14[c]

Study	Study I MTX-Naïve		Study II MTX-IR		Study III csDMARD-IR		Study IV MTX-IR			Study V bDMARD-IR	
	MTX	RINVOQ 15 mg	MTX	RINVOQ 15 mg	PBO	RINVOQ 15 mg	PBO	RINVOQ 15 mg	ADA 40 mg	PBO	RINVOQ 15 mg
N	**314**	**317**	**216**	**217**	**221**	**221**	**651**	**651**	**327**	**169**	**164**
Change from Baseline[a] Δ (95% CI)	-0.49	-0.83[d] -0.34 (-0.44, -0.25)	-0.32	-0.65[d] -0.33 (-0.43, -0.22)	-0.25	-0.59[d] -0.33 (-0.43, -0.24)	-0.28	-0.60[d] -0.31 (-0.37, -0.25)	-0.49	-0.17	-0.39[d] -0.22 (-0.34, -0.10)
HAQ-DI Responder Rates[e] (%)	54	77[d]	39	62[d]	43	67[d]	44	64[d]	64	27	56[d]

a. Data shown are least squares (LS) mean
b. Studies I, III, IV and V
c. Study II
d. p≤0.001 RINVOQ 15 mg vs placebo or MTX comparison
e. Percentage of patients with an improvement from baseline ≥0.30

Psoriatic Arthritis

The efficacy and safety of RINVOQ 15 mg once daily was assessed in two phase 3 randomized, double-blind, multicenter, placebo-controlled studies in patients 18 years of age or older with moderately to severely active psoriatic arthritis (Table 16). All patients had active psoriatic arthritis for at least 6 months based upon the Classification Criteria for Psoriatic Arthritis (CASPAR), at least 3 tender joints and at least 3 swollen joints, and active plaque psoriasis or history of plaque psoriasis. For both studies, the primary endpoint was the proportion of patients who achieved an ACR20 response at Week 12. The studies include long-term extensions for up to 5 years (SELECT-PsA 1) and 3 years (SELECT-PsA 2).

Table 16. Summary of Patient Demographics for Clinical Trials in Psoriatic Arthritis

Study #	Trial design	Dosage, route of administration and duration	Study subjects, N[c]	Mean age, years (SD)	Female, %	Mean Disease Duration, years (SD)[d]
Study-PsA I SELECT-PsA 1 (M15-572)	Randomized, double-blind, placebo- and active- controlled, multicenter, in non-biologic DMARD-IR[a] patients	RINVOQ 15 mg Upadacitinib 30 mg Placebo, orally, once daily Adalimumab 40 mg EOW Main treatment period: 24 weeks	1704	50.8 (12.22)	53.2	6.1 (6.97)
Study-PsA II SELECT-PsA 2 (M15-554)	Randomized, double-blind, placebo-controlled, multicenter, in bDMARD-IR[b] patients	RINVOQ 15 mg Upadacitinib 30 mg Placebo, orally, once daily Main treatment period: 24 weeks	641	53.4 (11.83)	54.3	10.1 (9.18)

a. Patients who had an inadequate response or intolerance to at least one non-biologic DMARD
b. Patients who had an inadequate response or intolerance to at least one bDMARD
c. Includes all randomized patients who received at least one dose of study drug
d. Years since psoriatic arthritis diagnosis

Study-PsA I (M15-572) was a 24-week trial in 1705 patients who had an inadequate response or intolerance to at least one non-biologic DMARD. At baseline, 1393 (82%) of patients were on at least one concomitant non-biologic DMARD, 1084 (64%) of patients received concomitant MTX only, and 311 (18%) of patients were on monotherapy. Patients received RINVOQ 15 mg or upadacitinib 30 mg once daily, adalimumab 40 mg EOW, or placebo. From Week 16, non-responding patients could be rescued with addition or modification of standard of care. At Week 24, all patients randomized to

placebo were switched to RINVOQ 15 mg or upadacitinib 30 mg once daily in a blinded manner based on pre-determined assignment at baseline.

Study-PsA II (M15-554) was a 24-week trial in 642 patients who had an inadequate response or intolerance to at least one biologic DMARD. At baseline, 296 (46%) of patients were on at least one concomitant non-biologic DMARD, 222 (35%) of patients received concomitant MTX only, and 345 (54%) of patients were on monotherapy. Patients received RINVOQ 15 mg or upadacitinib 30 mg once daily or placebo. From Week 16, non-responding patients could be rescued with addition or modification of standard of care. At Week 24, all patients randomized to placebo were switched to RINVOQ 15 mg or upadacitinib 30 mg once daily in a blinded manner based on pre-determined assignment at baseline.

Study Results

In both studies, a significantly greater proportion of patients treated with RINVOQ 15 mg achieved ACR20 response compared to placebo at Week 12 (

Table 17, Figure 2 for PsA-I). Onset of efficacy was seen as early as Week 2 for ACR20.

Treatment with RINVOQ 15 mg resulted in improvements in individual ACR components, including tender/painful and swollen joint counts, patient and physician global assessments, HAQ-DI, pain assessment, and hsCRP compared to placebo at Week 12 (Table 18).

In Study-PsA I, RINVOQ 15 mg achieved non-inferiority compared to adalimumab in the proportion of patients achieving ACR20 response at Week 12 with values of 71% and 65% for Rinvoq and adalimumab, respectively; superiority to adalimumab could not be demonstrated.

A higher proportion of patients treated with RINVOQ 15 mg achieved ACR50 and ACR70 responses at Week 12 compared to placebo.

The efficacy of RINVOQ 15 mg, as assessed by ACR20, was demonstrated regardless of subgroups evaluated including baseline BMI, baseline hsCRP, and number of prior non-biologic DMARDs (≤ 1 or >1).

Within each study, consistent responses were observed with RINVOQ 15 mg alone or in combination with non-biologic DMARDs for primary and key secondary endpoints.

Figure 2. Percent of Patients Achieving ACR20 in Study-PsA I

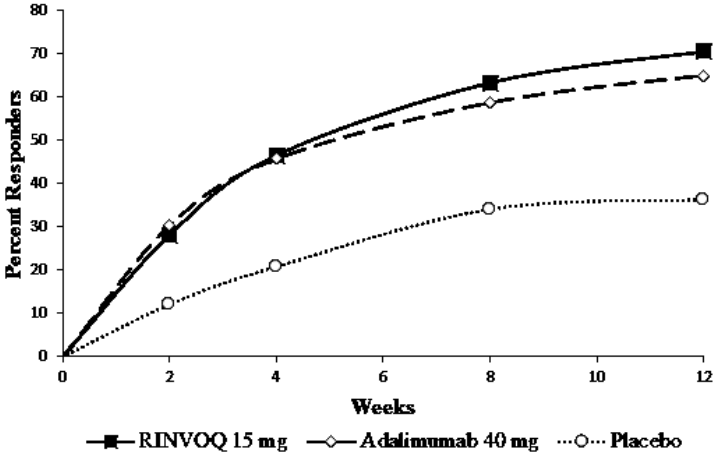


Table 17. Clinical Trial Summary

Efficacy Measure	Study	Study-PsA I non-biologic DMARD-IR			Study-PsA II bDMARD-IR	
	Treatment Group	PBO	RINVOQ 15 mg	ADA 40 mg	PBO	RINVOQ 15 mg
	N	423	429	429	212	211
ACR20 (% of patients)	Week 12	36	71[e]	65	24	57[e]
	Week 24	45	73[f]	67	20	59[f]
ACR50 (% of patients)	Week 12	13	38[f]	38	5	32[f]
	Week 24	19	52[f]	44	9	38[f]
ACR70 (% of patients)	Week 12	2	16[f]	14	1	9[f]
	Week 24	5	29[f]	23	1	19[f]
MDA (% of patients)	Week 24	12	37[e]	33	3	25[e]
Resolution of enthesitis (LEI=0; % of patients)[a]	Week 24	32	54[e]	47		
Resolution of dactylitis (LDI=0; % of patients)[b]	Week 24	40	77[b]	74		
PASI75 (% of patients)[c]	Week 16	21	63[e]	53	16	52[e]
	Week 24	27	64[f]	59	19	54[f]
sIGA 0/1 (% of patients)[d]	Week 16	11	42[e]	39	9	37[e]
Modified Sharp/van der Heijde Score	Baseline	13.05	13.44	14.89		
	Week 24	13.31	13.42[e]	14.92		

Patients who discontinued randomized treatment or were missing data at week of evaluation were imputed as non-responders in the analyses. For MDA, resolution of enthesitis, and resolution of dactylitis at Week 24, the subjects rescued at Week 16 were imputed as non-responders in the analyses.

a. In patients with enthesitis at baseline (n=241, 270, and 265, respectively)
b. In patients with dactylitis at baseline (n=126, 136, and 127, respectively). Statistical significance cannot be claimed for this endpoint based on step-down testing procedure.
c. In patients with ≥ 3% BSA psoriasis at baseline (n=211, 214, and 211, respectively, for Study-PsA I and n=131 and 130, respectively, for Study-PsA II)
d. In patients with sIGA ≥ 2 at baseline (n=313, 322, and 330, respectively, for Study-PsA I and n=163 and 171, respectively, for Study-PsA II)
e. multiplicity-controlled p≤0.001 upadacitinib vs placebo comparison. For modified Sharp/van der Heijde score, the comparison is based on analysis of covariance model for change from baseline with missing data handled by linear extrapolation.
f. nominal p≤0.001 upadacitinib vs placebo comparison

Radiographic response

In Study-PsA I, inhibition of progression of structural damage was assessed radiographically and expressed as the change from baseline in modified Sharp/van der Heijde Score (SHS). Treatment with RINVOQ 15 mg resulted in significantly greater inhibition of the progression of structural joint damage as measure by SHS compared to placebo at Week 24 (

Table 17**Error! Reference source not found.**). Similar results were observed for both of the SHS components, joint erosion and joint space narrowing scores.

Table 18. Components of ACR Response

ACR Component	Study	Study-PsA I non-biologic DMARD-IR			Study-PsA II bDMARD-IR	
	Treatment Group	PBO	RINVOQ 15 mg	ADA 40 mg	PBO	RINVOQ 15 mg
	N	423	429	429	212	211
Number of tender/painful joints (0-68)	Baseline	19.6	20.4	19.9	25.4	24.8
	Week 12	12.4	8.7[d]	9.3	19.3	12.2[d]
Number of swollen joints (0-66)	Baseline	10.9	11.5	11.6	11.8	11.2
	Week 12	5.6	3.4[d]	3.7	7.2	4.4[d]
Patient assessment of pain[a]	Baseline	6.1	6.2	5.9	6.6	6.3
	Week 12	5.1	3.8[d]	3.6	6.0	4.4[d]
Patient global assessment[a]	Baseline	6.3	6.6	6.3	6.9	6.8
	Week 12	5.2	3.8[d]	3.7	6.1	4.5[d]
Disability index (HAQ-DI)[b]	Baseline	1.11	1.15	1.11	1.23	1.08
	Week 12	0.98	0.72[c]	0.78	1.12	0.79[c]
Physician global assessment[a]	Baseline	6.5	6.7	6.6	6.4	6.5
	Week 12	4.3	3.0[d]	3.1	5.0	3.3[d]
hsCRP (mg/L)	Baseline	11.3	11.3	11.0	9.0	11.2
	Week 12	10.2	4.2[d]	3.7	9.6	3.9[d]

a. Numeric rating scale (NRS): 0 = best, 10 = worst
b. Health Assessment Questionnaire-Disability Index: 0=best, 3=worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
c. multiplicity-controlled p≤0.001 is based on mixed model for repeated measures for change from baseline for upadacitinib vs placebo comparison
d. nominal p≤0.001 is based on mixed model for repeated measures for change from baseline for upadacitinib vs placebo comparison

Response rates for ACR20/50/70, MDA, PASI75, sIGA, enthesitis resolution, and dactylitis resolution in patients treated with RINVOQ 15 mg were maintained through Week 56.

Physical function response and health-related outcomes

In both studies, patients treated with RINVOQ 15 mg showed significant improvement from baseline in physical function as assessed by HAQ-DI at Week 12 when compared to placebo (Table 18), which was maintained through Week 56.

Health-related quality of life was assessed by SF-36. In both studies, patients receiving RINVOQ 15 mg experienced significantly greater improvement from baseline in the Physical Component Summary score compared to placebo at Week 12. Improvements from baseline were maintained through Week 56 in both studies.

Patients receiving RINVOQ 15 mg experienced significantly greater improvement from baseline in fatigue, as measured by FACIT-F score, at Week 12 compared to placebo in both studies. Improvements from baseline were maintained through Week 56 in both studies.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology (single and repeat-dose studies)

In nonclinical studies, decreases in circulating lymphocytes and cellularity of lymphoid tissues, as well as suppression of erythropoiesis, were observed in rats and dogs at clinically relevant doses. In the 39-week dog study, secondary effects related to immunosuppression-induced opportunistic infections, such as demodicosis (mange) in dogs, were observed at exposures approximately two times the expected exposure (AUC) at the maximum recommended human dose (MRHD) of 15 mg daily, but there were no decreases in circulating lymphocytes and cellularity of lymphoid tissues. Immunotoxicity evaluations in male and female rats revealed complete suppression of IgM and IgG antibody responses to an injected test antigen (keyhole limpet hemocyanin) at all upadacitinib dose levels (5-50 mg/kg/day) in juvenile animals, and a dose-dependent suppression of IgM and IgG responses at all dose levels (5-60 mg/kg/day) in adult rats. The magnitude of the decreases in antibody responses were greater than the decreases in lymphocyte count in rats. The findings in juvenile and adult rats indicated upadacitinib-related suppression of antibody responses, consistent with JAK inhibition.

Carcinogenicity

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 daily MRHD exposure at 15 mg on an AUC basis for males and female rats, 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, at which systemic exposures to upadacitinib were less than 3 times that of the MRHD of 15 mg daily.

Genotoxicity

Upadacitinib was not mutagenic or genotoxic based on the results of an in vitro bacterial mutagenicity assay (Ames assay), an in vitro chromosome aberration assay in human peripheral blood lymphocytes, and an in vivo male rat bone marrow micronucleus assay for gene mutations and chromosomal aberrations.

Reproductive and Developmental Toxicology

Upadacitinib was teratogenic in rats and rabbits when given at exposures of 1.6 and 15 times the MRHD of 15 mg daily (on an AUC basis at maternal oral doses of 4 mg/kg/day and 25 mg/kg/day, respectively).

In two rat embryofetal development studies, pregnant animals were dosed orally during the period of organogenesis from gestation day (GD) 6 to GD 17. Upadacitinib was teratogenic at all dose levels studied in rats except the lowest dose of 1.5 mg/kg/day at which systemic exposure to upadacitinib was below that (approximately 0.3 times) at the MRHD of 15 mg daily on an AUC basis. At maternal oral doses of 4, 5, 25, and 75 mg/kg/day, upadacitinib-related effects included an increase in two particular skeletal malformations (i.e., misshapen humerus and bent scapula) and, at 75 mg/kg/day (at an exposure of approximately 84 times the MRHD on an AUC basis), an increase in bent bones of the fore- and hind-limbs in the absence of maternal toxicity. Additionally, at 25 and 75 mg/kg/day, there was an increase in bent ribs, a skeletal variation, which was also considered upadacitinib-related.

In a rabbit embryofetal development study, pregnant animals were dosed orally during the period of organogenesis from GD 7 to GD 19. Upadacitinib was teratogenic when given at 25 mg/kg/day. Developmental effects observed at 25 mg/kg/day in rabbits included an increase in post-implantation losses, increases in total and early resorptions, lower fetal body weights, and increased incidence of cardiac malformations. In addition, maternal toxicity was evident in the 25 mg/kg/day dose group from body weight loss, lower food consumption, and the increased occurrence of aborted pregnancies. Systemic exposure to upadacitinib at the no-effect dose of 10 mg/kg/day was about twice that at the MRHD of 15 mg daily.

In a pre-/postnatal development study in rats, development of the offspring consequent to exposure of the mothers from implantation through lactation and weaning was tested. Because manifestations of effects induced during this period may be delayed, observations were continued through sexual maturity of the pups. Mothers were dosed orally from GD 6 to Lactation Day 20. Upadacitinib had no effects at any dose level (2.5, 5, and 10 mg/kg/day) in mothers or their offspring in behavioral or reproductive endpoints.

In a fertility and early embryonic development study in rats, upadacitinib had no effect on fertility at oral doses up to 50 mg/kg/day in males and 75 mg/kg/day in females. However, maintenance of pregnancy was adversely affected at oral doses of 25 and 75 mg/kg/day as demonstrated by dose related increases in fetal resorptions associated with post-implantation losses, which were attributed to the developmental/teratogenic effects of upadacitinib in rats. The 5 mg/kg/day dose was the no-effect dose for early embryonic development.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrRINVOQ®

upadacitinib extended-release tablets

Read this carefully before you start taking **RINVOQ** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **RINVOQ**.

Serious Warnings and Precautions

Serious Infections

- You should not take RINVOQ if you have any kind of infection.
- RINVOQ is a medicine that affects your immune system. It can lower the ability of your body to fight infections. Examples of these types of infection are tuberculosis, shingles (herpes zoster) or cryptococcosis, or infections caused by other bacteria, fungi or viruses that can spread throughout your body.
- In some cases, these infections may lead to hospitalization or death.
- Most patients taking RINVOQ who developed these infections were also taking other medicines, such as methotrexate or corticosteroids. These medicines may have made it harder to fight infections.
- Contact your healthcare professional if you have:
    - fever, sweating, chills,
    - muscle aches,
    - cough,
    - shortness of breath,
    - coughing up blood,
    - weight loss,
    - warm, red, or painful skin or sores on your body,
    - diarrhea or stomach pain,
    - burning when you urinate or urinating more often than normal,
    - feeling very tired.

  These may be signs that you have an infection.
- Your healthcare professional will monitor you for the signs and symptoms of infection during and after your treatment with RINVOQ.

Cancers

Lymphoma and other cancers have been reported in patients treated with RINVOQ.

Blood clots

- Deep vein thrombosis (blood clots in the veins of your legs), pulmonary embolism (blood clots in the lungs) or arterial thrombosis (blood clot in an artery) have occurred in patients taking RINVOQ and other similar medications. These blood clots can be life-threatening and cause death.
- If you develop any signs or symptoms of a blood clot in your leg (such as swelling, pain or tenderness in the leg) or in your lung (such as sudden unexplained chest pain or shortness of breath) stop RINVOQ and seek immediate medical help.

What is RINVOQ used for?

RINVOQ is used to treat adults with:

- rheumatoid arthritis when treatment with methotrexate has not worked well or was not tolerated well. RINVOQ may be taken alone or in combination with other medicines.
- psoriatic arthritis when treatment with other medicines have not worked well or were not tolerated well. RINVOQ may be taken alone or in combination with methotrexate.

RINVOQ is not recommended for use in children and adolescents under 18 years of age.

How does RINVOQ work?

RINVOQ is a 'Janus kinase' (JAK) inhibitor. JAK is an enzyme in your body, which normally helps to turn on your immune system when you need it. The immune system then causes swelling and tenderness, which is called inflammation.

RINVOQ works by attaching to the JAK enzyme to lower its activity.

Rheumatoid arthritis

In people with rheumatoid arthritis RINVOQ can help to reduce inflammation and improve signs and symptoms like pain in and around their joints. It can help to slow down damage to the bone and joints.

Psoriatic arthritis

In people with psoriatic arthritis RINVOQ can help to reduce inflammation and improve signs and symptoms like pain, stiffness, and swelling in and around their joints, psoriatic skin rash, and tiredness. It can help to slow down damage to the bone and joints.

What are the ingredients in RINVOQ?

Medicinal ingredient: upadacitinib (as upadacitinib hemihydrate)

Non-medicinal ingredients: colloidal silicon dioxide, ferrosoferric oxide (E172), hypromellose, iron oxide red (E172), magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, tartaric acid, and titanium dioxide. The tablets are gluten-free.

RINVOQ comes in the following dosage forms:

Extended-release tablets: 15 mg upadacitinib

Do not use RINVOQ if:

- you are allergic to upadacitinib or any of the other ingredients in RINVOQ.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RINVOQ. Talk about any health conditions or problems you may have, including if you:

- have or have had tuberculosis (TB). You may need tests to check for TB before you are given RINVOQ. Tell your healthcare professional if you get a persistent cough, fever, night sweats and weight loss during RINVOQ treatment. These can be signs of TB.
- have had a herpes infection (shingles). This is because RINVOQ may allow it to come back. Tell your healthcare professional if you get a painful skin rash with blisters during RINVOQ treatment. These can be signs of shingles.
- have or have had liver problems or hepatitis B or C.
- have recently had or plan to have a vaccination (immunization). You should not be given certain types of vaccines while using RINVOQ.
- have or have had cancer. Your healthcare professional will decide if you can still be given RINVOQ.
- have high cholesterol.
- have or have had diverticulitis (inflammation in parts of your large intestine), or gastrointestinal perforation (tears in your stomach or intestine). Some people taking RINVOQ can get tears in their stomach or intestines. Patients taking medications called non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids or those who have diverticulitis are more likely to have a gastrointestinal perforation.
- have low blood cell counts. Treatment with RINVOQ can be associated with anemia (low red blood cells), neutropenia or lymphopenia (low white blood cells).
- have muscle pain and / or muscle weakness.
- are of Asian descent. This may increase your risk of having shingles.

Other warnings you should know about:

Cancer

Lymphoma and other cancers, including skin cancer, have been reported in patients treated with RINVOQ. Your healthcare professional will monitor you for the signs of skin cancer.

Blood tests

You may need blood tests before you start RINVOQ. These tests may be repeated while you are taking RINVOQ. These will help your healthcare professional to know how RINVOQ is affecting your blood and how well your liver is working.

Pregnancy and breastfeeding

- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your healthcare professional for advice before taking this medicine. You should not use RINVOQ if you are pregnant.
- Avoid becoming pregnant while taking RINVOQ. It may harm your unborn baby. Use effective birth control while you are taking RINVOQ, and for at least 4 weeks after your last dose of RINVOQ. If you become pregnant during this time, tell your healthcare professional right away.
- You should not use RINVOQ if you are breastfeeding. It is not known if RINVOQ passes into breast milk. You and your healthcare professional should decide if you will take RINVOQ or

breastfeed. Talk to your healthcare professional about the best way to feed your baby while you are being treated with RINVOQ.

Adults aged 65 years and older

Side effects have occurred more often in patients aged 65 years and older. This includes serious infections.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with RINVOQ:

- medications for fungal infections (such as ketoconazole, itraconazole, posaconazole or voriconazole).
- a medication to treat bacterial infections called clarithromycin.
- a medication to treat bacterial infections like TB called rifampicin.
- a medication to prevent seizures called phenytoin.
- medications that affect your immune system (such as azathioprine, cyclosporin, and tacrolimus).
- an herbal remedy used mainly for depression called St-John's Wort (hypericum perforatum).
- products or juices containing grapefruit. Avoid eating or drinking any products or juices containing grapefruit while taking RINVOQ.

These products may affect the amount of RINVOQ in your blood.

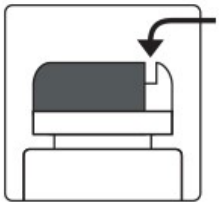
How to take RINVOQ:

- Take exactly as your healthcare professional tells you.
- Take once per day with or without food.
- Swallow tablets whole with water at about the same time each day.
- Do NOT split, crush or chew the tablets.
- Do not change your dose.
- Do not stop taking RINVOQ without first talking with your healthcare professional.

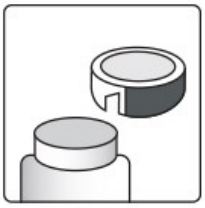
Your healthcare professional may prescribe RINVOQ alone or in combination with other medication. If you receive treatment with another drug, your healthcare professional will tell you how to take it. Be sure to read the package leaflet for the other drug as well as this one.

How to open the bottle and puncture the foil:

RINVOQ tablets will be given to you in bottles. Each bottle is sealed with foil and then closed with a cap. The cap has a cutting tool that can be used to help you puncture the foil seal.

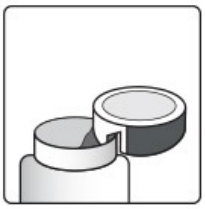


1. The cap of the RINVOQ bottle has a foil cutting tool.



2a. To remove the cap from the bottle, push down and (at the same time) turn the cap counterclockwise.

2b. Turn the cap over. Place the cutting tool near the edge of the foil seal.



3. Push down to make a hole in the foil. Move the cutting tool around the edge of the foil. This will cut the foil all the way around.

4. When you have taken your tablet, put the cap back on and close the bottle.

Usual dose:

One (15 mg) tablet per day.

Your healthcare professional may interrupt your treatment with RINVOQ if you have certain side effects.

Overdose:

If you think you, or a person you are caring for, have taken too much RINVOQ, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of RINVOQ, take your dose as soon as you remember. However, do not take more than 1 tablet per day.

What are possible side effects from using RINVOQ?

These are not all the possible side effects you may have when taking RINVOQ. If you experience any side effects not listed here, tell your healthcare professional.

- throat and nose infections
- cough
- headache
- nausea
- cold sores
- back pain
- acne
- weight gain

RINVOQ can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Bronchitis (inflammation in the lung): persistent cough with or without mucus, fatigue, shortness of breath		✓	
Herpes Zoster (shingles): painful skin rash with blisters and fever			✓
Pneumonia (lung infection): coughing, fever, fatigue		✓	
UNCOMMON			
Anemia (low red blood cells): shortness of breath, feeling very tired, pale skin, fast heartbeat, loss of energy, weakness		✓	
Cellulitis (skin infection): redness, swelling, painful skin		✓	
Deep vein thrombosis (blood clot in the deep veins of the leg or arm): swelling, pain, arm or leg may be warm to the touch and may appear red			✓
Fever		✓	
Liver problems: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, itching			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
New cancers (skin and other organs)		✓	
Osteoarthritis (wear and tear arthritis): pain, swelling, and stiffness in joints		✓	
Pulmonary embolism (blood clot in the lung): sharp chest pain, coughing up blood, sudden shortness of breath			✓
Urinary tract infection: difficulty or increased need to urinate, pain or burning sensation when peeing, pain in the pelvis or middle of the back, urine that is cloudy or bloody		✓	
RARE			
Arterial thrombosis (blood clot in an artery): chest pain, shortness of breath, dizziness, face drooping on one side, weakness in one arm, slurred speech, limbs may become painful, skin on limb may be pale or blue in colour and cold			✓
Gastrointestinal perforation (tear in the stomach or intestinal wall): abdominal pain, feeling sick, vomiting, constipation, fever			✓
Hypercholesterolemia (high cholesterol)		✓	
Increased Creatine Phosphokinase (CPK; CPK is an enzyme found in the blood when there is muscle damage): muscle aches, pain or stiffness; muscle weakness	✓		
Neutropenia, leukopenia or lymphocytopenia (low white blood cells): fever or infection, fatigue, aches and pains, flu-like symptoms, swollen lymph nodes, painful joints		✓	
Oral candidiasis (thrush in the mouth): thick white patches in the mouth, tongue or on the throat, sore throat		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 2 and 25°C in the original bottle to protect from moisture.

Keep out of reach and sight of children.

If you want more information about RINVOQ:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (www.abbvie.ca), or by calling 1-888-704-8271.

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