

リンヴォック錠 15 mg  
リンヴォック錠 7.5 mg  
に関する資料

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## 1.5 起原又は発見の経緯及び開発の経緯

### 1.5.1 起原又は発見の経緯

起原又は発見の経緯及び開発の経緯については、平成 13 年 6 月 21 日付け医薬審発第 899 号 医薬局審査管理課長通知「新医薬品の製造又は輸入の承認申請に際し承認申請書に添付すべき資料の作成要領について」の別紙 2 の 5 (1) に作成要領が示されているが、その中の「当該内容が第 2 部 (5) に記載できる場合は、第 1 部において提出を省略することができる。」との記述を基に、当該内容 (1.5 起原又は発見の経緯及び開発の経緯) を主に第 2 部 (5) (臨床に関する概括評価) に記載した。第 2 部 (5) での当該内容の記載場所を表 1.5-1 に示す。

表 1.5-1. 第 1 部 (5) に関する内容の第 2 部での記載場所

第 1 部(5) に記載すべき内容	第 2 部(5) での記載場所
起原又は発見の経緯、開発の経緯、治験相談、申請に至った経緯、開発計画	2.5.1 製品開発の根拠
本剤の有効性及び安全性	2.5.4 有効性の概括評価 2.5.5 安全性の概括評価
本剤の有効性及び安全性に基づく有用性に関する記載	2.5.6 ベネフィットとリスクに関する結論
非臨床試験成績	2.4 非臨床試験の概括評価 2.6 非臨床試験の概要文及び概要表

ウパダシチニブは、米国 AbbVie 社において創製された低分子のヤヌスキナーゼ (JAK) 1 阻害薬であり、JAK ファミリー (JAK1, JAK 2, JAK 3, 及びチロシンキナーゼ 2) のうち、JAK1 に対して選択的な阻害活性を有する。

本剤の臨床開発は、海外本社である AbbVie 社により、20 年 から関節リウマチを対象に開始され、本邦ではアッヴィ合同会社が 20 年 より臨床試験を開始した。

本剤は、2019 年 10 月時点で米国、欧州及び豪州等で関節リウマチの治療薬として承認申請し、米国においては 2019 年 8 月に承認されました。

本申請での開発経緯を表 1.5-2 に示す。

表 1.5-2. 開発の経緯

試験の相	試験番号	評価 / 参考 資料	国内 / 海外 試験	日本人を 含む試験 (Yes/No)	対象患者	実施期間							
						20■	20■	20■	20■	20■	20■	20■	20■
第 I 相	M15-878	評価	海外	Yes	健康成人								
	M13-543	評価	海外	Yes	健康成人								
	M19-952	評価	海外	Yes	健康成人								
	M13-547	参考	海外	No	健康成人								
	M14-677	参考	海外	No	健康成人								
	M14-174	参考	海外	No	健康成人								
	M14-680	参考	海外	No	健康成人								
	M14-678	参考	海外	No	健康成人								
	M14-679	参考	海外	No	健康成人								
	M16-552	参考	海外	No	健康成人								
	M16-094	参考	海外	No	健康成人								
	M15-868	参考	海外	No	健康成人								
	M13-401	参考	海外	No	健康成人								
	M13-845	参考	海外	No	健康成人								
	M13-548	参考	海外	No	健康成人								



試験の相	試験番号	評価 / 参考 資料	国内 / 海外 試験	日本人を 含む試験 (Yes/No)	対象患者	実施期間							
						20■	20■	20■	20■	20■	20■	20■	20■
	M13-539	参考	海外	No	健康成人								
	M13-551	参考	海外	No	健康成人								
	M15-558	参考	海外	No	健康成人								
	M13-540	参考	海外	No	健康成人								
	M13-541	参考	海外	No	健康成人								
	M14-624	参考	海外	No	健康成人								
	M14-625	参考	海外	No	健康成人								
	M17 221	参考	海外	No	健康成人								
第 II 相	M13-537	参考	海外	No	RA 患者								
	M13-550	参考	海外	No	RA 患者								
第 IIb/III 相	M14-663	評価	国内	Yes	RA 患者								
第 III 相	M15-555	評価	国際 共同	Yes	RA 患者								
	M13-545	評価	国際 共同	Yes	RA 患者								
	M14-465	評価	海外	No	RA 患者								
	M13-542	評価	海外	No	RA 患者								

1.6 外国における使用状況等に関する資料

1.6.1 外国における使用状況等

本剤は、2019 年 10 月時点で米国、欧州及び豪州等で関節リウマチの治療薬として承認申請し、米国においては 2019 年 8 月に承認されました。

1.6.2 海外における添付文書

1.6.2.1 米国における添付文書

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RINVOQ safely and effectively. See full prescribing information for RINVOQ.

RINVOQ™ (upadacitinib) extended-release tablets, for oral use  
Initial U.S. Approval: 2019

### WARNING: SERIOUS INFECTIONS, MALIGNANCY, AND THROMBOSIS

See full prescribing information for complete boxed warning.

- Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving RINVOQ. (5.1)
- If a serious infection develops, interrupt RINVOQ until the infection is controlled. (5.1)
- Prior to starting RINVOQ, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting RINVOQ. (5.1)
- Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative. (5.1)
- Lymphoma and other malignancies have been observed in patients treated with RINVOQ. (5.2)
- Thrombosis, including deep vein thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated with Janus kinase inhibitors used to treat inflammatory conditions. (5.3)

### INDICATIONS AND USAGE

RINVOQ is a Janus kinase (JAK) inhibitor indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. (1)

**Limitation of Use:** Use of RINVOQ in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1)

### DOSAGE AND ADMINISTRATION

- The recommended dose of RINVOQ is 15 mg once daily. (2.1)
- RINVOQ may be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs. (2.1)
- Avoid initiation or interrupt RINVOQ if absolute lymphocyte count is less than 500 cells/mm<sup>3</sup>, absolute neutrophil count is less than 1000 cells/mm<sup>3</sup>, or hemoglobin level is less than 8 g/dL. (2.2, 2.3, 5.4)

### DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 15 mg (3)

### CONTRAINDICATIONS

- None (4)

### WARNINGS AND PRECAUTIONS

- **Serious Infections:** Avoid use of RINVOQ in patients with active, serious infection, including localized infections. (5.1)
- **Malignancy:** Consider the risks and benefits of RINVOQ treatment prior to initiating therapy in patients with a known malignancy. (5.2)
- **Thrombosis:** Consider the risks and benefits prior to treating patients who may be at increased risk of thrombosis. Promptly evaluate patients with symptoms of thrombosis and treat appropriately. (5.3)
- **Gastrointestinal Perforations:** Use with caution in patients who may be at increased risk. (5.4)
- **Laboratory Monitoring:** Recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids. (5.5)
- **Embryo-Fetal Toxicity:** RINVOQ may cause fetal harm based on animal studies. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.6, 8.1, 8.3)
- **Vaccinations:** Avoid use of RINVOQ with live vaccines. (5.7)

### ADVERSE REACTIONS

Adverse reactions (greater than or equal to 1%) are: upper respiratory tract infections, nausea, cough, and pyrexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- RINVOQ should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors (e.g., ketoconazole). (7.1)
- Coadministration of RINVOQ with strong CYP3A4 inducers (e.g., rifampin) is not recommended. (7.2)

### USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2019

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## **FULL PRESCRIBING INFORMATION**

### **WARNING: SERIOUS INFECTIONS, MALIGNANCY, AND THROMBOSIS**

#### **SERIOUS INFECTIONS**

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

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

**Reported infections include:**

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

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

**Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with RINVOQ, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy [see Warnings and Precautions (5.1)].**

#### **MALIGNANCIES**

**Lymphoma and other malignancies have been observed in patients treated with RINVOQ [see Warnings and Precautions (5.2)].**

#### **THROMBOSIS**

**Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated with Janus kinase inhibitors used to treat 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 Warnings and Precautions (5.3)].**



## 1 INDICATIONS AND USAGE

### 1.1 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.

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

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Dosage in Rheumatoid Arthritis

The recommended oral dose of RINVOQ is 15 mg once daily with or without food [see *Clinical Pharmacology* (12.3)].

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

### 2.2 Important Administration Instructions

- RINVOQ initiation is not recommended in patients with an absolute lymphocyte count (ALC) less than 500 cells/mm<sup>3</sup>, absolute neutrophil count (ANC) less than 1000 cells/mm<sup>3</sup>, or hemoglobin level less than 8 g/dL [see *Warnings and Precautions* (5.4)].
- RINVOQ is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) [see *Use in Specific Populations* (8.7) and *Clinical Pharmacology* (12.3)].
- RINVOQ tablets should be swallowed whole. RINVOQ should not be split, crushed, or chewed.

### 2.3 Dose Interruption

RINVOQ treatment should be interrupted if a patient develops a serious infection until the infection is controlled [see *Warnings and Precautions* (5.1)].

Interruption of dosing may be needed 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 <sup>3</sup> and may be restarted once ANC return above this value
Absolute Lymphocyte Count (ALC)	Treatment should be interrupted if ALC is less than 500 cells/mm <sup>3</sup> and may be restarted once ALC return above this value
Hemoglobin (Hb)	Treatment should be interrupted if Hb is less than 8 g/dL

	and may be restarted once Hb return above this value
Hepatic transaminases	Treatment should be interrupted if drug-induced liver injury is suspected

### 3 DOSAGE FORMS AND STRENGTHS

RINVOQ 15 mg extended-release tablets for oral administration are purple, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with 'a15' on one side.

### 4 CONTRAINDICATIONS

None

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Serious Infections

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

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

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

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with RINVOQ. Interrupt RINVOQ if a patient develops a serious or opportunistic infection. A patient who develops a new infection during treatment with RINVOQ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and RINVOQ should be interrupted if the patient is not responding to antimicrobial therapy. RINVOQ may be resumed once the infection is controlled.

#### Tuberculosis

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 *Adverse Reactions* (6.1)]. 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 Phase 3 studies of RINVOQ. If hepatitis B virus DNA is detected while receiving RINVOQ, a liver specialist should be consulted.

### **5.2 Malignancy**

Malignancies were observed in clinical studies of RINVOQ [see *Adverse Reactions* (6.1)]. 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

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

### **5.3 Thrombosis**

Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, have occurred in patients treated for inflammatory conditions with Janus kinase (JAK) inhibitors, including RINVOQ. 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, patients should be evaluated promptly and treated appropriately.

### **5.4 Gastrointestinal Perforations**

Events of gastrointestinal perforation have been reported in clinical studies with RINVOQ, 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 NSAIDs). Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

## **5.5 Laboratory Parameters**

### Neutropenia

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

Evaluate neutrophil counts at baseline and thereafter according to routine patient management. Avoid initiation of or interrupt RINVOQ treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/mm<sup>3</sup>) [*see Dosage and Administration (2.2, 2.3)*].

### Lymphopenia

ALC less than 500 cells/mm<sup>3</sup> were reported in RINVOQ clinical studies.

Evaluate lymphocyte counts at baseline and thereafter according to routine patient management. Avoid initiation of or interrupt RINVOQ treatment in patients with a low lymphocyte count (i.e., less than 500 cells/mm<sup>3</sup>) [*see Dosage and Administration (2.2, 2.3)*].

### Anemia

Decreases in hemoglobin levels to less than 8 g/dL were reported in RINVOQ clinical studies.

Evaluate hemoglobin at baseline and thereafter according to routine patient management. Avoid initiation of or interrupt RINVOQ treatment in patients with a low hemoglobin level (i.e., less than 8 g/dL) [*see Dosage and Administration (2.2, 2.3)*].

### Lipids

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

Patients should be monitored 12 weeks after initiation of treatment, and thereafter according to the clinical guidelines for hyperlipidemia. Manage patients according to clinical guidelines for the management of hyperlipidemia.

### Liver Enzyme Elevations

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

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

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

## 5.6 Embryo-Fetal Toxicity

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

## 5.7 Vaccination

Use of live, attenuated vaccines during, or immediately prior to, RINVOQ therapy is not recommended. Prior to initiating RINVOQ, it is recommended that patients be brought up to date with all immunizations, including prophylactic zoster vaccinations, in agreement with current immunization guidelines.

# 6 ADVERSE REACTIONS

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

- Serious Infections [see *Warnings and Precautions* (5.1)]
- Malignancy [see *Warnings and Precautions* (5.2)]
- Thrombosis [see *Warnings and Precautions* (5.3)]
- Gastrointestinal Perforations [see *Warnings and Precautions* (5.4)]
- Laboratory Parameters [see *Warnings and Precautions* (5.5)]

## 6.1 Clinical Trials Experience

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

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

Patients could advance or switch to RINVOQ 15 mg from placebo, or be rescued to RINVOQ from active comparator or placebo from as early as Week 12 depending on the study design.

A total of 2630 patients received at least 1 dose of RINVOQ 15 mg, of whom 1860 were exposed for at least one year. In studies RA-I, RA-II, RA-III and RA-V, 1213 patients received at least 1 dose of RINVOQ 15 mg, of which 986 patients were exposed for at least one year, and 1203 patients received at least 1 dose of upadacitinib 30 mg, of which 946 were exposed for at least one year.

**Table 2: Adverse Reactions Reported in greater than or equal to 1% of Rheumatoid Arthritis Patients Treated with RINVOQ 15 mg in Placebo-controlled Studies**

Adverse Reaction	Placebo	RINVOQ 15 mg
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	n=1042 (%)	n=1035 (%)
Upper respiratory tract infection (URTI)*	9.5	13.5
Nausea	2.2	3.5
Cough	1.0	2.2
Pyrexia	0	1.2
*URTI includes: acute sinusitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, viral upper respiratory tract infection		

Other adverse reactions reported in less than 1% of patients in the RINVOQ 15 mg group and at a higher rate than in the placebo group through Week 12 included pneumonia, herpes zoster, herpes simplex (includes oral herpes), and oral candidiasis.

Four integrated datasets are presented in the Specific Adverse Reaction section:

**Placebo-controlled Studies:** Studies RA-III, RA-IV, and RA-V were integrated to represent safety through 12/14 weeks for placebo (n=1042) and RINVOQ 15 mg (n=1035). Studies RA-III and RA-V were integrated to represent safety through 12 weeks for placebo (n=390), RINVOQ 15 mg (n=385), upadacitinib 30 mg (n=384). Study RA-IV did not include the 30 mg dose and, therefore, safety data for upadacitinib 30 mg can only be compared with placebo and RINVOQ 15 mg rates from pooling studies RA-III and RA-V.

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

**12-Month Exposure Dataset:** Studies RA-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 reported in this section.

### Specific Adverse Reactions

#### *Infections*

**Placebo-controlled Studies:** In RA-III, RA-IV, and RA-V, infections were reported in 218 patients (95.7 per 100 patient-years) treated with placebo and 284 patients (127.8 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, infections were reported in 99 patients (136.5 per 100 patient-years) treated with placebo, 118 patients (164.5 per 100 patient-years) treated with RINVOQ 15 mg, and 126 patients (180.3 per 100 patient-years) treated with upadacitinib 30 mg.

**MTX-controlled Studies:** Infections were reported in 127 patients (119.5 per 100 patient-years) treated with MTX monotherapy, 104 patients (91.8 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 128 patients (115.1 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

**12-Month Exposure Dataset:** Infections were reported in 615 patients (83.8 per 100 patient-years) treated with RINVOQ 15 mg and 674 patients (99.7 per 100 patient-years) treated with upadacitinib 30 mg.

### Serious Infections

Placebo-controlled Studies: In RA-III, RA-IV, and RA-V, serious infections were reported in 6 patients (2.3 per 100 patient-years) treated with placebo, and 12 patients (4.6 per 100 patient-years) treated with RINVOQ 15 mg. In RA-III and RA-V, serious infections were reported in 1 patient (1.2 per 100 patient-years) treated with placebo, 2 patients (2.3 per 100 patient-years) treated with RINVOQ 15 mg, and 7 patients (8.2 per 100 patient-years) treated with upadacitinib 30 mg.

MTX-controlled Studies: Serious infections were reported in 2 patients (1.6 per 100 patient-years) treated with MTX monotherapy, 3 patients (2.4 per 100 patient-years) treated with RINVOQ 15 mg monotherapy, and 8 patients (6.4 per 100 patient-years) treated with upadacitinib 30 mg monotherapy.

12-Month Exposure Dataset: Serious infections were reported in 38 patients (3.5 per 100 patient-years) treated with RINVOQ 15 mg and 59 patients (5.6 per 100 patient-years) treated with upadacitinib 30 mg.

The most frequently reported serious infections were pneumonia and cellulitis.

### *Tuberculosis*

Placebo-controlled Studies and MTX-controlled Studies: In the placebo-controlled period, there were no active cases of tuberculosis reported in the placebo, RINVOQ 15 mg, and upadacitinib 30 mg groups. In the MTX-controlled period, there were no active cases of tuberculosis reported in the MTX monotherapy, RINVOQ 15 mg monotherapy, and upadacitinib 30 mg monotherapy groups.

12-Month Exposure Dataset: Active tuberculosis was reported for 2 patients treated with RINVOQ 15 mg and 1 patient treated with upadacitinib 30 mg. Cases of extra-pulmonary tuberculosis were reported.

### *Opportunistic Infections (excluding tuberculosis)*

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

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

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

### *Malignancy*

Placebo-controlled Studies: In RA-III, RA-IV, and RA-V, malignancies excluding NMSC were reported in 1 patient (0.4 per 100 patient-years) treated with placebo, and 1 patient (0.4 per 100



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

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

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

### *Gastrointestinal Perforations*

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

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

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

### *Thrombosis*

Placebo-controlled Studies: In RA-IV, venous thrombosis (pulmonary embolism or deep vein thrombosis) was observed in 1 patient treated with placebo and 1 patient treated with RINVOQ 15 mg. In RA-V, venous thrombosis was observed in 1 patient treated with RINVOQ 15 mg. There were no observed cases of venous thrombosis reported in RA-III. No cases of arterial thrombosis were observed through 12/14 weeks.

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

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

### Laboratory Abnormalities

#### *Hepatic Transaminase Elevations*

In placebo-controlled studies (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, alanine transaminase (ALT) and aspartate transaminase (AST) elevations  $\geq 3 \times$  upper limit of normal (ULN) in at least one measurement were observed in 2.1% and 1.5% of

patients treated with RINVOQ 15 mg, and in 1.5% and 0.7% of patients treated with placebo, respectively. In RA-III and RA-V, ALT and AST elevations  $\geq 3 \times$  ULN in at least one measurement were observed in 0.8% and 1.0% of patients treated with RINVOQ 15 mg, 1.0% and 0% of patients treated with upadacitinib 30 mg and in 1.3% and 1.0% of patients treated with placebo, respectively.

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

### *Lipid Elevations*

Upadacitinib treatment was associated with dose-related increases in total cholesterol, triglycerides and LDL cholesterol. Upadacitinib was also associated with increases in HDL cholesterol. Elevations in LDL and HDL cholesterol peaked by Week 8 and remained stable thereafter. In controlled 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 14.81 mg/dL and 17.17 mg/dL.
- Mean HDL cholesterol increased by 8.16 mg/dL and 9.01 mg/dL.
- The mean LDL/HDL ratio remained stable.
- Mean triglycerides increased by 13.55 mg/dL and 14.44 mg/dL.

### *Creatine Phosphokinase Elevations*

In placebo-controlled studies (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related increases in creatine phosphokinase (CPK) values were observed. CPK elevations  $> 5 \times$  ULN were reported in 1.0%, and 0.3% of patients over 12/14 weeks in the RINVOQ 15 mg and placebo groups, respectively. Most elevations  $> 5 \times$  ULN were transient and did not require treatment discontinuation. In RA-III and RA-V, CPK elevations  $> 5 \times$  ULN were observed in 0.3% of patients treated with placebo, 1.6% of patients treated with RINVOQ 15 mg, and none in patients treated with upadacitinib 30 mg.

### *Neutropenia*

In placebo-controlled studies (RA-III, RA-IV, and RA-V) with background DMARDs, for up to 12/14 weeks, dose-related decreases in neutrophil counts, below 1000 cells/mm<sup>3</sup> in at least one measurement occurred in 1.1% and  $< 0.1\%$  of patients in the RINVOQ 15 mg and placebo groups, respectively. In RA-III and RA-V, decreases in neutrophil counts below 1000 cells/mm<sup>3</sup> in at least one measurement occurred in 0.3% of patients treated with placebo, 1.3% of patients treated with RINVOQ 15 mg, and 2.4% of patients treated with upadacitinib 30 mg. In clinical studies, treatment was interrupted in response to ANC less than 500 cells/mm<sup>3</sup>.

### *Lymphopenia*

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



least one measurement occurred in 0.5% of patients treated with placebo, 0.5% of patients treated with RINVOQ 15 mg, and 2.4% of patients treated with upadacitinib 30 mg.

### *Anemia*

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

## **7 DRUG INTERACTIONS**

### **7.1 Strong CYP3A4 Inhibitors**

Upadacitinib exposure is increased when co-administered with strong CYP3A4 inhibitors (such as ketoconazole) [see *Clinical Pharmacology* (12.3)]. RINVOQ should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors.

### **7.2 Strong CYP3A4 Inducers**

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

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

The limited human data on use of RINVOQ in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects or miscarriage. Based on animal studies, upadacitinib has the potential to adversely affect a developing fetus.

In animal embryo-fetal development studies, oral upadacitinib administration to pregnant rats and rabbits at exposures equal to or greater than approximately 1.6 and 15 times the maximum recommended human dose (MRHD), respectively, resulted in dose-related increases in skeletal malformations (rats only), an increased incidence of cardiovascular malformations (rabbits only), increased post-implantation loss (rabbits only), and decreased fetal body weights in both rats and rabbits. No developmental toxicity was observed in pregnant rats and rabbits treated with oral upadacitinib during organogenesis at approximately 0.3 and 2 times the exposure at the MRHD. In a pre- and post-natal development study in pregnant female rats, oral upadacitinib administration at exposures approximately 3 times the MRHD resulted in no maternal or developmental toxicity [see *Animal Data*].

The estimated background risks of major birth defects and miscarriage for the indicated population(s) are unknown. All pregnancies have a background risk of birth defect, loss, or other

adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages are 2-4% and 15-20%, respectively.

### Clinical Considerations

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

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

### Data

#### *Animal Data*

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

In a second oral embryo-fetal development study, pregnant rats received upadacitinib at doses of 1.5 and 4 mg/kg/day during the period of organogenesis from gestation day 6 to 17. Upadacitinib was teratogenic (skeletal malformations that included bent humerus and scapula) at exposures approximately 1.6 times the MRHD (on an AUC basis at maternal oral doses of 4 mg/kg/day). No developmental toxicity was observed in rats at an exposure approximately 0.3 times the MRHD (on an AUC basis at a maternal oral dose of 1.5 mg/kg/day).

In an oral embryo-fetal developmental study, pregnant rabbits received upadacitinib at doses of 2.5, 10, and 25 mg/kg/day during the period of organogenesis from gestation day 7 to 19. Embryo lethality, decreased fetal body weights, and cardiovascular malformations were observed in the presence of maternal toxicity at an exposure approximately 15 times the MRHD (on an AUC basis at a maternal oral dose of 25 mg/kg/day). Embryo lethality consisted of increased post-implantation loss that was due to elevated incidences of both total and early resorptions. No developmental toxicity was observed in rabbits at an exposure approximately 2 times the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

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

## **8.2 Lactation**

### Risk Summary

There are no data on the presence of upadacitinib in human milk, the effects on the breastfed infant, or the effects on milk production. Available pharmacodynamic/toxicological data in



animals have shown excretion of upadacitinib in milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious adverse reactions in the breastfed infant, advise patients that breastfeeding is not recommended during treatment with upadacitinib, and for 6 days (approximately 10 half-lives) after the last dose.

## Data

### *Animal Data*

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

## **8.3 Females and Males of Reproductive Potential**

### Pregnancy Testing

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

### Contraception

#### *Females*

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

## **8.4 Pediatric Use**

The safety and efficacy of RINVOQ in children and adolescents aged 0 to 18 years have not yet been established. No data are available.

## **8.5 Geriatric Use**

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

## **8.6 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 *Clinical Pharmacology* (12.3)].

## **8.7 Hepatic Impairment**

No dose adjustment is required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. RINVOQ is not recommended for use in patients with severe hepatic

impairment (Child Pugh C) [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*].

## 10 OVERDOSAGE

Upadacitinib was administered in clinical trials up to doses equivalent in daily AUC 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.

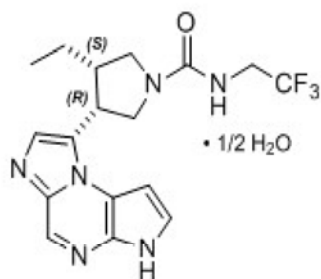
## 11 DESCRIPTION

RINVOQ is formulated with upadacitinib, a JAK inhibitor.

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

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

Upadacitinib has a molecular weight of 389.38 g/mol and a molecular formula of C<sub>17</sub>H<sub>19</sub>F<sub>3</sub>N<sub>6</sub>O • ½ H<sub>2</sub>O. The chemical structure of upadacitinib is:



RINVOQ 15 mg extended-release tablets for oral administration are purple, biconvex oblong, with dimensions of 14 x 8 mm, and debossed with 'a15' on one side.

Each tablet contains the following inactive ingredients: microcrystalline cellulose, hypromellose, mannitol, tartaric acid, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, ferrousferic oxide, and iron oxide red.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Upadacitinib is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to

influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Upadacitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs.

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

## **12.2 Pharmacodynamics**

### Inhibition of IL-6 induced STAT3 and IL-7 induced STAT5 phosphorylation

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

### Lymphocytes

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

### Cardiac Electrophysiology

At 6 times the mean maximum exposure of the 15 mg once daily dose, there was no clinically relevant effect on the QTc interval.

## **12.3 Pharmacokinetics**

Upadacitinib plasma exposures are proportional to dose over the therapeutic dose range. Steady-state plasma concentrations are achieved within 4 days with minimal accumulation after multiple once-daily administrations.

### Absorption

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



Coadministration of upadacitinib with a high-fat/ high-calorie meal had no clinically relevant effect on upadacitinib exposures (increased  $AUC_{inf}$  by 29% and  $C_{max}$  by 39%). In clinical trials, upadacitinib was administered without regard to meals [see *Dosage and Administration* (2.1)].

### 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 8 to 14 hours.

### Specific Populations

#### *Body Weight, Gender, Race, and Age*

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

#### *Renal Impairment*

Renal impairment has no clinically relevant effect on upadacitinib exposure. Upadacitinib  $AUC_{inf}$  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.

#### *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).

### Drug Interaction Studies

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

Upadacitinib is metabolized *in vitro* by CYP3A4 with a minor contribution from CYP2D6. The effect of co-administered drugs on upadacitinib plasma exposures is provided in Table 3 [see Drug Interactions (7)].

**Table 3: Change in Pharmacokinetics of Upadacitinib in the Presence of Co-administered Drugs**

Co-administered Drug	Regimen of Co-administered Drug	Ratio (90% CI) <sup>a</sup>	
		C <sub>max</sub>	AUC
Methotrexate	10 to 25 mg/week	0.97 (0.86-1.09)	0.99 (0.93- 1.06)
Strong CYP3A4 inhibitor: Ketoconazole	400 mg once daily x 6 days	1.70 (1.55-1.89)	1.75 (1.62-1.88)
Strong CYP3A4 inducer: Rifampin	600 mg once daily x 9 days	0.49 (0.44-0.55)	0.39 (0.37-0.42)
OATP1B inhibitor: Rifampin	600 mg single dose	1.14 (1.02-1.28)	1.07 (1.01-1.14)
CI: Confidence interval			
<sup>a</sup> Ratios for C <sub>max</sub> and AUC compare co-administration of the medication with upadacitinib vs. administration of upadacitinib alone.			

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

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

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

Clinical studies indicate that upadacitinib has no clinically relevant effects on the pharmacokinetics of co-administered drugs. Summary of results from clinical studies which evaluated the effect of upadacitinib on other drugs is provided in Table 4.

**Table 4: Change in Pharmacokinetics of Co-administered Drugs or In Vivo Markers of CYP Activity in the Presence of Upadacitinib**

Co-administered Drug or CYP Activity Marker	Multiple-Dose Regimen of Upadacitinib	Ratio (90% CI) <sup>a</sup>	
		C <sub>max</sub>	AUC