リンヴォック錠 15 mg
リンヴォック錠 7.5 mg
リンヴォック錠 30 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

ウパダシチニブはヤヌスキナーゼ（JAK）の選択的阻害剤であり，国内において，米国や欧州等と同様に，既存治療で効果不十分な関節リウマチに対する治療薬として承認されている。さらに，現在，乾癬性関節炎に関して本邦において申請中であり，体軸性脊椎関節炎，クローン病，潰瘍性大腸炎，巨細胞性動脈炎，高安動脈炎及び化膿性汗腺炎などの炎症性疾患を対象として臨床試験を実施している。

上記に加え，以下に示すアトピー性皮膚炎（AD）を対象とした第 III 相試験が，アッヴィ合同会社及び AbbVie Inc.社により実施された。

本申請での臨床データパッケージ及び開発の経緯を表 1.5-2 及び表 1.5-3 に示す。

表 1.5-2. 臨床データパッケージ

試験の相	試験番号、解析名（又は報告書名）	評価／参考	内容
第 II 相	M16-048	評価	ウパダシチニブ単剤の有効性，安全性を評価する用量設定試験
第 III 相	M16-045	評価	ウパダシチニブ単独療法の有効性，安全性をプラセボと比較する第 III 相無作為化二重盲検試験
第 III 相	M16-047	評価	ウパダシチニブと外用薬の併用療法の有効性及び安全性を外用薬単剤療法と比較する試験
第 III 相	M17-377	評価	ウパダシチニブのステロイド外用薬との併用療法の安全性を評価する第 III 相無作為化二重盲検試験
第 I 相	M20-017	参考	第 III 相試験で用いた製剤と市販予定製剤のバイオアベイラビリティを比較する臨床薬理試験

表 1.5-3. 開発の経緯

試験の相	試験番号	国内/海外試験	対象患者	実施期間
				20[redacted]	20[redacted]	20[redacted]	20[redacted]	20[redacted]
第 II 相	M16-048	国際共同試験	AD 患者	[redacted]
第 III 相	M16-045	国際共同試験	AD 患者	
第 III 相	M16-047	国際共同試験	AD 患者	
第 III 相	M17-377	国内試験	AD 患者	
第 I 相	M20-017	海外試験	健康成人	

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

2020 年 9 月 23 日現在，ウパダシチニブは，中等度から重度の活動性成人関節リウマチ患者に対する治療薬として，1 日 1 回 15mg の用量で，米国及び EU を含む 50 ヵ国以上で承認されている。

米国では，ウパダシチニブは，メトトレキサートに対して効果不十分又は不耐性の中等度から重度の活動性関節リウマチ成人患者の治療薬として米国食品医薬品局（FDA）により 2019 年 8 月に承認された。EU では，ウパダシチニブは，1 剤以上の疾患修飾性抗リウマチ薬（DMARD）で効果不十分又は忍容性がない中等度から重度の活動性関節リウマチの成人患者に対する治療薬として欧州医薬品庁（EMA）により中央審査方式で，2019 年 12 月に承認された。

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^3, absolute neutrophil count is less than 1000 cells/mm^3, or hemoglobin level is less than 8 g/dL. (2.2, 2.3, 5.5)

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.

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: 7/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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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^3, absolute neutrophil count (ANC) less than 1000 cells/mm^3, or hemoglobin level less than 8 g/dL *[see Warnings and Precautions (5.5)]*.
- 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^3 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^3 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^3).

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^3) *[see Dosage and Administration (2.2, 2.3)]*.

Lymphopenia

ALC less than 500 cells/mm^3 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^3) *[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
	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 ≥ 3 x upper limit of normal (ULN) in at least one measurement were observed in 2.1% and 1.5% of patients treated with RINVOQ 15 mg, and in 1.5% and 0.7% of patients treated with placebo,

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

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

Lipid Elevations

Upadacitinib treatment was associated with dose-related increases in total cholesterol, triglycerides and LDL cholesterol. Upadacitinib was also associated with increases in HDL cholesterol. Elevations in LDL and HDL cholesterol peaked by Week 8 and remained stable thereafter. In controlled 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 x ULN were reported in 1.0%, and 0.3% of patients over 12/14 weeks in the RINVOQ 15 mg and placebo groups, respectively. Most elevations >5 x ULN were transient and did not require treatment discontinuation. In RA-III and RA-V, CPK elevations > 5 x ULN were observed in 0.3% of patients treated with placebo, 1.6% of patients treated with RINVOQ 15 mg, and none in patients treated with upadacitinib 30 mg.

Neutropenia

In placebo-controlled 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^3 in at least one measurement occurred in 1.1% and <0.1% of patients in the RINVOQ 15 mg and placebo groups, respectively. In RA-III and RA-V, decreases in neutrophil counts below 1000 cells/mm^3 in at least one measurement occurred in 0.3% of patients treated with placebo, 1.3% of patients treated with RINVOQ 15 mg, and 2.4% of patients treated with upadacitinib 30 mg. In clinical studies, treatment was interrupted in response to ANC less than 1000 cells/mm^3.

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^3 in at least one measurement occurred in 0.9% and 0.7% of patients in the RINVOQ 15 mg and placebo groups, respectively. In RA-III and RA-V, decreases in lymphocyte counts below 500 cells/mm^3 in at

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

Anemia

In placebo-controlled 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. Embryolethality, 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). Embryolethality consisted of increased post-implantation loss that was due to elevated incidences of both total and early resorptions. No developmental toxicity was observed in rabbits at an exposure approximately 2 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_{0-t} values. Approximately 97% of drug-related material in milk was parent drug.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

Females

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

8.4 Pediatric Use

The safety and efficacy of RINVOQ in children and adolescents aged 0 to less than 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.

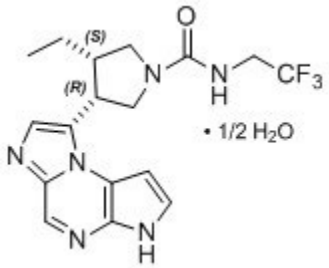
11 DESCRIPTION

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 ºC.

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



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

Each tablet contains the following inactive ingredients: microcrystalline cellulose, hypromellose, mannitol, tartaric acid, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, ferrosoferric 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)[a]	
		C_{max}	AUC
Methotrexate	10 to 25 mg/week	0.97 (0.86-1.09)	0.99 (0.93- 1.06)
Strong CYP3A4 inhibitor: Ketoconazole	400 mg once daily x 6 days	1.70 (1.55-1.89)	1.75 (1.62-1.88)
Strong CYP3A4 inducer: Rifampin	600 mg once daily x 9 days	0.49 (0.44-0.55)	0.39 (0.37-0.42)
OATP1B inhibitor: Rifampin	600 mg single dose	1.14 (1.02-1.28)	1.07 (1.01-1.14)
CI: Confidence interval [a] Ratios for C_{max} and AUC compare co-administration of the medication with upadacitinib vs. administration of upadacitinib alone.			

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

Potential for Upadacitinib to Influence the Pharmacokinetics of Other Drugs

In vitro studies indicate that upadacitinib does not inhibit 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)[a]	
		C_{max}	AUC
Methotrexate	6 mg to 24 mg BID[b]	1.03	1.14

		(0.86-1.23)	(0.91-1.43)
Sensitive CYP1A2 Substrate: Caffeine	30 mg QD[c]	1.13 (1.05-1.22)	1.22 (1.15-1.29)
Sensitive CYP3A Substrate: Midazolam	30 mg QD[c]	0.74 (0.68-0.80)	0.74 (0.68-0.80)
Sensitive CYP2D6 Substrate: Dextromethorphan	30 mg QD[c]	1.09 (0.98-1.21)	1.07 (0.95-1.22)
Sensitive CYP2C9 Substrate: S-Warfarin	30 mg QD[c]	1.07 (1.02-1.11)	1.11 (1.07-1.15)
Sensitive CYP2C19 Marker: 5-OH Omeprazole to Omeprazole metabolic ratio	30 mg QD[c]	--	1.09 (1.00-1.19)
CYP2B6 Substrate: Bupropion	30 mg QD[c]	0.87 (0.79-0.96)	0.92 (0.87-0.98)
Rosuvastatin	30 mg QD[c]	0.77 (0.63-0.94)	0.67 (0.56-0.82)
Atorvastatin	30 mg QD[c]	0.88 (0.79-0.97)	0.77 (0.70-0.85)
Ethinylestradiol	30 mg QD[c]	0.96 (0.89-1.02)	1.11 (1.04-1.19)
Levonorgestrel	30 mg QD[c]	0.96 (0.87-1.06)	0.96 (0.85-1.07)

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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

Impairment of Fertility

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

14 CLINICAL STUDIES

The efficacy and safety of RINVOQ 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 ACR/EULAR 2010 classification criteria. Patients 18 years of age and older were eligible to participate. The presence of at least 6 tender and 6 swollen joints and evidence of systemic inflammation based on elevation of hsCRP was required at baseline. Although other doses have been studied, the recommended dose of RINVOQ is 15 mg once daily.

Study RA-I (NCT02706873) was a 24-week monotherapy trial in 947 patients with moderately to severely active rheumatoid arthritis who were naïve to methotrexate (MTX). Patients received RINVOQ 15 mg or upadacitinib 30 mg once daily or MTX as monotherapy. At Week 26, non-responding patients on upadacitinib could be rescued with the addition of MTX, while patients on MTX could be rescued with the addition of blinded RINVOQ 15 mg or upadacitinib 30 mg once daily. The primary endpoint was the proportion of patients who achieved an ACR50 response at Week 12. Key secondary endpoints included disease activity score (DAS28-CRP) ≤3.2 at Week 12, DAS28-CRP <2.6 at Week 24, change from baseline in HAQ-DI at Week 12, and change from baseline in van der Heijde-modified total Sharp Score (mTSS) at Week 24.

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

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

included DAS28-CRP ≤3.2, DAS28-CRP<2.6, and change from baseline in HAQ-DI at Week 12.

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

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

Clinical Response

The percentages of RINVOQ-treated patients achieving ACR20, ACR50, and ACR70 responses, and DAS28(CRP) < 2.6 in all studies are shown in Table 5.

Patients treated with RINVOQ 15 mg, alone or in combination with cDMARDs, achieved higher ACR response rates compared to MTX monotherapy or placebo, respectively, at the primary efficacy timepoint (Table 5).

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

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

Treatment with RINVOQ 15 mg, alone or in combination with cDMARDs, resulted in greater improvements in the ACR components compared to MTX or placebo at the primary efficacy timepoint (Table 6).

Table 5: Clinical Response

	Study RA-I MTX-Naïve		**Study RA-II MTX-IR**		**Study RA-III cDMARD-IR**		**Study RA-IV MTX-IR**		**Study RA-V bDMARD-IR**	
	Monotherapy		Monotherapy		Background cDMARDs		Background MTX		Background cDMARDs	
	MTX	RINVOQ 15 mg %	MTX	RINVOQ 15 mg %	PBO	RINVOQ 15 mg %	PBO	RINVOQ 15 mg %	PBO	RINVOQ 15 mg %

		Δ (95% CI)		Δ (95% CI)		Δ (95% CI)		Δ (95% CI)		Δ (95% CI)
N	314	317	216	217	221	221	651	651	169	164
Week										
ACR20										
12[a]/14[b]	54	76 22 (14, 29)	41	68 26 (17, 36)	36	64 28 (19, 37)	36	71 34 (29, 39)	28	65 36 (26, 46)
24[c]/26[d]	59	79 20 (13, 27)					36	67 32 (27, 37)		
ACR50										
12[a]/14[b]	28	52 24 (16, 31)	15	42 27 (18, 35)	15	38 23 (15, 31)	15	45 30 (26, 35)	12	34 22 (14, 31)
24[c]/26[d]	33	60 27 (19, 34)					21	54 33 (28, 38)		
ACR70										
12[a]/14[b]	14	32 18 (12, 25)	3	23 20 (14, 26)	6	21 15 (9, 21)	5	25 20 (16, 24)	7	12 5 (-1, 11)
24[c]/26[d]	18	44 26 (19, 33)					10	35 25 (21, 29)		
DAS28-CRP <2.6										
12[a]/14[b]	14	36 22 (15, 28)	8	28 20 (13, 27)	10	31 21 (14, 28)	6	29 23 (19, 27)	9	29 19 (11, 27)
24[c]/26[d]	18	48 30 (23, 37)					9	41 32 (27, 36)		

Abbreviations: ACR20 (or 50 or 70) = American College of Rheumatology ≥20% (or ≥50% or ≥70%) improvement; bDMARD = biologic disease-modifying anti-rheumatic drug; CRP = c-reactive protein; DAS28 = Disease Activity Score 28 joints; cDMARDs = conventional disease-modifying anti-rheumatic drugs; MTX = methotrexate; PBO = placebo; IR = inadequate responder

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 RA-I, Study RA-III, Study RA-IV, Study RA-V

[b] Study RA-II

[c] Study RA-I

[d] Study RA-IV

Table 6: Components of ACR Response at Primary Efficacy Timepoint[a]

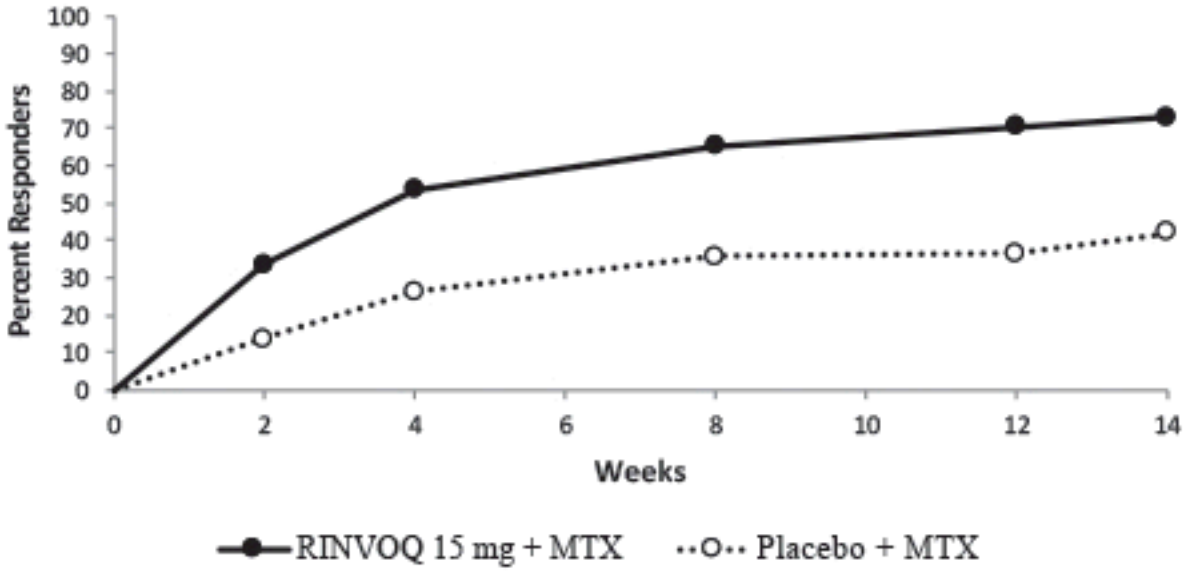
	Study RA-I MTX-Naïve		**Study RA-II[b] MTX-IR**		**Study RA-III cDMARD-IR**		**Study RA-IV MTX-IR**		**Study RA-V bDMARD-IR**	
	Monotherapy		Monotherapy		Background cDMARDs		Background MTX		Background cDMARDs	
	MTX	RINVOQ 15 mg	MTX	RINVOQ 15 mg	PBO	RINVOQ 15 mg	PBO	RINVOQ 15 mg	PBO	RINVOQ 15 mg
N	314	317	216	217	221	221	651	651	169	164
Number of tender joints (0-68)										

Baseline	26 (16)	25 (14)	25 (16)	24 (15)	25 (15)	25 (14)	26 (14)	26 (15)	28 (15)	28 (16)
Week 12/14	13 (15)	9 (12)	15 (16)	10 (13)	16 (17)	12 (14)	16 (15)	10 (13)	18 (17)	11 (14)
Number of swollen joints (0-66)										
Baseline	17 (11)	17 (10)	17 (12)	16 (11)	15 (9)	16 (10)	16 (9)	17 (10)	16 (10)	17 (11)
Week 12/14	6 (8)	5 (7)	9 (11)	6 (9)	9 (10)	7 (10)	9 (9)	5 (7)	9 (10)	6 (8)
Pain[c]										
Baseline	66 (21)	68 (21)	63 (21)	62 (23)	62 (21)	64 (19)	65 (21)	66 (21)	69 (21)	68 (20)
Week 12/14	41 (25)	31 (25)	49 (25)	36 (27)	51 (26)	33 (24)	49 (25)	33 (24)	55 (28)	41 (28)
Patient global assessment[c]										
Baseline	66 (21)	67 (22)	60 (22)	62 (22)	60 (20)	63 (22)	64 (21)	64 (22)	66 (23)	67 (20)
Week 12/14	42 (25)	31 (24)	48 (26)	37 (27)	50 (26)	32 (24)	48 (24)	33 (24)	54 (28)	40 (26)
Disability Index (HAQ-DI)[d]										
Baseline	1.60 (0.67)	1.60 (0.67)	1.47 (0.66)	1.47 (0.66)	1.42 (0.63)	1.48 (0.61)	1.61 (0.61)	1.63 (0.64)	1.56 (0.60)	1.67 (0.64)
Week 12/14	1.08 (0.72)	0.76 (0.69)	1.19 (0.69)	0.86 (0.67)	1.13 (0.70)	0.85 (0.66)	1.28 (0.67)	0.98 (0.68)	1.33 (0.66)	1.24 (0.77)
Physician global assessment[c]										
Baseline	69 (16)	67 (17)	62 (17)	66 (18)	64 (18)	64 (16)	66 (18)	66 (17)	67 (17)	69 (17)
Week 12/14	32 (22)	22 (19)	37 (24)	26 (21)	41 (24)	26 (21)	41 (25)	27 (21)	39 (25)	29 (22)
CRP (mg/L)										
Baseline	21.2 (22.1)	23.0 (27.4)	14.5 (17.3)	14.0 (16.5)	12.6 (14.0)	16.6 (19.2)	18.0 (21.5)	17.9 (22.5)	16.3 (21.1)	16.3 (18.6)
Week 12/14	10.9 (14.9)	4.2 (8.8)	12.8 (21.4)	3.7 (7.8)	13.1 (15.5)	4.6 (9.6)	16.2 (19.8)	5.5 (10.9)	13.9 (17.3)	5.0 (14.0)

Abbreviations: ACR = American College of Rheumatology; bDMARD = biologic disease-modifying anti-rheumatic drug; CRP = c-reactive protein; cDMARDs = conventional disease-modifying anti-rheumatic drugs; HAQ-DI = Health Assessment Questionnaire Disability Index; IR = inadequate responder; MTX = methotrexate; PBO = placebo

[a] Data shown are mean (standard deviation).
[b] Primary efficacy timepoint is at Week 14.
[c] Visual analog scale: 0 = best, 100 = worst.
[d] Health Assessment Questionnaire-Disability Index: 0=best, 3=worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

Figure 1. Percent of Patients Achieving ACR20 in Study RA-IV



Abbreviations: ACR20 = American College of Rheumatology ≥20% improvement; MTX = methotrexate
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 RA-I and RA-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 timepoint (Table 7).

Table 7: Proportion of Patients with DAS28-CRP Less Than 2.6 with Number of Residual Active Joints at Primary Efficacy Timepoint

	Study RA-I MTX-Naive	
	Monotherapy	
DAS28-CRP Less Than 2.6	**MTX** N = 314	**RINVOQ 15 mg** N = 317
Proportion of responders at Week 12 (n)	14% (43)	36% (113)
Of responders, proportion with 0 active joints (n)	51% (22)	45% (51)
Of responders, proportion with 1 active joint (n)	35% (15)	23% (26)
Of responders, proportion with 2 active joints (n)	9% (4)	17% (19)
Of responders, proportion with 3 or more active joints (n)	5% (2)	15% (17)
	Study RA-IV MTX-IR	
	Background MTX	
DAS28-CRP Less Than 2.6	**PBO** N = 651	**RINVOQ 15 mg** N = 651

Proportion of responders at Week 12 (n)	6% (40)	29% (187)
Of responders, proportion with 0 active joints (n)	60% (24)	48% (89)
Of responders, proportion with 1 active joint (n)	20% (8)	23% (43)
Of responders, proportion with 2 active joints (n)	15% (6)	13% (25)
Of responders, proportion with 3 or more active joints (n)	5% (2)	16% (30)
Abbreviations: CRP = c-reactive protein; DAS28 = Disease Activity Score 28 joints; MTX = methotrexate; PBO = placebo; IR = inadequate responder		

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 RA-IV and Week 24 in Study RA-I. The proportion of patients with no radiographic progression (mTSS change from baseline ≤ 0) was also assessed.

In Study RA-IV, treatment with RINVOQ 15 mg inhibited the progression of structural joint damage compared to placebo in combination with cDMARDs at Week 26 (Table 8). Analyses of erosion and joint space narrowing scores were consistent with overall results.

In the placebo plus MTX group, 76% of the patients experienced no radiographic progression at Week 26 compared to 83% of the patients treated with RINVOQ 15 mg.

In Study RA-I, treatment with RINVOQ 15 mg monotherapy inhibited the progression of structural joint damage compared to MTX monotherapy at Week 24 (Table 8). Analyses of erosion and joint space narrowing scores were consistent with overall results.

In the MTX monotherapy group, 78% of the patients experienced no radiographic progression at Week 24 compared to 87% of the patients treated with RINVOQ 15 mg monotherapy.

Table 8: Radiographic Changes

	Study RA-IV MTX-IR		
	Background MTX		
mTSS	PBO (N=651) Mean (SD)	RINVOQ 15 mg (N=651) Mean (SD)	Estimated Difference vs PBO at Week 26 (95% CI)[1]
Baseline	35.9 (52)	34.0 (50)	
Week 26[2]	0.78 (0.1)	0.15 (0.1)	-0.63 (-0.92, -0.34)
	Study RA-I MTX-naïve		
	Monotherapy		
	MTX (N=309) Mean (SD)	RINVOQ 15 mg (N=309) Mean (SD)	Estimated Difference vs MTX at Week 24 (95% CI)[3]
Baseline	13.3 (31)	18.1 (38)	
Week 24[4]	0.67 (2.8)	0.14 (1.4)	-0.53 (-0.85, -0.20)

Abbreviations: mTSS = modified Total Sharp Score, MTX = methotrexate; PBO = placebo; SD = standard deviation; IR = inadequate responders; bDMARDs = biologic disease modifying anti-rheumatic drugs; LS = least squares; CI = confidence intervals
[1] LS means and 95% CI based on a random coefficient model fit to the mTSS value adjusting for time, treatment group, prior bDMARDs use, treatment group-by-time interaction, with random slopes and random intercept.
[2] Estimated linear rate of structural progression by Week 26 and standard errors are presented.
[3] LS means and 95% CI based on a linear regression model fit to change from baseline in mTSS adjusting for treatment group, baseline mTSS, and geographic region.
[4] Mean change from baseline and standard deviation are presented.

Physical Function Response

Treatment with RINVOQ 15 mg, alone or in combination with cDMARDs, resulted in a greater improvement in physical function at Week 12/14 compared to all comparators as measured by HAQ-DI.

Other Health-Related Outcomes

In all studies except for Study RA-V, patients receiving RINVOQ 15 mg had 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 cDMARDs or MTX monotherapy at Week 12/14.

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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.

30 tablets in a bottle; NDC: 0074-2306-30

16.2 Storage and Handling

Store at 2˚C to 25˚C (36˚F to 77˚F).

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

17 PATIENT COUNSELING INFORMATION

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

Serious Infections

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

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

Malignancies

Inform patients that RINVOQ may increase their risk of certain cancers. Instruct patients to inform their healthcare provider if they have ever had any type of cancer *[see Warnings and Precautions (5.2)]*.

Thrombosis

Advise patients that events of DVT and PE have been reported in clinical studies with RINVOQ. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of a DVT or PE *[see Warnings and Precautions (5.3)]*.

Laboratory Abnormalities

Inform patients that RINVOQ may affect certain lab tests, and that blood tests are required before and during RINVOQ treatment *[see Warnings and Precautions (5.5)]*.

Pregnancy

Advise pregnant women and females of reproductive potential that exposure to RINVOQ during pregnancy may result in fetal harm. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.1)]*. Advise females of reproductive potential that effective contraception should be used during treatment and for 4 weeks following the final dose of upadacitinib *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with RINVOQ *[see Use in Specific Populations (8.2)]*.

Administration

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

Manufactured by: AbbVie Ireland NL B.V., Sligo, Ireland
Packed and Distributed by: AbbVie Inc., North Chicago, IL 60064
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Medication Guide
RINVOQ™ (rin-ˈvōk)
(upadacitinib)

extended-release tablets, for oral use

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

RINVOQ may cause serious side effects, including:

1. Serious Infections.

RINVOQ is a medicine that affects your immune system. RINVOQ can lower the ability of your immune system to fight infections. Some people have had serious infections while taking RINVOQ, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have died from these infections.

- Your healthcare provider should test you for TB before starting treatment with RINVOQ.
- Your healthcare provider should watch you closely for signs and symptoms of TB during treatment with RINVOQ.
- You should not start taking RINVOQ if you have any kind of infection unless your healthcare provider tells you it is okay. You may be at a higher risk of developing shingles (herpes zoster).
- **Before starting RINVOQ, tell your healthcare provider if you**:
  - are being treated for an infection.
  - have had an infection that does not go away or that keeps coming back.
  - have diabetes, chronic lung disease, HIV, or a weak immune system.
  - have TB or have been in close contact with someone with TB.
  - have had shingles (herpes zoster).
  - have had hepatitis B or C.
  - live or have lived, or have traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections. These infections may happen or become more severe if you use RINVOQ. Ask your healthcare provider if you do not know if you have lived in an area where these infections are common.
  - think you have an infection or have symptoms of an infection such as:
    - fever, sweating, or chills
    - shortness of breath
    - warm, red, or painful skin or sores on your body
    - muscle aches
    - feeling tired
    - blood in your phlegm
    - diarrhea or stomach pain
    - cough
    - weight loss
    - burning when you urinate or urinating more often than usual

After starting RINVOQ, call your healthcare provider right away if you have any symptoms of an infection. RINVOQ can make you more likely to get infections or make worse any infections that you have.

2. Cancer.

RINVOQ may increase your risk of certain cancers by changing the way your immune system works.

Lymphoma and other cancers, including skin cancers can happen in people taking RINVOQ. Tell your healthcare provider if you have ever had any type of cancer.

3. Blood Clots (thrombosis).

Blood clots in the veins of your legs (deep vein thrombosis, DVT) or lungs (pulmonary embolism, PE) and arteries (arterial thrombosis) can happen in some people taking RINVOQ. This may be life-threatening and cause death.

- Tell your healthcare provider if you have had blood clots in the veins of your legs or lungs in the past.
- Tell your healthcare provider right away if you have any signs and symptoms of blood clots during treatment with RINVOQ, including:
  - swelling
  - sudden unexplained

- pain or tenderness in the leg
- chest pain
- shortness of breath

4. Tears (perforation) in the stomach or intestines.

- Tell your healthcare provider if you have had diverticulitis (inflammation in parts of the large intestine) or ulcers in your stomach or intestines. Some people taking RINVOQ can get tears in their stomach or intestines. This happens most often in people who take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.
- Tell your healthcare provider right away if you have fever and stomach-area pain that does not go away, and a change in your bowel habits.

5. Changes in certain laboratory test results.

Your healthcare provider should do blood tests before you start taking RINVOQ and while you take RINVOQ to check for the following:

- **low neutrophil and lymphocyte counts.** Neutrophils and lymphocytes are types of white blood cells that help the body fight off infections.
- **low red blood cell counts.** Red blood cells carry oxygen. Low red blood cells means you may have anemia, which may make you feel weak and tired.
- **increased cholesterol levels.** Your healthcare provider should do blood tests to check your cholesterol levels approximately 12 weeks after you start taking RINVOQ, and as needed.
- **elevated liver enzymes.** Liver enzymes help to tell if your liver is functioning normally. Elevated liver enzymes may indicate that your healthcare provider needs to do additional tests on your liver.

You should not take RINVOQ if your neutrophil count, lymphocyte count, or red blood cell count is too low or your liver tests are too high. Your healthcare provider may stop your RINVOQ treatment for a period of time if needed because of changes in these blood test results.
See **"What are the possible side effects of RINVOQ?"** for more information about side effects.

What is RINVOQ?

- RINVOQ is a prescription medicine that is a Janus kinase (JAK) inhibitor. RINVOQ is used to treat adults with moderate to severe rheumatoid arthritis in whom methotrexate did not work well or could not be tolerated.

It is not known if RINVOQ is safe and effective in children under 18 years of age.

Before taking RINVOQ, tell your healthcare provider about all of your medical conditions, including if you:

- See **"What is the most important information I should know about RINVOQ?"**
- have an infection.
- have liver problems.
- have low red or white blood cell counts.
- have recently received or are scheduled to receive an immunization (vaccine). People who take RINVOQ should not receive live vaccines.
- are pregnant or plan to become pregnant. Based on animal studies, RINVOQ may harm your unborn baby. Your healthcare provider will check whether or not you are pregnant before you start RINVOQ. You should use effective birth control (contraception) to avoid becoming pregnant while taking RINVOQ, and for at least 4 weeks after your last dose of RINVOQ.
- are breastfeeding or plan to breastfeed. RINVOQ may pass into your breast milk. You and your healthcare provider should decide if you will take RINVOQ or breastfeed. You should not do both. You should not breastfeed until 6 days after your last dose of RINVOQ.

Tell your healthcare provider about all the medicines you take, including prescription and

over-the-counter medicines, vitamins, and herbal supplements. RINVOQ and other medicines may affect each other causing side effects.

Especially tell your healthcare provider if you take:

- medicines for fungal infections (such as ketoconazole, itraconazole, posaconazole or voriconazole) or clarithromycin (for bacterial infections) as these medicines may increase the amount of RINVOQ in your blood.
- rifampicin (for bacterial infections) or phenytoin (for neurological disorders) as these medicines may decrease the effect of RINVOQ.
- medicines that affect your immune system (such as azathioprine and cyclosporine) as these medicines may increase your risk of infection.

Ask your healthcare provider or pharmacist, if you are not sure if you are taking any of these medicines.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take RINVOQ?

- Take RINVOQ exactly as your healthcare provider tells you to use it.
- Take RINVOQ 1 time a day with or without food.
- Swallow RINVOQ whole with water at about the same time each day. Do not split or break, crush, or chew the tablets.

What are the possible side effects of RINVOQ?

RINVOQ can cause serious side effects including:

See **"What is the most important information I should know about RINVOQ?"**

Common side effects of RINVOQ include: upper respiratory tract infections (common cold, sinus infections), nausea, cough, and fever.

These are not all the possible side effects of RINVOQ. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store RINVOQ?

- Store RINVOQ in original container at 36°F to 77°F (2°C to 25°C) to protect it from moisture.
- **Keep RINVOQ and all medicines out of the reach of children.**

General information about the safe and effective use of RINVOQ.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use RINVOQ for a condition for which it was not prescribed.

Do not give RINVOQ to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about RINVOQ that is written for health professionals.

What are the ingredients in RINVOQ?

Active ingredient: upadacitinib

Inactive ingredients: microcrystalline cellulose, hypromellose, mannitol, tartaric acid, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, ferrosoferric oxide, and iron oxide red.

Manufactured by: AbbVie Ireland NL B.V., Sligo, Ireland

Marketed by: AbbVie Inc., North Chicago, IL 60064

RINVOQ is a trademark of AbbVie Biotechnology Ltd.

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For more information, call 1-800-2-RINVOQ (1-800-274-6867) or go to www.RINVOQ.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration Issued: 07/2020
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添付文書ハイライト

これらのハイライトには RINVOQ（本剤）の安全かつ有効な使用に必要な全ての情報が含まれているわけではない。本剤の処方情報の全文を参照すること。

RINVOQ™（ウパダシチニブ）経口徐放錠　米国における初回承認：2019

警告：重篤な感染，悪性腫瘍及び血栓症
処方情報全文の枠組み警告を確認すること。

- **結核，細菌感染，侵襲性真菌感染，ウイルス感染及びその他の日和見感染を含む，入院又は死亡に至る重篤な感染が本剤を投与した患者に発現している。（5.1）**
- **重篤な感染が発現した場合は，感染が制御されるまで本剤の投与を中断すること。（5.1）**
- **本剤の投与開始前に潜伏結核の検査を行うこと。陽性の場合は，本剤の投与を始める前に結核の治療を開始すること。（5.1）**
- **初回の潜伏結核の検査が陰性の場合でも，治療中は活動性結核について全ての患者を観察すること。（5.1）**
- **本剤を投与した患者において，リンパ腫及びその他の悪性腫瘍が認められている（5.2）**
- **炎症性疾患の治療に用いられるヤヌスキナーゼ阻害剤の投与を受けた患者において，深部静脈血栓症，肺塞栓症及び動脈血栓症を含む血栓症が認められている（5.3）**

---------- 効能・効果 ----------
本剤はメトトレキサート（MTX）に効果不十分又は不耐容であった中等症から重症の関節リウマチの成人患者に対する治療を適応とするヤヌスキナーゼ（JAK）阻害薬である。（1）
使用に関する制限事項：他の JAK 阻害薬，生物学的疾患修飾性抗リウマチ薬（DMARDs）又はアザチオプリンやシクロスポリンなどの強力な免疫抑制剤と本剤の併用は推奨されない。（1）

---------- 用法・用量 ----------
- 本剤の推奨用量は 1 日 1 回 15 mg である。（2.1）
- 本剤は，単剤療法あるいはメトトレキサート（MTX）や他の非生物学的 DMARDs との併用療法として使用できる。（2.1）
- リンパ球絶対数が 500 cells/mm^3 未満，好中球絶対数が 1000 cells/mm^3 未満又はヘモグロビン値が 8 g/dL 未満の場合は，本剤の投与を開始しない，あるいは中断するようにすること。数値がこれらの制限値を上回り改善したら，治療を開始してもよい。（2.2, 2.3, 5.5）

---------- 剤形及び含量 ----------
徐放錠：15 mg（3）

----------禁忌----------
- なし（4）

---------- 警告及び使用上の注意 ----------
- 重篤な感染：限局性感染を含む，活動性の重篤な感染を有する患者には本剤を使用しないようにすること。（5.1）
- 悪性腫瘍：悪性腫瘍のリスクが増大している可能性がある患者に治療を開始する前に，本剤による治療のリスクとベネフィットについて検討すること。（5.2）
- 血栓症：血栓症のリスクが増大している可能性がある患者に治療を開始する前に，本剤による治療のリスクとベネフィットについて検討すること。血栓症の症状が認められた場合には，速やかに評価し，適切な治療を行うこと。（5.3）
- 消化管穿孔：消化管穿孔のリスクが増大している能性がある患者には慎重に使用すること。（5.4）
- 臨床検査値のモニタリング：リンパ球，好中球，ヘモグロビン，肝酵素及び脂質が変化する可能性があるため推奨されている。（5.5）
- 胚・胎児毒性：動物を用いた試験に基づくと，本剤は胎児に害を及ぼす可能性がある。妊娠可能な女性には，胎児への潜在的なリスクがあることを説明し，有効な避妊法を用いるよう指導すること。（5.6, 8.1, 8.3）
- 予防接種：本剤を生ワクチンと併用しないようにすること。（5.7）

---------- 副作用 ----------
副作用（1%以上）は次の通りである：上気道感染，悪心，咳嗽及び発熱。（6.1）

「副作用の疑い」を報告するには，AbbVie Inc.（1-800-633-9110），FDA（1-800-FDA-1088）又は www.fda.gov/medwatch に連絡すること。

---------- 薬物相互作用 ----------
- 強力な CYP3A4 阻害剤（ケトコナゾールなど）の長期治療を受けている患者には，本剤を注意して使用すること。（7.1）
- 本剤と強力な CYP3A4 誘導剤（リファンピンなど）との併用投与は推奨されない。（7.2）

---------- 特別な患者集団への投与 ----------
- 授乳：授乳しないように指導すること。（8.2）
- 肝機能障害：重度の肝機能障害を有する患者には本剤は推奨されない。（8.7）

患者カウンセリング情報及び患者向け医薬品ガイドについては 17 項を参照すること。

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処方情報全文

警告：重篤な感染，悪性腫瘍及び血栓症

重篤な感染

本剤による治療を受けている患者は，入院又は死亡に至ることがある重篤な感染を発症するリスクが高まる［*警告及び使用上の注意（5.1 項），副作用（6.1 項）参照*。］これらの感染を発症した患者のほとんどが，メトトレキサートやコルチコステロイドなどの免疫抑制剤を併用していた。

重篤な感染が発現した場合は，感染が制御されるまで本剤の投与を中断すること。

報告された感染は以下のとおりである：

- 肺疾患又は肺外疾患としての活動性結核。患者は本剤の使用前と治療中に潜伏結核の検査を受けること。本剤の使用前に潜伏結核の治療を検討すること。
- クリプトコッカス症などの侵襲性真菌感染及びニューモシスチス症。
- 細菌感染，帯状疱疹などのウイルス感染及び日和見病原体によるその他の感染。

慢性又は反復性感染を有する患者に治療を開始する前に，本剤による治療のリスクとベネフィットについて慎重に検討すること。

治療開始前に潜伏結核感染の検査で陰性であった患者における結核発現の可能性を含め，本剤による治療中及び治療後には感染の徴候及び症状が発現しないか患者を注意深く観察すること［*警告及び使用上の注意（5.1 項）参照*］。

悪性腫瘍

リンパ腫などの悪性腫瘍が本剤を投与した患者に認められている［警告及び使用上の注意（5.2 項）参照］。

血栓症

深部静脈血栓症，肺塞栓症及び動脈血栓症を含む血栓症が，炎症を抑制するためにヤヌスキナーゼ阻害薬を投与した患者に発現している。これらの有害事象の多くは重篤であり，死亡例もあった。血栓症のリスクが増大している可能性がある患者に治療を開始する前に，本剤による治療のリスクとベネフィットについて検討すること。血栓症の症状を有する患者を速やかに評価し，適切な治療を行うこと［警告及び使用上の注意（5.3 項）参照］。

1. 効能・効果

1.1 関節リウマチ

本剤（ウパダシチニブ）は，メトトレキサート（MTX）に効果不十分又は不耐容であった中等症から重症の活動性関節リウマチの成人患者に対する治療を適応とする。

使用に関する制限事項：他の JAK 阻害薬，生物学的疾患修飾性抗リウマチ薬（DMARDs）又はアザチオプリンやシクロスポリンなどの強力な免疫抑制剤と本剤の併用は推奨されない。

2. 用法・用量

2.1 関節リウマチにおける用量

本剤の経口投与の推奨用量は食事摂取の有無にかかわらず 1 日 1 回 15 mg である*［臨床薬理（12.3 項）参照］*。

本剤は，単剤療法あるいはメトトレキサート（MTX）や他の非生物学的 DMARDs との併用療法として使用できる。

2.2 重要な投与指示

- リンパ球絶対数（ALC）が 500 cells/mm^3 未満，好中球絶対数（ANC）が 1000 cells/mm^3 未満又はヘモグロビン値が 8 g/dL 未満の患者には，本剤の投与開始は推奨されない*［警告及び使用上の注意（5.5 項）参照］*。
- 重度の肝機能障害（チャイルド・ピュー分類 C）を有する患者には本剤の使用は推奨されない*［特別な患者集団への投与（8.7 項）及び臨床薬理（12.3 項）参照］*。
- 本剤の錠剤は丸ごと飲み込むこと。本剤は割ったり，砕いたり，噛んだりしないこと。

2.3 投与中断

重篤な感染が発現した場合は，感染が制御されるまで本剤による治療を中断すること*［警告及び使用上の注意（5.1 項）参照］*。

表 1 に記載されているように，臨床検査値異常の管理に投与中断が必要になる場合がある。

表 1.　　臨床検査値異常に推奨される投与中断

臨床検査値の指標	対応
好中球絶対数（ANC）	ANC が 1000 cells/mm^3 未満の場合は治療を中断し，ANC がこれを上回る数値に戻ったら再開してもよい。
リンパ球絶対数（ALC）	ALC が 500 cells/mm^3 未満の場合は治療を中断し，ALC がこれを上回る数値に戻ったら再開してもよい。
ヘモグロビン（Hb）	Hb が 8 g/dL 未満の場合は治療を中断し，Hb がこれを上回る数値に戻ったら再開してもよい。
肝トランスアミナーゼ	薬物性肝障害が疑われる場合は治療を中断すること。

3.　剤形及び含量

本剤 15 mg 経口徐放錠は，紫色の両凸形の楕円であり，サイズは 14 × 8 mm，片面に「a15」の刻印がある。

4.　禁忌

なし

5.　警告及び使用上の注意

5.1　重篤な感染

本剤を投与した患者に，時として致死的な重篤な感染が報告されている。本剤投与により最も高い頻度で報告された重篤な感染には肺炎及び蜂巣炎があった*［副作用（6.1 項）参照］*。日和見感染の中では，結核，播種性帯状疱疹，口腔/食道カンジダ症及びクリプトコッカス症が本剤の使用で報告された。

限局性感染を含む，活動性の重篤な感染を有する患者には本剤を使用しないようにすること。以下の患者に本剤の使用を開始する前に，治療のリスクとベネフィットについて検討すること：

- 慢性又は反復性感染を有する患者
- 結核患者に接触したことがある患者
- 重篤な感染又は日和見感染の既往歴がある患者
- 結核流行地域又は風土性真菌症流行地域での居住又は渡航経験がある患者
- 感染を誘発する可能性のある基礎疾患を有する患者

本剤による治療中及び治療後には，感染の徴候及び症状が発現しないか患者を注意深く観察すること。患者が重篤な感染又は日和見感染を発症した場合は本剤の投与を中断すること。本剤による治療中に新たに感染を発症した患者は，免疫不全患者に適した，迅速で精密な診断検査を受

ける必要がある。適切な抗菌薬療法を開始し，患者を注意深く観察すること。患者が抗菌薬療法に反応を示していない場合は本剤の投与を中断すること。感染が制御されたら本剤の投与を再開してもよい。

結核

患者は，本剤の投与開始前に，結核（TB）のスクリーニング検査を受けること。活動性 TB を有する患者には本剤を投与しないこと。未治療の潜伏 TB を有する患者又は十分な治療が行われていることが確認できない活動性 TB 患者や潜伏 TB 感染の検査が陰性であったが TB 感染のリスクがある患者に本剤の投与を開始する場合は，その前に抗結核療法を検討すること。

抗結核療法の開始が個々の患者に適切であるか判断する上での補助として，TB 治療の専門知識がある医師に相談することが望ましい。

治療開始前に潜伏 TB 感染の検査で陰性であった患者を含め，TB の徴候及び症状が発現しないか患者を観察すること。

ウイルスの再活性化

ヘルペスウイルスの再活性化（帯状疱疹など）を含む，ウイルスの再活性化及び B 型肝炎ウイルスの再活性化が臨床試験において報告された*［副作用（6.1 項）参照］*。患者が帯状疱疹を発症した場合は，その症状が消失するまで本剤の一時的な中断を検討すること。

本剤による治療の開始前及び治療中に，臨床ガイドラインに従って，ウイルス肝炎のスクリーニング検査及び再活性化のモニタリングを実施すること。C 型肝炎抗体及び C 型肝炎ウイルス RNA が陽性であった患者は臨床試験から除外された。B 型肝炎表面抗原又は B 型肝炎ウイルス DNA が陽性であった患者は臨床試験から除外された。しかし，B 型肝炎ウイルスの再活性化例が，本剤の第 3 相試験に組み入れられた患者でなお報告された。本剤の投与中に B 型肝炎ウイルス DNA が検出された場合は，肝臓専門医に相談すること。

5.2 悪性腫瘍

本剤の臨床試験で悪性腫瘍が認められた*［副作用（6.1 項）参照］*。治療に成功した非黒色腫皮膚癌（NMSC）以外の既知の悪性腫瘍を有する患者に治療を開始する前，あるいは悪性腫瘍を発症した患者に本剤の継続を考慮する場合には，本剤による治療のリスクとベネフィットについて検討すること。

非黒色腫皮膚癌

本剤による治療を受けている患者に NMSC が報告されている。皮膚癌のリスクが増大している患者は，定期的な皮膚検査を受けることが望ましい。

5.3 血栓症

深部静脈血栓症，肺塞栓症及び動脈血栓症を含む血栓症が，炎症を抑制するために本剤を含むヤヌスキナーゼ（JAK）阻害薬を投与した患者に発現している。これらの有害事象の多くは重篤であり，死亡例もあった。

血栓症のリスクが増大している可能性がある患者に治療を開始する前に，本剤による治療のリスクとベネフィットについて検討すること。血栓症の症状が発現した場合は，患者を速やかに評価し，適切な治療を行うこと。

5.4 消化管穿孔

本剤の臨床試験で消化管穿孔の発現が報告されている。ただし，これらの消化管穿孔におけるJAK 阻害薬の関連性は不明である。これらの臨床試験では，関節リウマチ患者の多くが基礎療法として非ステロイド性抗炎症薬（NSAIDs）を服用していた。

消化管穿孔のリスクが増大している能性がある患者（憩室炎の既往歴を有する患者又はNSAIDs を服用している患者など）には，本剤を慎重に使用すること。

新たに腹部症状を発症した患者は，消化管穿孔を早期に同定するために速やかに評価すること。

5.5 臨床検査項目

好中球減少症

本剤による治療は好中球減少症（ANC が 1000 cells/mm^3 未満）の発現率の上昇と関連性があった。

通常の患者管理のとおり，ベースライン時とその後に好中球数の評価を行うこと。好中球数低値（ANC 1000 cells/mm^3 未満）の患者には，本剤による治療を開始しない，又は治療を中断すること［用法・用量（*2.2* 項，*2.3* 項）参照］。

リンパ球減少症

本剤の臨床試験で ALC 500 cells/mm^3 未満が報告された。

通常の患者管理のとおり，ベースライン時とその後にリンパ球数の評価を行うこと。リンパ球数低値（ANC 500 cells/mm^3 未満）の患者には，本剤による治療を開始しない，又は治療を中断すること［用法・用量（*2.2* 項，*2.3* 項）参照］。

貧血

本剤の臨床試験でヘモグロビン値の 8 g/dL 未満への減少が報告された。

通常の患者管理のとおり，ベースライン時とその後にヘモグロビン値の評価を行うこと。ヘモグロビン低値（8 g/dL 未満）の患者には，本剤による治療を開始しない，又は治療を中断すること［用法・用量（*2.2* 項，*2.3* 項）参照］。

脂質

本剤による治療は，総コレステロール，低比重リポ蛋白（LDL）コレステロール及び高比重リポ蛋白（HDL）コレステロールを含む脂質値の上昇と関連性があった*［副作用（6.1 項）参照］*。LDL コレステロール値の上昇は，スタチン治療に反応を示し，治療前の数値に低下した。このような脂質値の上昇の心血管疾患罹患率及び死亡率への影響は確認されていない。

治療開始後 12 週間及びその後は，高脂血症の臨床ガイドラインに従って患者を観察すること。高脂血症の臨床ガイドラインに従って患者を管理すること。

肝酵素増加

本剤による治療は，プラセボ群と比較して，肝酵素増加の発現率の上昇と関連性があった。

通常の患者管理のとおり，ベースライン時とその後に評価を行うこと。薬物性肝障害の潜在的な症例を特定するために，肝酵素増加の原因を迅速に究明することが望ましい。

通常の患者管理の中で ALT 又は AST の増加が認められ，薬物性肝障害が疑われる場合は，この診断が除外されるまで本剤の投与を中断すること。

5.6 胚・胎児毒性

動物を用いた試験結果に基づくと，本剤は妊婦に投与すると胎児に害を及ぼす可能性がある。器官形成期にラット及びウサギにウパダシチニブを投与すると，胎児奇形の発現増加を引き起こした。妊婦には胎児への潜在的なリスクについて説明すること。妊娠可能な女性には，本剤による治療中及び本剤の最終投与後 4 週間は有効な避妊法を用いるよう指導すること［特別な患者集団への投与（*8.1* 項，*8.3* 項）参照］。

5.7 予防接種

本剤の投与中又は投与直前に生ワクチンや弱毒生ワクチンを接種することは推奨されない。患者は本剤の投与開始前に，最新の予防接種ガイドラインに従って，帯状疱疹の予防接種を含む全予防接種を受けることが推奨されている。

6. 副作用

以下の重大な副作用は添付文書の他の部分に記載されている。

- 重篤な感染*［警告及び使用上の注意（5.1 項）参照］*。
- 悪性腫瘍*［警告及び使用上の注意（5.2 項）参照］*。
- 血栓症*［警告及び使用上の注意（5.3 項参照）］*。
- 消化管穿孔*［警告及び使用上の注意（5.4 項）参照］*。
- 検査値［警告及び使用上の注意（*5.5* 項）参照］。

6.1 臨床試験成績

臨床試験は多様な条件で実施されるため，ある薬剤の臨床試験で認められた副作用の発現率を別の薬剤の臨床試験での発現率と直接比較することはできず，また臨床試験での発現率が診療現場での発現率に一致するとは限らない。

第 3 相臨床試験では，合計 3833 例の関節リウマチ患者にウパダシチニブを投与し，そのうちの 2806 例は曝露期間が 1 年以上であった。

試験デザインに従って，患者は本剤投与を継続すること，Week 12 という早期からプラセボから本剤 15 mg に切り替えること，実対照薬又はプラセブから本剤のレスキュー療法に移行することが可能であった。

合計 2630 例の患者に本剤 15 mg を 1 回以上投与し，そのうちの 1860 例は曝露期間が 1 年以上であった。RA-I，RA-II，RA-III 及び RA-V 試験では，1213 例の患者に本剤 15 mg を 1 回以上投与し，そのうちの 986 例は曝露期間が 1 年以上であった。1203 例にウパダシチニブ 30 mg を 1 回以上投与し，そのうち 946 例は曝露期間が 1 年以上であった。

表 2. プラセボ対照試験における本剤 15 mg 治療群の関節リウマチ患者の 1%以上に報告された副作用

副作用	プラセボ群	本剤 15 mg 群
	n = 1042 (%)	n = 1035 (%)
上気道感染（URTI）*	9.5	13.5
悪心	2.2	3.5
咳嗽	1.0	2.2
発熱	0	1.2

* URTI には以下を含む：急性副鼻腔炎，喉頭炎，上咽頭炎，口腔咽頭痛，咽頭炎，咽頭扁桃炎，鼻炎，副鼻腔炎，扁桃炎，ウイルス性上気道感染

Week 12 を通して本剤 15 mg 群の 1%未満及びプラセボ群より高い割合で報告されたその他の副作用には，肺炎，帯状疱疹，単純ヘルペス（口腔ヘルペスを含む）及び口腔カンジダ症があった。

4 つの統合データセットが特定の副作用欄に記載されている。

プラセボ対照試験：RA-III，RA-IV 及び RA-V 試験を統合し，プラセボ群（n = 1042）及び本剤 15 mg 群（n = 1035）の 12/14 週間にわたる安全性を提示した。RA-III 試験及び RA-IV 試験を統合し，プラセボ群（n = 390），本剤 15 mg 群（n = 385）及びウパダシチニブ 30 mg 群（n = 384）の 12 週間の安全性を提示した。RA-IV 試験には 30 mg 群はないため，ウパダシチニブ 30 mg 群の安

全性データは，RA-III 試験及び RA-IV 試験のプールデータを基に，プラセボ群及び本剤 15 mg 群の発現率とのみ比較することが可能である。

MTX 対照試験：RA-I 試験及び RA-II 試験を統合し，MTX 群（n = 530），本剤 15 mg 群（n = 534）及びウパダシチニブ 30 mg 群（n = 529）の 12/14 週間の安全性を提示した。

12 ヵ月間の曝露データセット：RA-I，RA-II，RA-III 及び RA-V 試験を統合し，本剤 15 mg 群（n = 1213）及びウパダシチニブ 30 mg 群（= 1203）の長期安全性を提示した。

曝露調整後発現率は本項で報告した全有害事象について，試験別に調整した。

特定の副作用

感染症

プラセボ対照試験：RA-III，RA-IV 及び RA-V 試験において，感染症がプラセボ群で 218 例（95.7 件/100 人年），本剤 15 mg 群で 284 例（127.8 件/100 人年）に報告された。RA-III 試験及び RA-IV 試験では，感染症はプラセボ群で 99 例（136.5 件/100 人年），本剤 15 mg 群で 118 例（164.5 件/100 人年）及びウパダシチニブ 30 mg 群で 126 例（180.3 件/100 人年）に報告された。

MTX 対照試験：感染症は MTX 単剤療法群で 127 例（119.5 件/100 人年），本剤 15 mg 単剤療法群で 104 例（91.8 件/100 人年）及びウパダシチニブ 30 mg 単剤療法群で 128 例（115.1 件/100 人年）に報告された。

12 ヵ月間の曝露データセット：感染症は本剤 15 mg 群で 615 例（83.8 件/100 人年）及びウパダシチニブ 30 mg 群で 674 例（99.7 件/100 人年）に報告された。

重篤な感染

プラセボ対照試験：RA-III，RA-IV 及び RA-V 試験において，重篤な感染がプラセボ群で 6 例（2.3 件/100 人年），本剤 15 mg 群で 12 例（4.6 件/100 人年）に報告された。RA-III 試験及び RA-IV 試験では，重篤な感染はプラセボ群で 1 例（1.2 件/100 人年），本剤 15 mg 群で 2 例（2.3 件/100 人年），ウパダシチニブ 30 m 群で 7 例（8.2 件/100 人年）に報告された。

MTX 対照試験：重篤な感染は MTX 単剤療法群で 2 例（1.6 件/100 人年），本剤 15 mg 単剤療法群で 3 例（2.4 件/100 人年）及びウパダシチニブ 30 mg 単剤療法群で 8 例（6.4 件/100 人年）に報告された。

12 ヵ月間の曝露データセット：重篤な感染は本剤 15 mg 群で 38 例（3.5 件/100 人年）及びウパダシチニブ 30 mg 群で 59 例（5.6 件/100 人年）に報告された。

最も報告件数の多かった重篤な感染は肺炎及び蜂巣炎であった。

結核

プラセボ対照試験及び MTX 対照試験：プラセボ対照試験期間中に，プラセボ群，本剤 15 mg 群及びウパダシチニブ 30 mg 群で活動性結核の発現例は認められなかった。MTX 対照試験期間中

に，MTX 単剤療法群，本剤 15 mg 単剤療法群及びウパダシチニブ 30 mg 単剤療法群で活動性結核の発現例は認められなかった。

12 ヵ月間の曝露データセット：活動性結核は本剤 15 mg 群で 2 例及びウパダシチニブ 30 mg 群で 1 例に報告された。肺外結核例が報告された。

日和見感染 （結核を除く）

プラセボ対照試験：RA-III，RA-IV 及び RA-V 試験において，日和見感染はプラセボ群で 3 例（1.2 件/100 人年）及び本剤 15 mg 群で 5 例（1.9 件/100 人年）に報告された。RA-III 試験及び RA-V 試験では，日和見感染はプラセボ群で 1 例（1.2 件/100 人年），本剤 15 mg 群で 2 例（2.3 件/100 人年）及びウパダシチニブ 30 mg 群で 6 例（7.1 件/100 人年）に報告された。

MTX 対照試験：日和見感染は MTX 単剤療法群で 1 例（0.8 件/100 人年），本剤 15 mg 単剤療法群では報告がなく，ウパダシチニブ 30 mg 単剤療法群で 4 例（3.2 件/100 人年）に報告された。

12 ヵ月間の曝露データセット：日和見感染は本剤 15 mg 群 7 例（0.6 件/100 人年）及びウパダシチニブ 30 mg 群で 15 例（1.4 件/100 人年）に報告された。

悪性腫瘍

プラセボ対照試験：RA-III，RA-IV 及び RA-V 試験において，悪性腫瘍（NMSC を除く）はプラセボ群で 1 例（0.4 件/100 人年）及び本剤 15 mg 群で 1 例（0.4 件/100 人年）に報告された。RA-III 試験及び RA-V 試験では，悪性腫瘍（NMSC を除く）はプラセボ群では報告がなく，本剤 15 mg 群で 1 例（1.1 件/100 人年）及びウパダシチニブ 30 mg 群で 3 例（3.5 件/100 人年）に報告された。

MTX 対照試験：悪性腫瘍（NMSC を除く）は，MTX 単剤療法群で 1 例（0.8 件/100 人年），本剤 15 mg 単剤療法群で 3 例（2.4 件/100 人年）に報告され，ウパダシチニブ 30 mg 単剤療法群では報告がなかった。

12 ヵ月間の曝露データセット：悪性腫瘍（NMSC を除く）は本剤 15 mg 群で 13 例（1.2 件/100 人年）及びウパダシチニブ 30 mg 群で 14 例（1.3 件/100 人年）に報告された。

消化管穿孔

プラセボ対照試験：プラセボ群，本剤 15 mg 群及びウパダシチニブ 30 mg 群で（メディカルレビューに基づくと）消化管穿孔例は認められなかった。

MTX 対照試験：MTX 群及び本剤 15 mg 群において 12/14 週間に消化管穿孔例は報告されなかった。ウパダシチニブ 30 mg 群で消化管穿孔が 2 例認められた。

12 ヵ月間の曝露データセット：消化管穿孔が本剤 15 mg 群で 1 例及びウパダシチニブ 30 mg 群で 4 例に報告された。

血栓症

プラセボ対照試験：RA-IV 試験では，静脈血栓症（肺塞栓症又は深部静脈血栓症）がプラセブ群で 1 例及び本剤 15 mg 群で 1 例に認められた。RA-V 試験では，静脈血栓症が本剤 15 mg 群で

1 例に認められた。RA-III 試験では静脈塞栓症は 1 例も認められなかった。12/14 週間にわたり動脈血栓症は 1 例も認められなかった。

MTX 対照試験：RA-II 試験では，静脈血栓症は MTX 単剤療法群では認められず，本剤 15 mg 群で 1 例に認められ，ウパダシチニブ 30 mg 群では 14 週間にわたり認められなかった。RA-II 試験では，動脈血栓症は 12/14 週間にわたり 1 例も認められなかった。RA-I 試験では，静脈血栓症は MTX 群で 1 例に認められ，本剤 15 mg 群では認められず，ウパダシチニブ 30 mg 群では 24 週間で 1 例に認められた。RA-I 試験では，動脈血栓症がウパダシチニブ 30 mg 群では 24 週間で 1 例に認められた。

12 ヵ月間の曝露データセット：静脈血栓症は本剤 15 mg 群で 5 例（0.5 件/100 人年）及びウパダシチニブ 30 mg 群で 4 例（0.4 件/100 人年）に報告された。動脈血栓症は本剤 15 mg 群では 1 例も報告されず，ウパダシチニブ 30 mg 群で 2 例（0.2 件/100 人年）に報告された。

<u>臨床検査値異常</u>

肝トランスアミナーゼ上昇

基礎療法として DMARDs を投与するプラセボ対照試験（RA-III，RA-IV 及び RA-V 試験）において，最長 12/14 週間にわたり，少なくとも 1 回の測定で基準値上限（ULN）の 3 倍以上のアラニントランスアミナーゼ（ALT）及びアスパラギン酸トランスアミナーゼ（AST）の増加が，プラセボ群のそれぞれ 1.5%と 0.7%と比較して，本剤 15 mg 群ではそれぞれ 2.1%と 1.5%で認められた。RA-III 試験及び RA-V 試験では，少なくとも 1 回の測定で ULN の 3 倍以上の ALT 及び AST の増加が，プラセボ群のそれぞれ 1.3%と 1.0%と比較して，本剤 15 mg 群ではそれぞれ 0.8%と 1.0%及びウパダシチニブ 30 mg 群ではそれぞれ 1.0%と 0%に認められた。

MTX 対照試験では，最長 12/14 週間にわたり，少なくとも 1 回の測定で ULN の 3 倍以上の ALT 及び AST の増加が，MTX 群のそれぞれ 1.9%と 0.9%と比較して，本剤 15 mg 群ではそれぞれ 0.8%と 0.4%及びウパダシチニブ 30 mg 群ではそれぞれ 1.7%と 1.3%に認められた。

脂質上昇

ウパダシチニブによる治療は，総コレステロール，トリグリセリド及び LDL コレステロールの用量依存性の上昇と関連性があった。ウパダシチニブは HDL コレステロールの上昇とも関連性があった。LDL 及び HDL コレステロールの増加は Week 8 までに最大値を示し，その後一定となった。対照試験における本剤 15 mg 群及びウパダシチニブ 30 mg 群の最長 12/14 週間にわたるそれぞれの脂質値のベースラインからの変化を以下に要約する：

・平均 LDL コレステロールは 14.81 mg/dL 及び 17.17 mg/dL 増加した。
・平均 HDL コレステロールは 8.16 mg/dL 及び 9.01 mg/dL 増加した。
・平均 LDL/HDL 比に変化は認められなかった。
・平均トリグリセリドは 13.55 mg/dL 及び 14.44 mg/dL 増加した。

クレアチンホスホキナーゼ増加

基礎療法として DMARDs を投与するプラセボ対照試験（RA-III, RA-IV 及び RA-V 試験）において，最長 12/14 週間にわたり，クレアチンホスホキナーゼ（CPK）値の用量依存性の増加が認められた。12/14 週間にわたり，ULN の 5 倍を上回る CK 増加が，本剤 15 mg 群で 1.0%及びプラセボ群で 0.3%に報告された。ULN の 5 倍を上回る増加はほとんどが一過性であり，治療を中止する必要はなかった。RA-III 試験及び RA-V 試験において，ULN の 5 倍を上回る CPK 増加が，プラセボ群で 0.3%，本剤 15 mg 群では 1.6%で認められ，ウパダシチニブ 30 mg 群では 1 例も認められなかった。

好中球減少症

基礎療法として DMARDs を投与するプラセボ対照試験（RA-III, RA-IV 及び RA-V 試験）において，最長 12/14 週間にわたり，少なくとも 1 回の測定で 1000 cells/mm^3 を下回る用量依存性の好中球数減少が，本剤 15 mg 群で 1.1%及びプラセボ群で 0.1%未満に発現した。RA-III 試験及び RA-V 試験において，少なくとも 1 回の測定で 1000 cells/mm^3 を下回る好中球数減少が，プラセボ群で 0.3%，本剤 15 mg 群で 1.3%及びウパダシチニブ 30 mg 群で 2.4%に発現した。臨床試験では，ANC が 1000 cells/mm^3 未満に減少した場合は，治療が中断された。

リンパ球減少症

基礎療法として DMARDs を投与するプラセボ対照試験（RA-III, RA-IV 及び RA-V 試験）において，最長 12/14 週間にわたり，少なくとも 1 回の測定で 500 cells/mm^3 を下回るリンパ球数減少が，本剤 15 mg 群で 0.9%及びプラセボ群で 0.7%に発現した。RA-III 試験及び RA-V 試験において，少なくとも 1 回の測定で 500 cells/mm^3 を下回るリンパ球数減少が，プラセボ群で 0.5%，本剤 15 mg 群で 0.5%及びウパダシチニブ 30 mg 群で 2.4%に発現した。

貧血

基礎療法として DMARDs を投与するプラセボ対照試験（RA-III, RA-IV 及び RA-V 試験）において，最長 12/14 週間にわたり，少なくとも 1 回の測定で 8 g/L を下回るヘモグロビン減少が，本剤 15 mg 群及びプラセボ群の両群で 0.1%未満に発現した。RA-III 試験及び RA-V 試験において，少なくとも 1 回の測定で 8 g/L を下回るヘモグロビン減少が，プラセボ群では 0.3%に認められ，本剤 15 mg 群及びウパダシチニブ 30 mg 群の両群では 1 例も認められなかった。

7. 薬物相互作用

7.1 強力な CYP3A4 阻害剤

ウパダシチニブは，強力な CYP3A4 阻害剤（ケトコナゾールなど）と併用投与した場合，曝露量が多くなる*［臨床薬理（12.3 項）参照］*。強力な CYP3A4 阻害剤の長期治療を受けている患者には，本剤を注意して使用すること。

7.2 強力な CYP3A4 誘導剤

ウパダシチニブは，強力な CYP3A4 誘導剤（リファンピンなど）と併用投与した場合，曝露量が少なくなり，本剤の治療効果の低下を招く可能性がある*［臨床薬理（12.3 項）参照］*。本剤と強力な CYP3A4 誘導剤との併用投与は推奨されない。

8. 特別な患者集団への投与

8.1 妊婦への投与

リスクの概要

妊娠女性における本剤のヒトデータは限定的であり，重大な先天性異常及び流産の薬剤関連性リスクについて情報提供できるほど十分ではない。動物を用いた試験によると，ウパダシチニブは発育中の胎児に有害な影響を及ぼす可能性がある。

動物の胚・胎児発生試験では，妊娠ラット及びウサギに対し，器官形成期にそれぞれヒトでの最大推奨臨床用量（MRHD）の約 1.6 倍と 15 倍以上の曝露量でウパダシチニブを経口投与したところ，用量依存性の骨格奇形の増加（ラットのみ），心血管奇形発現率の増加（ウサギのみ），着床後死亡の増加（ウサギのみ）及びラット及びウサギの両方で胎仔体重の減少が認められた。器官形成期に MRHD の約 0.3 倍と 2 倍でウパダシチニブを経口投与した妊娠ラット及びウサギには，発生毒性は認められなかった。妊娠ラットを用いた出産前/出産後の発達試験において，MRHD の約 3 倍の曝露量でウパダシチニブを経口投与したところ，母体毒性及び発生毒性は認められなかった［動物データ参照］。

ウパダシチニブ適応集団における重大な先天性異常及び流産が発生する推定背景リスクは明らかではない。全ての妊娠症例に，先天性異常，胎児消失又はその他の有害転帰の背景リスクが伴っている。米国の一般集団における重大な先天性異常及び流産が発生する推定背景リスクは，それぞれ 2～4%と 15～20%である。

臨床的考察

疾患関連の母体及び/又は胚・胎児のリスク

公表されたデータは，疾患活動性の増大は関節リウマチの女性に有害妊娠転帰が生じるリスクと関連性があることを示唆している。有害妊娠転帰には早期産（妊娠 37 週前），低出生体重（2500 g 未満）児及び出生時に妊娠期間に比して小さい児がある。

データ

動物試験データ

経口投与による胚・胎児発生試験では，妊娠（GD）6 日目～GD17 日目の器官形成期に妊娠ラットに用量 5，25 及び 75 mg/kg/日のウパダシチニブの投与が行われた。ウパダシチニブは（母ラ

ットの経口投与量 5 mg/kg/日以上における AUC を基に）MRHD の約 1.7 倍以上の曝露量で催奇形性が認められた（上腕骨の変形及び肩甲骨の弯曲から構成される骨格奇形）。それ以外の骨格奇形（前肢及び後肢の骨弯曲及び肋骨/椎骨欠損）及び胎仔体重の減少が，（母ラットの経口投与量 75 mg/kg/日における AUC を基に）MRHD の約 84 倍の曝露量において母体毒性のない状態で認められた。

経口投与による 2 番目の胚・胎児発生試験では，GD6 日目～GD17 日目の器官形成期に妊娠ラットに用量 1.5 及び 4 mg/kg/日のウパダシチニブの投与が行われた。ウパダシチニブは（母ラットの経口投与量 4 mg/kg/日における AUC を基に）MRHD の約 1.6 倍の曝露量で催奇形性が認められた（上腕骨及び肩甲骨の弯曲を含む骨格奇形）。（母ラットの経口投与量 1.5 mg/kg/日以上における AUC を基に）MRHD の約 0.3 倍の曝露量では，ラットに発生毒性は認められなかった。

経口投与による胚・胎児発生試験では，GD7 日目～GD19 日目の器官形成期に妊娠ウサギに用量 2.5，10 及び 25 mg/kg/日のウパダシチニブの投与が行われた。胎児致死作用，胎仔体重の減少及び心血管奇形が，（母ウサギの経口投与量 25 mg/kg/日における AUC を基に）MRHD の約 15 倍の曝露量において母体毒性の存在下で認められた。胎児致死作用には総吸収胚数及び早期吸収胚数の増加による着床後死亡の増加が含まれた。（母ウサギの経口投与量 10 mg/kg/日における AUC を基に）MRHD の約 2 倍の曝露量において，ウサギに発生毒性は認められなかった。

経口投与による出産前/出産後の発生試験では，GD6 日目～授乳（LD）20 日目に妊娠ラットへの用量 2.5，5 及び 10 mg/kg/日のウパダシチニブの投与が行われた。（母ラットの経口投与量 10 mg/kg/日における AUC を基に）MRHD の約 3 倍の曝露量において，母体毒性と発生毒性は，それぞれ母ラットと出生ラットに認められなかった。

8.2 授乳婦への投与

リスクの概要

ウパダシチニブがヒト乳汁中へ分泌されるかどうか，授乳中の新生児/乳児に対する影響あるいは乳汁産生への影響に関するデータはない。動物から得られた薬力学的/毒性学的データではウパダシチニブの乳汁中への分泌が認められている。ある薬剤が動物の乳汁中に分泌される場合は，その薬剤はヒト乳汁中に分泌される可能性が高い。授乳中の新生児/乳児に対する重篤な副作用の可能性があるため，ウパダシチニブによる治療期間中及び最終投与後 6 日間（約 10 半減期）は，授乳は推奨されないことを患者に指導すること。

データ

動物試験データ

放射性同位体で標識された単回経口用量 10 mg/kg のウパダシチニブを出産後 7～8 日目の授乳 Sprague-Dawley ラットに投与した。乳汁中の経時的なウパダシチニブ濃度は母体血漿濃度と比べて約 30 倍であった。乳汁中薬剤関連物質の約 97%が親薬物であった。

8.3 生殖可能な年齢の男女

妊娠検査

本剤による治療を開始する前に，女性の妊娠可能性について確認すること［特別な患者集団への投与（*8.1 項*）参照］。

避妊

女性

動物を用いた試験によると，ウパダシチニブを妊婦へ投与すると胚・胎児毒性を引き起こす可能性がある［特別な患者集団への投与（*8.1* 項）参照］。妊娠可能な女性には，本剤による治療中及び本剤の最終投与後 4 週間は有効な避妊法を用いるよう指導すること。

8.4 小児等への投与

0～18 歳未満の小児及び青年における本剤の安全性及び有効性は確立していない。データは得られていない。

8.5 高齢者への投与

5 つの第 3 相臨床試験における対象患者 4381 例のうち，合計 906 例の関節リウマチ患者が 65 歳以上であり，そのうち 146 例は 75 歳以上であった。これらの患者と若年患者の間に有効性の差は認められていないが，全体的な有害事象の発現率は高齢者の方が高かった。

8.6 腎機能障害患者

軽度，中等度又は重度の腎機能障害患者では，用量調節は不要である。末期腎不全の被験者を対象とした本剤使用の試験は行われていない。腎外クリアランスが本剤の全体的な排泄に大きく寄与しているため，血液透析が本剤の血漿曝露に臨床的に重要な影響を及ぼすとは考えられていない*［臨床薬理（12.3 項）参照］*。

8.7 肝機能障害患者

軽度（チャイルド・ピュー分類 A）又は中等度（チャイルド・ピュー分類 B）の肝機能障害患者では，用量調節は不要である。重度（チャイルド・ピュー分類 C）の肝機能障害患者に本剤を使用することは推奨されない*［用法・用量（2.2 項）及び臨床薬理（12.3 項）参照］*。

10. 過量投与

臨床試験において，ウパダシチニブは 1 日 AUC で 60 mg 徐放錠 1 日 1 回投与に相当する用量まで投与された。有害事象は低用量でみられるものと同等であり，特定の毒性は確認されなかった。体循環のウパダシチニブの約 90%が投与して 24 時間以内に排泄される（臨床試験で評価された用量範囲内）。過量投与が起こった場合は，副作用の徴候及び症状について患者を観察することが望ましい。副作用を発症した患者には適切な治療を行うこと。

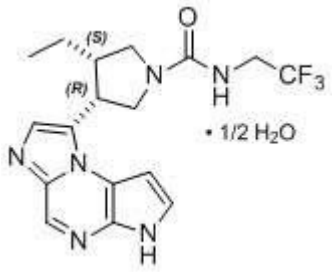
11. 組織・性状

本剤は JAK 阻害薬であるウパダシチニブで製剤化されている。

ウパダシチニブは次の化学名を有する白色～薄茶色の粉末である：
(3*S*,4*R*)-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)

ウパダシチニブの含量は無水ウパダシチニブに基づいている。ウパダシチニブの水への溶解度は 38 で，37°C において pH 領域 2～9 で 0.2 mg/mL 未満までであった。

ウパダシチニブの分子量は 389.38 g/mol，分子式は $C_{17}H_{19}F_3N_6O \cdot ½\ H_2O$ である。ウパダシチニブの化学構造式：



本剤 15 mg 経口徐放錠は，紫色の両凸形の楕円であり，サイズは 14 × 8 mm，片面に「a15」の刻印がある。

各錠剤は次の添加物を含有する：結晶セルロース，ヒプロメロース，マンニトール，酒石酸，軽質無水ケイ酸，ステアリン酸マグネシウム，ポリビニルアルコール，ポリエチレングリコール，タルク，二酸化チタン，黒酸化鉄及び三二酸化鉄。

12. 臨床薬理

12.1 作用機序

ウパダシチニブはヤヌスキナーゼ（JAK）阻害薬である。JAK は造血の細胞プロセスや免疫細胞の機能に影響を及ぼす細胞膜上のサイトカイン又は成長因子受容体との相互作用から生じるシグナルを伝達する細胞内酵素である。シグナル伝達経路において，JAK は遺伝子発現を含む細

胞機能を調整するシグナル伝達兼転写活性化因子（STATs）をリン酸化して活性化する。ウパダシチニブはシグナル伝達経路の JAK 発現部位を調整し，STATs のリン酸化と活性化を阻害する。

酵素である JAK は対になって作用し（JAK1/JAK2，JAK1/JAK3，JAK1/TYK2，JAK2/JAK2 及び JAK2/TYK2 など），サイトカインのシグナルを伝達する。無細胞で行う cell-free 酵素アッセイでは，ウパダシチニブは JAK3 と TYK2 に比較し，JAK1 および JAK2 でより高い阻害活性を示した。ヒト白血球の細胞アッセイでは，ウパダシチニブは JAK2/JAK2 を介した STAT リン酸化よりも，JAK1 及び JAK1/JAK3 を介したサイトカイン誘導による STAT リン酸化をより強力に阻害した。しかし，特異的な JAK を阻害することの治療効果への関連性は，現在不明である。

12.2 薬力学

IL-6 誘導 STAT3 及び IL-7 誘導 STAT5 リン酸化の阻害

健常人において，ウパダシチニブ（速放性製剤）の投与は，全血で IL-6（JAK1/JAK2）誘導 STAT3 及び IL-7（JAK1/JAK3）誘導 STAT5 リン酸化の用量及び濃度依存的阻害をもたらした。最大阻害は投与後 1 時間でみられ，投与間隔の終わりまでにベースラインに近い値に戻った。

リンパ球

ウパダシチニブによる治療により，Week 36 までに平均 ALC のベースラインからのわずかな一過性の増加がみられ，継続投与することで徐々にベースライン値又はベースラインに近い値まで戻った。

免疫グロブリン

対照期間中に，ウパダシチニブによる治療により，平均 IgG 及び IgM 値のベースラインからのわずかな低下が認められたが，ベースライン時及び全来院時の平均値は正常基準範囲内であった。

心臓電気生理学

平均最大曝露量 15 mg の 1 日 1 回投与の 6 倍では，QTc 間隔への臨床的に重要な影響は認められなかった。

12.3 薬物動態

ウパダシチニブの血漿曝露は治療量域における用量に比例する。定常状態での血漿濃度は，最少の蓄積で 1 日 1 回の反復投与後 4 日以内に達成された。

吸収

ウパダシチニブの徐放錠を経口投与後に，ウパダシチニブは平均 T_{max} が 2～4 時間で吸収される。

高脂肪食/高カロリー食摂取時のウパダシチニブ投与は，同剤の曝露量に臨床的に重要な影響は及ぼさなかった（AUC_{inf} が 29%，C_{max} が 39%増加）。臨床試験では，食事摂取とは関係なくウパダシチニブの投与が行われた［用法・用量（*2.1* 項）参照］。

分布

ウパダシチニブの血漿タンパク結合率は 52%である。ウパダシチニブは血漿と血液細胞成分を血液/血漿濃度比 1.0 で同様に分配する。

代謝

ウパダシチニブは主に CYP3A4 を介して代謝される（若干 CYP2D6 による代謝を受ける可能性あり）。ウパダシチニブの薬理活性は親分子に起因する。放射性同位体で標識されたウパダシチニブを用いたヒト試験において，同剤の未変化体は血漿中の総放射能の 79%を占めたが，検出された主な代謝物（一酸素原子添加反応［monooxidatio］に続いてグルクロン酸化による生成物）が血漿中の総放射能の 13%を占めた。ウパダシチニブの活性代謝物は同定されていない。

排泄

[14C]ウパダシチニブ速放性溶液の単回投与後に，ウパダシチニブは未変化体親化合物として主に尿中（24%）及び糞便中（38%）に排泄された。ウパダシチニブの約 34%は代謝物として排泄された。ウパダシチニブの平均消失半減期は 8～14 時間であった。

特殊集団

体重，性別，人種及び年齢

体重，性別，人種，民族及び年齢は，ウパダシチニブの曝露量に臨床的に重要な影響を及ぼさなかった*［特別な患者集団への投与（8.5 項）参照］*。

腎機能障害

腎機能障害はウパダシチニブの曝露量に臨床的に重要な影響を及ぼさない。ウパダシチニブの AUC_{inf} は，腎機能が正常な被験者と比較して，軽度，中等度及び重度の腎機能障害を有する被験者で，それぞれ 18%，33%及び 44%高値であった。ウパダシチニブの C_{max} は，腎機能が正常な被験者と腎機能障害を有する被験者で同様であった。

肝機能障害患者

軽度（チャイルド・ピュー分類 A）及び中等度（チャイルド・ピュー分類 B）の肝機能障害はウパダシチニブの曝露量に臨床的に重要な影響を及ぼさない。ウパダシチニブの AUC_{inf} は，肝機能が正常な被験者と比較して，軽度及び中等度の肝機能障害を有する被験者で，それぞれ 28%及び 24%高値であった。ウパダシチニブの C_{max} は，軽度の肝機能障害を有する被験者では変化はなく，中等度の肝機能障害を有する被験者では，肝機能が正常な被験者と比較して 43%高値であっ

た。重度の肝機能障害（チャイルド・ピュー分類 C）を有する被験者を対象としたウパダシチニブの試験は行われなかった。

薬物相互作用試験

他の薬剤がウダパシチニブの薬物動態に影響を及ぼす可能性

ウパダシチニブは *in vitro* で CYP3A4 によって代謝され，わずかに CYP2D6 も寄与する。併用薬がウパダシチニブの血漿曝露に及ぼす影響については 3 に示す*［薬物相互作用（7 項）参照］*。

表 3.　　併用薬の存在下におけるウパダシチニブの薬物動態の変動

併用薬	併用薬のレジメン	比率（90% CI）[a]	
		C_{max}	AUC
メトトレキサート	10–25 mg/週	0.97 (0.86–1.09)	0.99 (0.93–1.06)
強力な CYP3A4 阻害剤：ケトコナゾール	400 mg, 1 日 1 回 × 6 日間	1.70 (1.55–1.89)	1.75 (1.62–1.88)
強力な CYP3A4 誘導剤：リファンピン	600 mg, 1 日 1 回 × 9 日間	0.49 (0.44–0.55)	0.39 (0.37–0.42)
OATP1B 阻害剤：リファンピン	600 mg，単回投与	1.14 (1.02–1.28)	1.07 (1.01–1.14)

CI：信頼区間

[a]　C_{max} 及び AUC の比率はウパダシチニブと薬剤との併用療法と薬剤単剤療法とを比較したものである。

In vitro 評価及び母集団薬物動態解析に基づくと，pH 調整剤（制酸薬又はプロトンポンプ阻害薬など）はウパダシチニブの血漿曝露に影響を及ぼさない。（母集団薬物動態解析に基づくと）CYP2D6 代謝表現型はウパダシチニブの薬物動態に影響を及ぼさない。これは CYP2D6 の阻害剤はウパダシチニブの曝露量に臨床的に重要な影響を及ぼさないことを示唆している。

ウパダシチニブが他の薬剤の薬物動態に影響を及ぼす可能性

In vitro 試験において，ウパダシチニブは，臨床的に重要な用量ではシトクロム P450（CYP）酵素（CYP1A2，CYP2B6，CYP2C8，CYP2C9，CYP2C19，CYP2D6 及び CYP3A4）の活性を阻害も誘導もしないことが示唆されている。In vitro 試験では，ウパダシチニブは，臨床的に重要な用量ではトランスポーターである P-gp，BCRP，OATP1B1，OATP1B3，OCT1，OCT2，OAT1，OAT3，MATE1 及び MATE2K を阻害しないことが示唆されている。

臨床研究において，ウパダシチニブは，併用薬の薬物動態に臨床的に重要な影響を及ぼさないことが示唆されている。ウパダシチニブが他の薬剤に及ぼす影響を評価した臨床研究の要約を表 4 に示す。

表 4.　ウパダシチニブの存在下における併用薬又は CYP 活性の in vivo マーカーの薬物動態の変動

併用薬又は CYP 活性のマーカー	ウパダシチニブの反復投与レジメン	比率（90% CI）[a]	
		C_{max}	AUC
メトトレキサート	6–24 mg BID[b]	1.03 (0.86–1.23)	1.14 (0.91–1.43)
CYP1A2 の基質薬（sensitive substrate）（カフェイン）	30 mg QD[c]	1.13 (1.05–1.22)	1.22 (1.15–1.29)
CYP3A の基質薬（sensitive substrate）（ミダゾラム）	30 mg QD[c]	0.74 (0.68–0.80)	0.74 (0.68–0.80)
CYP2D6 の基質薬（sensitive substrate）（デキストロメトルファン）	30 mg QD[c]	1.09 (0.98–1.21)	1.07 (0.95–1.22)
CYP2C9 の基質薬（sensitive substrate）（S-ワルファリン）	30 mg QD[c]	1.07 (1.02–1.11)	1.11 (1.07–1.15)
CYP2C19 (sensitive marker)5-OH オメプラゾール/オメプラゾール代謝比	30 mg QD[c]	–	1.09 (1.00–1.19)
CYP2B6 基質薬：ブプロピオン	30 mg QD[c]	0.87 (0.79–0.96)	0.92 (0.87–0.98)
ロスバスタチン	30 mg QD[c]	0.77 (0.63–0.94)	0.67 (0.56–0.82)
アトルバスタチン	30 mg QD[c]	0.88 (0.79–0.97)	0.77 (0.70–0.85)
エチニルエストラジオール	30 mg QD[c]	0.96 (0.89–1.02)	1.11 (1.04–1.19)
レボノルゲストレル	30 mg QD[c]	0.96 (0.87–1.06)	0.96 (0.85–1.07)

CYP：シトクロム P450，CI：信頼区間，BID：1 日 2 回，QD：1 日 1 回

[a] C_{max} 及び AUC の比率はウパダシチニブと薬剤との併用療法と薬剤単剤療法とを比較したものである。

[b] 速放性製剤

[c] 徐放性製剤

13. 非臨床毒性

13.1 がん原性，変異原性，生殖能障害

がん原性

Sprague-Dawley（SD）ラット及び Tg.rasH2 マウスを用いて，ウパダシチニブのがん原性の可能性の評価が行われた。ウパダシチニブそれぞれ最大 15 又は 20 mg/kg/日を最長 101 週間にわたり経口投与した雄又は雌ラットにおいて，発がん性の徴候は認められなかった（AUC 換算で，雄及び雌それぞれ MRHD の約 4 倍及び 10 倍）。ウパダシチニブ最大 20 mg/kg/日を 26 週間にわたり Tg.rasH2 マウスの雄又は雌に経口投与したところ，Tg.rasH2 マウスに発がん性の徴候は認められなかった。

変異原性

ウパダシチニブは以下の遺伝毒性試験において遺伝毒性を示さなかった。細菌を用いた in vitro 変異原性試験（エームズ試験），ヒト末梢血リンパ球を用いた in vitro 染色体異常試験及びラット骨髄を用いた in vivo 小核試験。

生殖能障害

最大 50 mg/kg/日を経口投与した雄ラットと 75 mg/kg/日を経口投与した雌ラットでは（AUC に基づくと雄ラットでは MRHD の約 42 倍，雌ラットでは約 84 倍），ウパダシチニブは生殖能に影響を及ぼさなかった。しかし，着床後消失の増加（吸収増加）及び平均生存胚数の減少が用量依存性に認められた結果に基づくと，25 及び 75 mg/kg/日の経口投与は妊娠の継続に有害な影響を及ぼした。ウパダシチニブ 5 mg/kg/日を経口投与し，同用量（AUC に基づくと MRHD の約 2 倍）のウパダシチニブを投与した雄ラットと交配させた雌ラットでは，生存胚数は影響を受けなかった。

14. 臨床成績

本剤 1 日 1 回 15 mg の有効性及び安全性は，中等症から重症の活動性関節リウマチを有し，ACR/EULAR 関節リウマチ分類基準(2010 年)を満たす患者を対象とする 5 つの第 3 相無作為化，二重盲検，多施設共同試験において検討された。参加資格があるのは 18 歳以上の患者であった。患者にはベースライン時に，6 箇所以上の圧痛関節及び 6 箇所以上の腫脹関節を有し，hsCRP 上昇に基づく全身性炎症の徴候があることが求められた。他の用量を検討したが，本剤の推奨用量は 1 日 1 回 15 mg である。

RA-I 試験（NCT02706873）は，メトトレキサート（MTX）未治療の中等症から重症の活動性関節リウマチ患者 947 例を対象とした 24 週間の単剤療法試験である。本剤 15 mg 又はウパダシチニブ 30 mg を 1 日 1 回投与する単剤療法，あるいは MTX を 1 日 1 回投与する単剤療法が行われた。Week 26 にウパダシチニブに効果不十分な患者には，MTX の追加併用によるレスキュー療

法を行うことができ，MTX 単剤療法が行われていた患者には盲検下で本剤 15 mg 又はウパダシチニブ 30 mg の 1 日 1 回投与を追加してレスキュー療法を行うことができた。主要評価項目は Week 12 に ACR50 を達成した患者の割合であった。主な副次評価項目は，Week 12 の疾患活動性スコア（DAS28-CRP）≤ 3.2, Week 24 の DAS28-CRP < 2.6, Week 12 のベースラインからの HAQ-DI 変化量及び Week 24 時点のベースラインからの van der Heijde-modified total Sharp スコア（mTSS）の変化量であった。

RA-II 試験（NCT02706951）は，MTX に効果不十分な中等症から重症の活動性関節リウマチ患者 648 例を対象とした 14 週間の単剤療法試験である。本剤 15 mg 又はウパダシチニブ 30 mg を 1 日 1 回投与する単剤療法，あるいは MTX の固定用量を投与する単剤療法を継続した。ベースライン時に事前に規定されていた割付に基づき，MTX 群に無作為割付けされた患者を，Week 14 に盲検下で本剤 15 mg 又はウパダシチニブ 30 mg を 1 日 1 回投与する単剤療法群に移行した。主要評価項目は Week 14 に ACR20 を達成した患者の割合であった。主な副次評価項目は，DAS28-CRP ≤ 3.2, DAS28-CRP < 2.6 及び Week 14 のベースラインからの HAQ-DI 変化量であった。

RA-III 試験（NCT02675426）は，従来型合成疾患修飾性抗リウマチ薬（cDMARDs）に効果不十分な中等症から重症の活動性関節リウマチ患者 661 例を対象とした 12 週間の試験である。本剤 15 mg 又はウパダシチニブ 30 mg を 1 日 1 回投与，又は基礎療法としての cDMARDs にプラセボの追加投与が行われた。ベースライン時に事前に規定されていた割付に基づき，プラセボ群に無作為割付けされた患者を，Week 12 に盲検下で本剤 15 mg 又はウパダシチニブ 30 mg の 1 日 1 回投与群に移行した。主要評価項目は Week 12 に ACR20 を達成した患者の割合であった。主な副次評価項目は, DAS28-CRP ≤ 3.2, DAS28-CRP < 2.6 及び Week 12 のベースラインからの HAQ-DI 変化量であった。

RA-IV 試験（NCT02629159）は，MTX に効果不十分な中等症から重症の活動性関節リウマチ患者 1629 例を対象とした 48 週間の試験である。本剤 15 mg の 1 日 1 回投与，実対照薬投与又は基礎療法としての MTX にプラセボの追加投与が行われた。Week 14 から，本剤 15 mg に効果不十分な患者には，盲検下で実対照薬によるレスキュー療法を行うことができ，実薬対照又はプラセボに効果不十分な患者には，盲検下で本剤 15 mg によるレスキュー療法を行うことができた。プラセボ群に無作為割付けされた全例を，Week 26 に盲検下で本剤 15 mg の 1 日 1 回投与に切り替えた。主要評価項目はプラセボ群に比較し Week 12 に ACR20 を達成した患者の割合であった。主な副次評価項目は, DAS28-CRP ≤ 3.2, DAS28-CRP < 2.6, Week 12 のベースラインからの HAQ-DI 変化量及び Week 26 のベースラインからの mTSS の変化量であった。

RA-V 試験（NCT02706847）は，生物学的 DMARDs に効果不十分又は不耐容であった中等症から重症の活動性関節リウマチ患者 499 例を対象とした 12 週間の試験である。本剤 15 mg 又はウパダシチニブ 30 mg を 1 日 1 回投与，又は基礎療法としての cDMARDs にプラセボの追加投与が行われた。ベースライン時に事前に規定されていた割付に基づき，プラセボ群に無作為割付けされた患者を，Week 12 に盲検下で本剤 15 mg 又はウパダシチニブ 30 mg の 1 日 1 回投与群に移行

した。主要評価項目は Week 12 に ACR20 を達成した患者の割合であった。主な副次評価項目は，DAS28-CRP ≤3.2 及び Week 12 のベースラインからの HAQ-DI 変化量であった。

臨床効果

全ての試験において ACR20，ACR50，ACR70 及び DAS28（CRP）＜2.6 を達成した本剤投与患者の割合を表 5 に示す。

本剤 15 mg の単剤療法又は cDMARDs との併用療法が行われた患者は，主要有効性評価項目の評価時点において MTX 単剤療法群又はプラセボ群に比べ，ACR 反応率が高かった（表 5）。

RA-IV 試験では，来院日別の ACR20 を達成した患者の割合を図 1 に示す。

RA-III 試験及び RA-V 試験では，本剤 15 mg 群はプラセボ群に比べ，ACR20 反応率が Week 1 で高かった。

本剤 15 mg の単剤療法又は cDMARDs との併用療法は，MTX 群又はプラセボ群と比較して，主要有効性評価項目の評価時点において ACR の構成要素が改善した（表 6）。

表 5.　臨床効果

	RA-I 試験 MTX 未治療		RA-II 試験 MTX-IR		RA-III 試験 cDMARD-IR		RA-IV 試験 MTX-IR		RA-V 試験 bDMARD-IR	
	単剤療法		単剤療法		基礎療法として cDMARD		基礎療法として MTX		基礎療法として bDMARD	
	MTX 群	本剤 15 mg 群 % Δ (95% CI)	MTX 群	本剤 15 mg 群 % Δ (95% CI)	PBO 群	本剤 15mg 群 % Δ (95% CI)	PBO 群	本剤 15 mg 群 % Δ (95% CI)	PBO 群	本剤 15 mg 群 % Δ (95% CI)
N	314	317	216	217	221	221	651	651	169	164
Week										
ACR20										
12[a]/14[b]	54	76 22 (14, 29)	41	68 26 (17, 36)	36	64 28 (19, 37)	36	71 34 (29, 39)	28	65 36 (26, 46)
24[c]/26[d]	59	79 20 (13, 27)					36	67 32 (27, 37)		
ACR50										
12[a]/14[b]	28	52 24 (16, 31)	15	42 27 (18, 35)	15	38 23 (15, 31)	15	45 30 (26, 35)	12	34 22 (14, 31)
24[c]/26[d]	33	60 27 (19, 34)					21	54 33 (28, 38)		

表 5.　臨床効果（続き）

	RA-I 試験 MTX 未治療		RA-II 試験 MTX-IR		RA-III 試験 cDMARD-IR		RA-IV 試験 MTX-IR		RA-V 試験 bDMARD-IR	
	単剤療法		単剤療法		基礎療法として cDMARD		基礎療法として MTX		基礎療法として bDMARD	
	MTX 群	本剤 15 mg 群 % Δ (95% CI)	MTX 群	本剤 15 mg 群 % Δ (95% CI)	PBO 群	本剤 15mg 群 % Δ (95% CI)	PBO 群	本剤 15 mg 群 % Δ (95% CI)	PBO 群	本剤 15 mg 群 % Δ (95% CI)
N	314	317	216	217	221	221	651	651	169	164
Week										
ACR70										
12[a]/14[b]	14	32 18 (12, 25)	3	23 20 (14, 26)	6	21 15 (9, 21)	5	25 20 (16, 24)	7	12 5 (–1, 11)
24[c]/26[d]	18	44 26 (19, 33)					10	35 25 (21, 29)		
DAS28-CRP <2.6										
12[a]/14[b]	14	36 22 (15, 28)	8	28 20 (13, 27)	10	31 21 (14, 28)	6	29 23 (19, 27)	9	29 19 (11, 27)
24[c]/26[d]	18	48 30 (23, 37)					9	41 32 (27, 36)		

略語：ACR20（又は 50 又は 70）＝米国リウマチ学会基準の≥20%（又は≥50%又は≥70%）改善，bDMARD＝生物学的疾患修飾性抗リウマチ薬，CRP＝C-反応性蛋白，DAS28＝28 関節疾患活動性スコア，cDMARDs＝従来型合成疾患修飾性抗リウマチ薬，MTX＝メトトレキサート，PBO＝プラセボ，IR＝効果不十分例
無作為割付された治療を中止した患者，又は無作為割付された治療をクロスオーバーされた患者，あるいは評価週のデータが欠測している患者は，解析ではノンレスポンダーとして補完された。

[a] RA-I，RA-III，RA-IV，RA-V 試験
[b] RA-II 試験
[c] RA-I 試験
[d] RA-IV 試験

表 6.　主要有効性評価項目の評価時点における ACR の構成要素 [a]

	RA-I 試験 MTX 未治療		RA-II[b] 試験 MTX-IR		RA-III 試験 cDMARD-IR		RA-IV 試験 MTX-IR		RA-V 試験 bDMARD-IR	
	単剤療法		単剤療法		基礎療法として bDMARD		基礎療法として MTX		基礎療法として bDMARD	
	MTX 群	本剤 15 mg 群	MTX 群	本剤 15 mg 群	PBO 群	本剤 15 mg 群	PBO 群	本剤 15 mg 群	PBO 群	本剤 15 mg 群
N	314	317	216	217	221	221	651	651	169	164
圧痛関節数（0–68）										
ベースライン	26 (16)	25 (14)	25 (16)	24 (15)	25 (15)	25 (14)	26 (14)	26 (15)	28 (15)	28 (16)
Week12/14	13 (15)	9 (12)	15 (16)	10 (13)	16 (17)	12 (14)	16 (15)	10 (13)	18 (17)	11 (14)
腫脹関節数（0–66）										
ベースライン	17 (11)	17 (10)	17 (12)	16 (11)	15 (9)	16 (10)	16 (9)	17 (10)	16 (10)	17 (11)
Week12/14	6 (8)	5 (7)	9 (11)	6 (9)	9 (10)	7 (10)	9 (9)	5 (7)	9 (10)	6 (8)
疼痛 [c]										
ベースライン	66 (21)	68 (21)	63 (21)	62 (23)	62 (21)	64 (19)	65 (21)	66 (21)	69 (21)	68 (20)
Week12/14	41 (25)	31 (25)	49 (25)	36 (27)	51 (26)	33 (24)	49 (25)	33 (24)	55 (28)	41 (28)
患者による全般評価 [c]										
ベースライン	66 (21)	67 (22)	60 (22)	62 (22)	60 (20)	63 (22)	64 (21)	64 (22)	66 (23)	67 (20)
Week12/14	42 (25)	31 (24)	48 (26)	37 (27)	50 (26)	32 (24)	48 (24)	33 (24)	54 (28)	40 (26)
機能障害指数（HAQ-DI）[d]										
ベースライン	1.60 (0.67)	1.60 (0.67)	1.47 (0.66)	1.47 (0.66)	1.42 (0.63)	1.48 (0.61)	1.61 (0.61)	1.63 (0.64)	1.56 (0.60)	1.67 (0.64)
Week12/14	1.08 (0.72)	0.76 (0.69)	1.19 (0.69)	0.86 (0.67)	1.13 (0.70)	0.85 (0.66)	1.28 (0.67)	0.98 (0.68)	1.33 (0.66)	1.24 (0.77)

表 6.　主要有効性評価項目の評価時点における ACR の構成要素[a]（続き）

	RA-I 試験 MTX 未治療		RA-II[b] 試験 MTX-IR		RA-III 試験 cDMARD-IR		RA-IV 試験 MTX-IR		RA-V 試験 bDMARD-IR	
	単剤療法		単剤療法		基礎療法として bDMARD		基礎療法として MTX		基礎療法として bDMARD	
	MTX 群	本剤 15 mg 群	MTX 群	本剤 15 mg 群	PBO 群	本剤 15 mg 群	PBO 群	本剤 15 mg 群	PBO 群	本剤 15 mg 群
N	314	317	216	217	221	221	651	651	169	164
医師による全般評価[c]										
ベースライン	69 (16)	67 (17)	62 (17)	66 (18)	64 (18)	64 (16)	66 (18)	66 (17)	67 (17)	69 (17)
Week12/14	32 (22)	22 (19)	37 (24)	26 (21)	41 (24)	26 (21)	41 (25)	27 (21)	39 (25)	29 (22)
CRP（mg/L）										
ベースライン	21.2 (22.1)	23.0 (27.4)	14.5 (17.3)	14.0 (16.5)	12.6 (14.0)	16.6 (19.2)	18.0 (21.5)	17.9 (22.5)	16.3 (21.1)	16.3 (18.6)
Week12/14	10.9 (14.9)	4.2 (8.8)	12.8 (21.4)	3.7 (7.8)	13.1 (15.5)	4.6 (9.6)	16.2 (19.8)	5.5 (10.9)	13.9 (17.3)	5.0 (14.0)

略語：ACR = 米国リウマチ学会，bDMARD = 生物学的疾患修飾性抗リウマチ薬，CRP = C-反応性蛋白，cDMARDs ＝従来型合成疾患修飾性抗リウマチ薬，HAQ-DI = 健康評価質問票を用いた機能障害指数，IR ＝効果不十分例，MTX = メトトレキサート，PBO = プラセボ

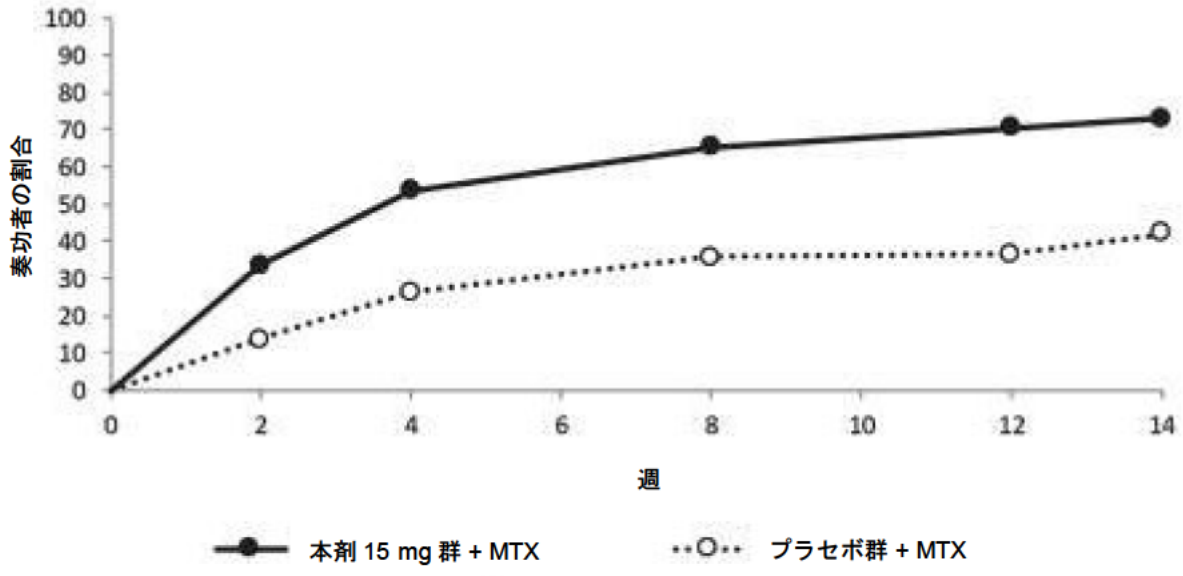
[a] 示されているデータは平均値（標準偏差）。

[b] 主要有効性評価項目の評価時点は Week 14 である。

[c] 視覚的アナログ尺度：0 = 最も良い，100 = 最も悪い。

[d] 健康評価質問票を用いた機能障害指数：0 = 最も良い，3 = 最も悪い，20 項目の質問，8 つのカテゴリー：衣類の着脱と身支度，起立，食事，歩行，衛生，届く範囲，握力及び家事や雑用。

図 1. RA-IV 試験で ACR20 を達成した患者の場合



略語：ACR20 = 米国リウマチ学会基準の≥20%改善，MTX = メトトレキサート
無作為割付された治療を中止した患者又は ACR20 の結果が欠測している患者，あるいは追跡不能もしくは試験から脱落した患者は，ノンレスポンダーとして補完された。

RA-I 試験及び RA-IV 試験では，本剤 15 mg の単剤療法又は MTX との併用療法は，MTX 群又はプラセボ群と比較して，主要有効性評価項目の評価時点において DAS28-CRP < 2.6 を達成した患者の割合が高かった（表 7）。

表 7.　主要有効性評価項目の評価時点において，活動性が残存している関節数と DAS28-CRP < 2.6 を達成した患者の割合

	RA-I 試験 MTX 未治療	
	単剤療法	
DAS28-CRP < 2.6	MTX 群 N = 314	本剤 15 mg 群 N = 317
Week12 のレスポンダーの割合（n）	14% (43)	36% (113)
レスポンダーの中で，活動性関節数が 0 の割合（n）	51% (22)	45% (51)
レスポンダーの中で，活動性関節数が 1 の割合（n）	35% (15)	23% (26)
レスポンダーの中で，活動性関節数が 2 の割合（n）	9% (4)	17% (19)
レスポンダーの中で，活動性関節数が 3 以上の割合（n）	5% (2)	15% (17)
Week12 のレスポンダーの割合（n）	6% (40)	29% (187)
レスポンダーの中で，活動性関節数が 0 の割合（n）	60% (24)	48% (89)
レスポンダーの中で，活動性関節数が 1 の割合（n）	20% (8)	23% (43)
レスポンダーの中で，活動性関節数が 2 の割合（n）	15% (6)	13% (25)
レスポンダーの中で，活動性関節数が 3 以上の割合（n）	5% (2)	16% (30)
略語：CRP = CRP = C-反応性蛋白，DAS28 = 28 関節疾患活動性スコア，MTX = メトトレキサート，PBO = プラセボ，IR = 効果不十分例		

X 線画像上の反応

関節の構造的損傷の進展防止効果は，RA-IV 試験では Week 26，RA-I 試験では Week 24 において，modified Total Sharp スコア（mTSS）及びその構成要素である骨びらんスコアならびに関節裂隙狭小化スコアを用いて検討された。X 線画像上の進展（ベースラインからの mTSS 変化量 ≤ 0）を認めない患者の割合も評価された。

本剤 15 mg による治療は，RA-IV 試験では Week 26 に cDMARDs と併用したプラセボ群と比較して，関節の構造的損傷の進展を有意に防止した（表 8）。骨びらんスコア及び関節裂隙狭小化スコアの解析結果も全体の結果と一致した。

プラセボ+MTX 群では, Week 26 に患者の 76%が X 線画像上の進展を認めなかったのに比較し，本剤 15 mg 群では 83%に X 線画像上の進展を認めた。

本剤 15 mg 単剤療法は RA-I 試験では，Week 24 に MTX 単剤療法と比較して，関節の構造的損傷の進展を有意に防止した（表 8）。骨びらんスコア及び関節裂隙狭小化スコアの解析結果も全体の結果と一致した。

MTX 単剤療法群では, Week 24 に患者の 78%が X 線画像上の進展を認めなかったのに比較し，本剤 15 mg 単剤療法群では 87%に X 線画像上の進展を認めた。

表 8.　　X 線画像上の変化

	RA-IV 試験 MTX-IR		
	基礎療法として MTX		
mTSS	PBO 群 (N = 651) 平均値（SD）	本剤 15 mg 群 (N = 651) 平均値（SD）	Week 26 の PBO 群に比較した差の推定量 （95% CI）[1]
ベースライン	35.9 (52)	34.0 (50)	
Week 26[2]	0.78 (0.1)	0.15 (0.1)	–0.63 (–0.92, –0.34)
	RA-I 試験 MTX 未治療		
	単剤療法		
	MTX 群 (N = 309) 平均値（SD）	本剤 15 mg 群 (N = 309) 平均値（SD）	Week 24 の MTX 群に比較した差の推定量 （95% CI）[3]
ベースライン	13.3 (31)	18.1 (38)	
Week 24[4]	0.67 (2.8)	0.14 (1.4)	–0.53 (–0.85, –0.20)

略語 : mTSS = modified Total Sharp スコア，MTX = メトトレキサート，PBO = プラセボ，SD ＝標準偏差，IR ＝効果不十分例，bDMARD = 生物学的疾患修飾性抗リウマチ薬，LS = 最小二乗，CI = 信頼区間

1 ランダム係数モデルに基づく LS 平均及び 95%CI は時間，治療群，前治療における bDMARDs の使用及び治療群と時間の相互作用を調整した後で mTSS に適合し，ランダム傾きとランダム切片を持つ。

2 Week 26 までの構造的損傷の進展の推定線形率及び標準偏差を示す。

3 線形回帰モデルに基づく LS 平均及び 95%CI は治療群，ベースライン時の mTSS 及び地理的地域を調整した後でベースラインからの mTSS 変化量に適合する。

4 ベースラインからの平均変化量と標準偏差を示す。

身体機能の反応

本剤 15 mg 単剤療法又は csDMARDs との併用療法は，Week 12/14 にわたる HAQ-DI による評価で，全ての対照薬と比較して身体機能を大きく改善した。

その他の健康関連評価項目

RA-V 試験を除いた全ての試験において，本剤 15 mg 群は cDMARD とプラセボ併用療法群又は MTX 単剤療法群と比較して，Week 12/14 に身体的構成要素サマリー（PCS）スコア，精神的構成要素サマリー（MCS）スコア及びショートフォーム健康調査（SF-36）の全 8 領域でベースラインから大きな改善を示した。

RA-I, RA-III 及び RA-IV 試験において, 疲労は慢性疾患治療-疲労スコアの機能評価（FACIT-F）によって検討された。本剤 15 mg 治療群は cDMARD とプラセボ併用療法群又は MTX 単剤療法群と比較して，Week 12 に疲労の改善が認められた。

16. 供給形態/保存及び取り扱い方法

16.1 供給形態

本剤 15 mg 経口徐放錠は, 紫色又はまだらな紫色の両凸形の楕円であり, サイズは 14 × 8 mm, 片面に「a15」の刻印がある。

各瓶に 30 錠含有；NDC: 0074-2306-30

16.2 貯法及び取り扱い

2°C～25°C（36°F～77°F）で保存すること。

湿気から保護するため，元のボトルのまま保存すること。

17. 患者カウンセリング情報

FDA 承認済みの患者向け情報を参照するよう患者に指導すること（患者向け医薬品ガイド）。

重篤な感染

本剤を投与すると感染を発症しやすくなる可能性があることを患者に説明すること。治療中に感染の徴候や症状が発現した場合は，直ちに担当の医療提供者に連絡を取るよう患者に指導すること*［警告及び使用上の注意（5.1 項）参照］*。

本剤の投与患者で帯状疱疹のリスクが増大し，一部の症例では重篤になる可能性があることを患者に指導すること*［警告及び使用上の注意（5.1 項）参照］*。

悪性腫瘍

本剤は特定のがんのリスクを増大させる可能性があることを患者に説明すること。どんな種類のがんでも発症したことがある場合は，担当の医療提供者に知らせるよう患者に指導すること*［警告及び使用上の注意（5.2 項）参照］*。

血栓症

本剤の臨床試験において，DVT 及び PE が報告されていることを患者に説明すること。DVT や PE の徴候や症状が発現した場合は，担当の医療提供者に連絡を取るよう患者に指導すること［警告及び使用上の注意（5.3 項）参照］。

臨床検査値異常

本剤は特定の臨床検査に影響を及ぼす可能性があるため，本剤による治療前及び治療中に血液検査を実施する必要があることを患者に説明すること*［警告及び使用上の注意（5.5 項）参照］*。

妊婦

妊婦や妊娠可能な女性には，本剤を妊娠期間中に投与すると胎児に害を及ぼす可能性があることを説明すること。患者が本剤の投与中に妊娠したことがわかった場合，または疑われる場合は，担当の医療提供者に連絡を取るよう患者に指導すること［警告及び使用上の注意（*5.6* 項）及び特別な患者集団への投与（*8.1* 項）参照］。妊娠可能な女性には，本剤による治療中及び本剤の最終投与後 4 週間は有効な避妊法を用いるよう指導すること。患者が本剤の投与中に妊娠した場合は，胎児への潜在的リスクについて患者に説明すること［*特別な患者集団への投与（8.3 項）参照］*。

授乳婦

女性には，本剤による治療中は授乳しないよう指導すること*［特別な患者集団への投与（8.2 項）参照］*。

用法

本剤の錠剤を噛んだり，潰したり，割ったりしないよう患者に指導すること［用法及び用量（*2.2* 項）参照］。

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患者向け医薬品ガイド
RINVOQ™（リンヴォック）
（ウパダシチニブ）
経口徐放錠

本剤について知っておくべき最も重要な情報は何ですか？本剤は以下の重篤な副作用を引き起こす可能性があります：

1　重篤な感染

本剤は免疫系に影響を及ぼす薬剤です。本剤は感染と闘う免疫力を低下させる可能性があります。本剤の服用中に，結核（TB）及び細菌，真菌又は全身に広がるウイルスによる感染などの重篤な感染を発症した例もあります。このような感染で死亡した例もあります。

- 担当の医療提供者は，本剤による治療を開始する前に TB の検査を実施する必要があります。
- 担当の医療提供者は，本剤による治療中は TB の徴候及び症状について，あなたを注意深く観察する必要があります。
- いかなる感染でも発症している場合は，担当の医療提供者の了承を得ていない限り，本剤の服用を開始してはいけません。帯状疱疹を発症するリスクが高まることがあります。
- **（帯状疱疹）本剤の服用を開始する前に，次の場合は担当の医療提供者に伝えてください：**
  - 感染の治療を受けている。
  - 治らない又は再発を繰り返す感染がある。
  - 糖尿病，慢性肺疾患，HIV を発症している又は免疫系が弱っている。
  - TB を発症している又は TB 患者と密接な接触があった。
  - 帯状疱疹を発症している。（帯状疱疹）
  - B 型又は C 型肝炎を発症している。
  - 何らかの真菌感染を発症する可能性が高まっている国の特定の地域（オハイオ川とミシシッピ川流域及び南西部など）に居住しているか居住したことがある，又は渡航したことがある。このような感染は，本剤を使用した場合に発現するか重症化することがあります。このような感染が一般的である地域に居住したことがあるかどうか不明な場合には，担当の医療提供者に相談してください。
  - 感染を発症していると思う又は以下のような感染の症状がある：
    - 発熱，発汗又は悪寒
    - 息切れ
    - 皮膚熱感，発赤又は疼痛，あるいは体の痛み
    - 筋肉痛
    - 疲労感
    - 血痰
    - 下痢又は胃痛
    - 咳嗽
    - 体重減少
    - 排尿時の灼熱感又は通常よりも頻度が増した排尿

本剤の服用開始後に何らかの感染の症状が現れた場合は，直ちに担当の医療提供者に電話連絡をしてください。本剤は感染を発症しやすくする，又は発症している感染を悪化させることがあります。

2　がん

本剤は免疫系の働きを変化させることで，特定のがんのリスクを高めることがあります。
皮膚癌を含むリンパ腫などのがんが，本剤を服用している人に発現する可能性があります。
これまでに，どんな種類のがんでも発症したことがある場合は，担当の医療提供者に伝えてください。

3. 血餅（血栓症）

本剤を服用している人の脚の静脈（深部静脈血栓：DVT）や肺の静脈（肺塞栓症：PE），又は動脈（動脈血栓症）に血餅が発現する可能性があります。これらの血餅は命にかかわることや死亡につながることがあります。

- これまでに脚や肺の静脈に血餅が発現したことがある場合は，担当の医療提供者に伝えてください。
- 本剤の投与期間中に以下のような何らかの血餅の徴候や症状が現れた場合は，直ちに担当の医療提供者に電話連絡をしてください。
  - むくみ
  - 説明できない突然の胸痛
  - 脚の痛み又は圧痛
  - 息切れ

4. 胃又は腸に穴があくこと（穿孔）

- これまでに憩室炎（大腸の一部の炎症）又は胃や腸に潰瘍を発症したことがある場合は，担当の医療提供者に伝えてください。本剤を服用している人は，胃や腸に穴があくことがあります。非ステロイド性抗炎症薬（NSAIDs），コルチコステロイド又はメトトレキサートを服用している人で起こることが多いです。
- 発熱や胃の付近に痛みがあり，痛みが消えない場合や排便習慣が変化した場合は，直ちに担当の医療提供者に電話連絡をしてください。

5. 特定の臨床検査結果の変化

担当の医療提供者は，あなたが本剤の服用を開始する前と服用中に，血液検査を行って以下について確認します：

- **好中球数とリンパ球数が少ない。**好中球とリンパ球は白血球の一種で，体が感染と闘うのを助けます。
- **赤血球数が少ない。**赤血球は酸素を運びます。赤血球が少ないと，貧血を起こす可能性があります。赤血球数が少ないと，脱力感や疲れを感じることがあります。
- **コレステロール値が高い。**担当の医療提供者は，あなたが本剤の服用を開始してから約 12 週間後に，またその後も必要に応じて血液検査を実施しコレステロール値を確認します。
- **肝酵素の増加。**肝酵素は肝臓が正常に機能しているか判断するのに役立ちます。肝酵素の増加は，担当の医師があなたの肝臓について追加検査を行う必要があることを示唆していることがあります。

好中球数，リンパ球数又は赤血球数が少な過ぎる，あるいは肝臓検査値が高過ぎる場合は，本剤を服用しないでください。担当の医療提供者は，これらの血液検査結果の変化により，必要に応じて本剤による治療をしばらくの間中止することがあります。副作用の詳しい情報については**「本剤ではどのような副作用が起こる可能性がありますか？」**をご覧ください。

本剤はどんな薬ですか？

- 本剤はヤヌスキナーゼ（JAK）阻害薬という処方箋医薬品です。本剤は，メトトレキサートが効かない，又は耐えられない，成人の中等症から重症の関節リウマチ患者の治療に使用されます。

本剤を 18 歳以下の小児に対して用いた場合の安全性及び有効性については明らかになっていません。

本剤の服用を開始する前に，以下の情報を含む健康状態について全てを担当の医療提供者に伝えてください：

- **「本剤について知っておくべき最も重要な情報は何ですか？」**を参照してください。
- 感染を発症している。
- 肝疾患を発症している。
- 赤血球数又は白血球数が少ない。
- 最近，予防接種（ワクチン接種）を受けた又は受ける予定である。本剤を服用する人は生ワクチンを接種しないでください。
- 妊娠している又は妊娠する予定がある。動物を用いた試験によると，本剤は胎児に害を及ぼす可能性があります。本剤の服用を開始する前に，担当の医療提供者はあなたが妊娠しているかどうかを確認します。本剤の服用中及び本剤の最終投与後少なくとも 4 週間は，妊娠を避けるために有効な避妊法（避妊）を用いる必要があります。
- 授乳中又は授乳の予定がある。本剤は乳汁中に移行する可能性があります。あなたと担当の医療提供者は，本剤を服用するか授乳するかを決めなければなりません。両方を行わないでください。本剤の最終投与後 6 日間は，授乳は行わないでください。

処方箋医薬品や大衆薬，ビタミン剤及びハーブサプリメントなど，**使用している全ての薬剤を担当の医療提供者に伝えてください**。本剤と他の薬剤は相互に作用し，副作用を引き起こすことがあります。

特に，以下を服用する場合は担当の医療提供者に伝えてください：

- 真菌感染に対する薬剤（ケトコナゾール，イトラコナゾール，ポサコナゾール又はボリコナゾールなど）又はクラリスロマイシン（細菌感染に対する）。これらの薬剤は本剤の血中濃度を高める可能性があります。
- リファンピシン（細菌感染に対する）又はフェニトイン（神経疾患に対する）。これらの薬剤は本剤の効果を低下させる可能性があります。
- 免疫系に影響を及ぼす薬剤（アザチオプリン，シクロスポリン及びタクロリムスなど）。これらの薬剤は感染のリスクを高める可能性があります。

これらの薬剤を服用しているかどうかがはっきりしない場合は，担当の医療提供者又は薬剤師に聞いてください。

服用している薬剤を認識しておいてください。薬剤リストを保管し，新たな薬剤が処方される際には担当の医療提供者や薬剤師に見せてください。

本剤はどのように使用すべきですか？

- 本剤は必ず担当の医療提供者の指示に従って服用してください。
- 食事摂取の有無にかかわらず，本剤を 1 日 1 回服用してください。
- 本剤は毎日ほぼ同じ時間に水と一緒に丸ごと飲み込んでください。錠剤を割ったり，潰したり，噛んだりしないでください。

本剤ではどのような副作用が起こる可能性がありますか？

本剤は次のような重篤な副作用を引き起こす可能性があります：

「本剤について知っておくべき最も重要な情報は何ですか？」を参照してください。

本剤による頻度の高い副作用は以下の通りです。上気道感染症（風邪，副鼻腔炎），悪心，咳嗽及び発熱。

（これらは本剤によって起こり得る副作用の全てではありません）：副作用について医学的な助言を得るには担当医師に電話連絡をしてください。FDA（1-800-FDA-1088）に副作用を報告することもできます。

本剤はどのように保管したらよいですか？

- 湿気から保護するため，2°C～25°C（36°F～77°F）で元の容器のまま本剤を保存してください。
- **本剤を含め全ての医薬品を，お子さまの手の届かないところに保管してください。**

本剤の安全かつ効果的な使用についての一般的情報

医薬品は患者向け医薬品ガイドに記載されている以外の目的で処方されることがあります。
処方された目的とは異なる症状のために本剤を使用しないでください。
たとえ症状が同じであっても，本剤を他人に譲渡しないで下さい。譲った人に害を及ぼす可能性があります。
医薬従事者用に作成された本剤についての情報を，担当の医療提供者や薬剤師に求めることができます。

本剤の成分は何ですか？

有効成分：ウパダシチニブ
添加物：結晶セルロース，ヒプロメロース，マンニトール，酒石酸，軽質無水ケイ酸，ステアリン酸マグネシウム，ポリビニルアルコール，ポリエチレングリコール，タルク，二酸化チタン，黒酸化鉄及び三二酸化鉄

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詳細情報については，1-800-2-RINVOQ（1-800-274-6867）に電話するか www.RINVOQ.com.を閲覧してください。

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20064702

1.6.2.2 欧州における添付文書

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

RINVOQ 15 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains upadacitinib hemihydrate, equivalent to 15 mg of upadacitinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

Purple 14 x 8 mm, oblong biconvex prolonged-release tablets imprinted on one side with 'a15'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

RINVOQ is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). RINVOQ may be used as monotherapy or in combination with methotrexate.

Psoriatic arthritis

RINVOQ is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. RINVOQ may be used as monotherapy or in combination with methotrexate.

Ankylosing spondylitis

RINVOQ is indicated for the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.

4.2 Posology and method of administration

Treatment with upadacitinib should be initiated and supervised by physicians experienced in the diagnosis and treatment of conditions for which upadacitinib is indicated.

Posology

The recommended dose of upadacitinib is 15 mg once daily.

Consideration should be given to discontinuing treatment in patients with ankylosing spondylitis who have shown no clinical response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks.

Treatment should not be initiated in patients with an absolute lymphocyte count (ALC) that is < 500 cells/mm^3, an absolute neutrophil count (ANC) that is < 1,000 cells/mm^3 or who have haemoglobin (Hb) levels that are < 8 g/dL (see sections 4.4 and 4.8).

Dose interruption

Treatment should be interrupted if a patient develops a serious infection until the infection is controlled.

Interruption of dosing may be needed for management of laboratory abnormalities as described in Table 1.

Table 1. Laboratory measures and monitoring guidance

Laboratory measure	Action	Monitoring guidance
Absolute Neutrophil Count (ANC)	Treatment should be interrupted if ANC is < 1,000 cells/mm^3 and may be restarted once ANC returns above this value	Evaluate at baseline and thereafter according to routine patient management
Absolute Lymphocyte Count (ALC)	Treatment should be interrupted if ALC is < 500 cells/mm^3 and may be restarted once ALC returns above this value	
Haemoglobin (Hb)	Treatment should be interrupted if Hb is < 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	
Lipids	Patients should be managed according to international clinical guidelines for hyperlipidaemia	12 weeks after initiation of treatment and thereafter according to international clinical guidelines for hyperlipidaemia

Special populations

Elderly

No dose adjustment is required in patients aged 65 years and older. There are limited data in patients aged 75 years and older.

Renal impairment

No dose adjustment is required in patients with mild or moderate renal impairment. There are limited data on the use of upadacitinib in subjects with severe renal impairment (see section 5.2). Upadacitinib should be used with caution in patients with severe renal impairment. The use of upadacitinib has not been studied in subjects with end stage renal disease.

Hepatic impairment

No dose adjustment is required in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment (see section 5.2). Upadacitinib should not be used in patients with severe (Child-Pugh C) hepatic impairment (see section 4.3).

Paediatric population

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

Method of administration

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active tuberculosis (TB) or active serious infections (see section 4.4).
- Severe hepatic impairment (see section 4.2).
- Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Immunosuppressive medicinal products

Combination with other potent immunosuppressants such as azathioprine, ciclosporin, tacrolimus, and biologic DMARDs or other Janus kinase (JAK) inhibitors has not been evaluated in clinical studies and is not recommended as a risk of additive immunosuppression cannot be excluded.

Serious infections

Serious and sometimes fatal infections have been reported in patients receiving upadacitinib. The most frequent serious infections reported with upadacitinib included pneumonia and cellulitis (see section 4.8). Cases of bacterial meningitis have been reported in patients receiving upadacitinib. Among opportunistic infections, tuberculosis, multidermatomal herpes zoster, oral/oesophageal candidiasis, and cryptococcosis were reported with upadacitinib.

Upadacitinib should not be initiated in patients with an active, serious infection, including localised infections.

Consider the risks and benefits of treatment prior to initiating upadacitinib 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 travelled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with upadacitinib. Upadacitinib therapy should be interrupted if a patient develops a serious or opportunistic infection. A patient who develops a new infection during treatment with upadacitinib 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 upadacitinib therapy should be interrupted if the patient is not responding to antimicrobial therapy. Upadacitinib therapy may be resumed once the infection is controlled.

As there is a higher incidence of infections in the elderly ≥ 65 years of age, caution should be used when treating this population.

Tuberculosis

Patients should be screened for tuberculosis (TB) before starting upadacitinib therapy. Upadacitinib should not be given to patients with active TB (see section 4.3). Anti-TB therapy should be considered prior to initiation of upadacitinib in patients with previously untreated latent TB or in patients with 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.

Patients should be monitored 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), was reported in clinical studies (see section 4.8). If a patient develops herpes zoster, interruption of upadacitinib therapy should be considered until the episode resolves.

Screening for viral hepatitis and monitoring for reactivation should be performed before starting and during therapy with upadacitinib. 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. If hepatitis B virus DNA is detected while receiving upadacitinib, a liver specialist should be consulted.

Vaccination

No data are available on the response to vaccination with live or inactivated vaccines in patients receiving upadacitinib. Use of live, attenuated vaccines during or immediately prior to upadacitinib therapy is not recommended. Prior to initiating upadacitinib, it is recommended that patients be brought up to date with all immunisations, including prophylactic zoster vaccinations, in agreement with current immunisation guidelines.

Malignancy

The risk of malignancies, including lymphoma is increased in patients with rheumatoid arthritis. Immunomodulatory medicinal products may increase the risk of malignancies, including lymphoma. The clinical data are currently limited and long-term studies are ongoing.

Malignancies were observed in clinical studies of upadacitinib. The risks and benefits of upadacitinib treatment should be considered prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing upadacitinib therapy in patients who develop a malignancy.

Non-melanoma skin cancer

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

Haematological abnormalities

Absolute Neutrophil Count (ANC) < 1 x 10^9 cells/L, Absolute Lymphocyte Count (ALC) < 0.5 x 10^9 cells/L and haemoglobin < 8 g/dL were reported in ≤1 % of patients in clinical trials (see section 4.8). Treatment should not be initiated, or should be temporarily interrupted, in patients with an ANC < 1 x 10^9 cells/L, ALC < 0.5 x 10^9 cells/L or haemoglobin < 8 g/dL observed during routine patient management (see section 4.2).

Cardiovascular risk

Rheumatoid arthritis patients have an increased risk for cardiovascular disorders. Patients treated with upadacitinib should have risk factors (e.g., hypertension, hyperlipidaemia) managed as part of usual standard of care.

Lipids

Treatment with upadacitinib was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol (see section 4.8). Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy, although evidence is limited. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined (see section 4.2 for monitoring guidance).

Hepatic transaminase elevations

Treatment with upadacitinib was associated with an 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, upadacitinib therapy should be interrupted until this diagnosis is excluded.

Venous thromboembolism

Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving JAK inhibitors including upadacitinib. Upadacitinib should be used with caution in patients at high risk for DVT/PE. Risk factors that should be considered in determining the patient's risk for DVT/PE include older age, obesity, a medical history of DVT/PE, patients undergoing major surgery, and prolonged immobilisation. If clinical features of DVT/PE occur, upadacitinib treatment should be discontinued and patients should be evaluated promptly, followed by appropriate treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to affect the pharmacokinetics of upadacitinib

Upadacitinib is metabolised mainly by CYP3A4. Therefore, upadacitinib plasma exposures can be affected by medicinal products that strongly inhibit or induce CYP3A4.

Coadministration with CYP3A4 inhibitors

Upadacitinib exposure is increased when co-administered with strong CYP3A4 inhibitors (such as ketoconazole, itraconazole, posaconazole, voriconazole, and clarithromycin). In a clinical study, coadministration of upadacitinib with ketoconazole resulted in 70% and 75% increases in upadacitinib C_{max} and AUC, respectively. Upadacitinib should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors. Consider alternatives to strong CYP3A4 inhibitor medications when used in the long-term.

Coadministration with CYP3A4 inducers

Upadacitinib exposure is decreased when co-administered with strong CYP3A4 inducers (such as rifampin and phenytoin), which may lead to reduced therapeutic effect of upadacitinib. In a clinical study, coadministration of upadacitinib after multiple doses of rifampicin (strong CYP3A inducer) resulted in approximately 50% and 60% decreases in upadacitinib C_{max} and AUC, respectively. Patients should be monitored for changes in disease activity if upadacitinib is co-administered with strong CYP3A4 inducers.

Methotrexate and pH modifying medicinal products (e.g., antacids or proton pump inhibitors) have no effect on upadacitinib plasma exposures.

Potential for upadacitinib to affect the pharmacokinetics of other medicinal products

Administration of multiple 30 mg once daily doses of upadacitinib (a dose that is twice the recommended upadacitinib dose) to healthy subjects had a limited effect on midazolam (sensitive drug substrate for CYP3A) plasma exposures (26% decrease in midazolam AUC and C_{max}), indicating that upadacitinib 30 mg once daily may have a weak induction effect on CYP3A. In a clinical study, rosuvastatin and atorvastatin AUC were decreased by 33% and 23%, respectively, and rosuvastatin C_{max} was decreased by 23% following the administration of multiple 30 mg once daily doses of upadacitinib to healthy subjects. Upadacitinib had no relevant effect on atorvastatin C_{max} or on plasma exposures of ortho-hydroxyatorvastatin (major active metabolite for atorvastatin). No dose adjustment is recommended for CYP3A substrates or for rosuvastatin or atorvastatin when coadministered with upadacitinib.

Upadacitinib has no relevant effects on plasma exposures of ethinylestradiol, levonorgestrel, methotrexate, or medicinal products that are substrates for metabolism by CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be advised to use effective contraception during treatment and for 4 weeks following the final dose of upadacitinib.

Pregnancy

There are no or limited data on the use of upadacitinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Upadacitinib was teratogenic in rats and rabbits with effects in bones in rat foetuses and in the heart in rabbit foetuses when exposed *in utero*.

Upadacitinib is contraindicated during pregnancy (see section 4.3).

If a patient becomes pregnant while taking upadacitinib the parents should be informed of the potential risk to the foetus.

Breast-feeding

It is unknown whether upadacitinib/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of upadacitinib in milk (see section 5.3).

A risk to newborns/infants cannot be excluded.

Upadacitinib should not be used during breast-feeding. A decision must be made whether to discontinue breast-feeding or to discontinue upadacitinib therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effect of upadacitinib on human fertility has not been evaluated. Animal studies do not indicate effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Upadacitinib has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse drug reactions (ADRs) were upper respiratory tract infections, bronchitis, nausea, blood creatine phosphokinase (CPK) increased and cough. The most common serious adverse reactions were serious infections (see section 4.4).

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical studies.
The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2. Adverse reactions

System Organ Class	Very common	Common	Uncommon
Infections and infestations	Upper respiratory tract infections (URTI)[a]	Bronchitis[b] Herpes zoster Herpes simplex[c]	Pneumonia Oral candidiasis
Blood and lymphatic system disorders		Neutropaenia	
Metabolism and nutrition disorders		Hypercholesterolaemia	Hypertriglyceridaemia
Respiratory, thoracic and mediastinal disorders		Cough	
Gastrointestinal disorders		Nausea	
Skin and subcutaneous tissue disorders		Acne	
General disorders and administration site conditions		Pyrexia	
Investigations		Blood CPK increased ALT increased AST increased Weight increased	

[a] Includes upper respiratory tract infection, acute sinusitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, viral upper respiratory tract infection
[b] Includes bronchitis, bronchitis viral, bronchitis bacterial, and tracheobronchitis
[c] Includes herpes simplex and oral herpes

Rheumatoid arthritis

Description of selected adverse reactions

Infections

In placebo-controlled clinical studies with background DMARDs, the frequency of infection over 12/14 weeks in the upadacitinib 15 mg group was 27.4% compared to 20.9% in the placebo group. In methotrexate (MTX)-controlled studies, the frequency of infection over 12/14 weeks in the upadacitinib 15 mg monotherapy group was 19.5% compared to 24.0% in the MTX group. The overall long-term rate of infections for the upadacitinib 15 mg group across all five Phase 3 clinical studies (2,630 patients) was 93.7 events per 100 patient-years.

In placebo-controlled clinical studies with background DMARDs, the frequency of serious infection over 12/14 weeks in the upadacitinib 15 mg group was 1.2% compared to 0.6% in the placebo group. In MTX-controlled studies, the frequency of serious infection over 12/14 weeks in the upadacitinib 15 mg monotherapy group was 0.6% compared to 0.4% in the MTX group. The overall long-term rate of serious infections for the upadacitinib 15 mg group across all five Phase 3 clinical studies was 3.8 events per 100 patient-years. The most common serious infection was pneumonia. The rate of serious infections remained stable with long-term exposure.

There was a higher rate of serious infections in patients ≥ 75 years of age, although data are limited.

The frequencies of infection ADRs for upadacitinib compared to placebo were: URTI (13.5% vs 9.5%), pneumonia (0.5% vs 0.3%), herpes zoster (0.7% vs 0.2%), herpes simplex (0.8% v 0.5%), and

oral candidiasis (0.4% vs. <0.1%). Most of the herpes zoster events involved a single dermatome and were non-serious.

Opportunistic infections (excluding tuberculosis)

In placebo-controlled clinical studies with background DMARDs, the frequency of opportunistic infections over 12/14 weeks in the upadacitinib 15 mg group was 0.5% compared to 0.3% in the placebo group. In MTX-controlled studies, there were no cases of opportunistic infection over 12/14 weeks in the upadacitinib 15 mg monotherapy group and 0.2% in the MTX group. The overall long-term rate of opportunistic infections for the upadacitinib 15 mg group across all five Phase 3 clinical studies was 0.6 events per 100 patient-years.

Hepatic transaminase elevations

In placebo-controlled studies with background DMARDs, for up to 12/14 weeks, alanine transaminase (ALT) and aspartate transaminase (AST) elevations ≥ 3 x upper limit of normal (ULN) in at least one measurement were observed in 2.1% and 1.5% of patients treated with upadacitinib 15 mg, compared to 1.5% and 0.7%, respectively, of patients treated with placebo. Most cases of hepatic transaminase elevations were asymptomatic and transient.

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

The pattern and incidence of elevation in ALT/AST remained stable over time including in long-term extension studies.

Lipid elevations

Upadacitinib 15 mg treatment was associated with dose-dependent increases in lipid parameters including total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol. There was no change in the LDL/HDL ratio. Elevations were observed at 2 to 4 weeks of treatment and remained stable with longer-term treatment. Among patients in the controlled studies with baseline values below the specified limits, the following frequencies of patients were observed to shift to above the specified limits on at least one occasion during 12/14 weeks (including patients who had an isolated elevated value):

- Total cholesterol ≥ 5.17 mmol/L (200 mg/dL): 62% vs. 31%, in the upadacitinib 15 mg and placebo groups, respectively
- LDL cholesterol ≥ 3.36 mmol/L (130 mg/dL): 42% vs. 19%, in the upadacitinib 15 mg and placebo groups, respectively
- HDL cholesterol ≥ 1.03 mmol/L (40 mg/dL): 89% vs. 61%, in the upadacitinib 15 mg and placebo groups, respectively
- Triglycerides ≥ 2.26 mmol/L (200 mg/dL): 25% vs. 15%, in the upadacitinib 15 mg and placebo groups, respectively

Creatine phosphokinase

In placebo-controlled studies with background DMARDs, for up to 12/14 weeks, increases in CPK values were observed. CPK elevations > 5 x upper limit of normal (ULN) were reported in 1.0% and 0.3% of patients over 12/14 weeks in the upadacitinib 15 mg and placebo groups, respectively. Most elevations > 5 x ULN were transient and did not require treatment discontinuation. Mean CPK values increased by 4 weeks with a mean increase of 60 U/L at 12 weeks and then remained stable at an increased value thereafter including with extended therapy.

Neutropaenia

In placebo-controlled studies with background DMARDs, for up to 12/14 weeks, decreases in neutrophil counts below 1,000 cells/mm^3 in at least one measurement occurred in 1.1% and <0.1% of patients in the upadacitinib 15 mg and placebo groups, respectively. In clinical studies, treatment was interrupted in response to ANC < 1,000 cells/mm^3 (see section 4.2). Mean neutrophil counts decreased over 4 to 8 weeks. The decreases in neutrophil counts remained stable at a lower value than baseline over time including with extended therapy.

Psoriatic arthritis

Overall, the safety profile observed in patients with active psoriatic arthritis treated with upadacitinib 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis. A higher incidence of acne and bronchitis was observed in patients treated with upadacitinib 15 mg (1.3% and 3.9%, respectively) compared to placebo (0.3% and 2.7%, respectively). A higher rate of serious infections (2.6 events per 100 patient-years and 1.3 events per 100 patient-years, respectively) and hepatic transaminase elevations (ALT elevations Grade 3 and higher rates 1.4% and 0.4%, respectively) was observed in patients treated with upadacitinib in combination with MTX therapy compared to patients treated with monotherapy. There was a higher rate of serious infections in patients ≥ 65 years of age, although data are limited.

Ankylosing spondylitis

Overall, the safety profile observed in patients with active ankylosing spondylitis treated with upadacitinib 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis. No new safety findings were identified.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Upadacitinib was administered in clinical studies up to doses equivalent in daily AUC to 60 mg prolonged-release once daily. Adverse reactions 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants ATC code: L04AA44

Mechanism of action

Janus Kinases (JAKs) are intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, hematopoiesis and immune surveillance. The JAK family of enzymes contains four members, JAK1, JAK2, JAK3 and TYK2 which work in pairs to phosphorylate and activate signal transducers and activators of transcription (STATs). This phosphorylation, in turn, modulates gene expression and cellular function.

JAK1 is important in inflammatory cytokine signals while JAK2 is important for red blood cell maturation and JAK3 signals play a role in immune surveillance and lymphocyte function.

Upadacitinib is a selective and reversible JAK inhibitor. In human cellular assays, upadacitinib preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2.

Pharmacodynamic effects

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.

hsCRP

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

Clinical efficacy and safety

Rheumatoid arthritis

The efficacy and safety of upadacitinib 15 mg once daily was assessed in five Phase 3 randomised, double-blind, multicentre studies in patients with moderately to severely active rheumatoid arthritis and fulfilling the ACR/EULAR 2010 classification criteria (see Table 3). Patients 18 years of age and older were eligible to participate. The presence of at least 6 tender and 6 swollen joints and evidence of systemic inflammation based on elevation of hsCRP was required at baseline. All studies included long-term extensions for up to 5 years.

The primary analysis for each of these studies included all randomised subjects who received at least 1 dose of study drug, and non-responder imputation was used for categorical endpoints.

Across the Phase 3 studies, the efficacy seen with upadacitinib 15 mg QD was generally similar to that observed with upadacitinib 30 mg QD.

Table 3: Clinical trials summary

Study name	Population (n)	Treatment arms	Key outcome measures
SELECT-EARLY	MTX-naïve[a] (947)	• Upadacitinib 15 mg • Upadacitinib 30 mg • MTX Monotherapy	• Primary endpoint: clinical remission (DAS28-CRP) at week 24 • Low disease activity (DAS28-CRP) • ACR50 • Radiographic progression (mTSS) • Physical function (HAQ-DI) • SF-36 PCS

SELECT-MONOTHERAPY	MTX-IR[b] (648)	• Upadacitinib 15 mg • Upadacitinib 30 mg • MTX Monotherapy	• Primary endpoint: low disease activity (DAS28-CRP) at week 14 • Clinical remission (DAS28-CRP) • ACR20 • Physical function (HAQ-DI) • SF-36 PCS • Morning stiffness
SELECT-NEXT	csDMARD-IR[c] (661)	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo On background csDMARDs	• Primary endpoint: low disease activity (DAS28-CRP) at week 12 • Clinical remission (DAS28-CRP) • ACR20 • Physical function (HAQ-DI) • SF-36 PCS • Low disease activity (CDAI) • Morning stiffness • FACIT-F
SELECT-COMPARE	MTX-IR[d] (1,629)	• Upadacitinib 15 mg • Placebo • Adalimumab 40 mg On background MTX	• Primary endpoint: clinical remission (DAS28-CRP) at week 12 • Low disease activity (DAS28-CRP) • ACR20 • Low disease activity (DAS28-CRP) vs adalimumab • Radiographic progression (mTSS) • Physical function (HAQ-DI) • SF-36 PCS • Low disease activity (CDAI) • Morning stiffness • FACIT-F
SELECT-BEYOND	bDMARD-IR[e] (499)	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo On background csDMARDs	• Primary endpoint: low disease activity (DAS28-CRP) at week 12 • ACR20 • Physical function (HAQ-DI) • SF-36 PCS

Abbreviations: ACR20 (or 50) = American College of Rheumatology ≥20% (or ≥50%) improvement; bDMARD = biologic disease-modifying anti-rheumatic drug, CRP = C-Reactive Protein, DAS28 = Disease Activity Score 28 joints, mTSS = modified Total Sharp Score, csDMARD = conventional synthetic disease-modifying anti-rheumatic drug, HAQ-DI = Health Assessment Questionnaire-Disability Index, SF-36 PCS = Short Form (36) Health Survey (SF-36) Physical Component Summary, CDAI = Clinical Disease Activity Index, FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue score, IR = inadequate responder, MTX = methotrexate, n = number randomised

[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

Clinical response

Remission and low disease activity

In the studies, a significantly higher proportion of patients treated with upadacitinib 15 mg achieved low disease activity (DAS28-CRP ≤3.2) and clinical remission (DAS28-CRP <2.6) compared to placebo, MTX or adalimumab (Table 4). Compared to adalimumab, significantly higher rates of low disease activity were achieved at week 12 in SELECT-COMPARE. Overall, both low disease activity and clinical remission rates were consistent across patient populations, with or without MTX.

ACR response

In all studies, more patients treated with upadacitinib 15 mg achieved ACR20, ACR50, and ACR70 responses at 12 weeks compared to placebo, MTX, or adalimumab (Table 4). Time to onset of efficacy was rapid across measures with greater responses seen as early as week 1 for ACR20. Durable response rates were observed (with or without MTX), with ACR20/50/70 responses maintained for at least 1 year.

Treatment with upadacitinib 15 mg, alone or in combination with csDMARDs, resulted in improvements in individual ACR components, including tender and swollen joint counts, patient and physician global assessments, HAQ-DI, pain assessment and hsCRP.

Table 4: Response and remission

Study	SELECT EARLY MTX-Naïve		SELECT MONO MTX-IR		SELECT NEXT csDMARD-IR		SELECT COMPARE MTX-IR			SELECT BEYOND bDMARD-IR	
	MTX	UPA 15mg	MTX	UPA 15mg	PBO	UPA 15mg	PBO	UPA 15mg	ADA 40mg	PBO	UPA 15mg
N	314	317	216	217	221	221	651	651	327	169	164
Week											
LDA DAS28-CRP ≤3.2 (% of patients)											
12[a]/14[b]	28	53[g]	19	45[e]	17	48[e]	14	45[e,h]	29	14	43[e]
24[c]26[d]	32	60[f]					18	55[g,h]	39		
48	39	59[g]						50[h]	35		
CR DAS28-CRP <2.6 (% of patients)											
12[a]/14[b]	14	36[g]	8	28[e]	10	31[e]	6	29[e,h]	18	9	29[g]
24[c]26[d]	18	48[e]					9	41[g,h]	27		
48	29	49[g]						38[i]	28		
ACR20 (% of patients)											
12[a]/14[b]	54	76[g]	41	68[e]	36	64[e]	36	71[e,j]	63	28	65[e]
24[c]/26[d]	59	79[g]					36	67[g,i]	57		
48	57	74[g]						65[i]	54		
ACR50 (% of patients)											
12[a]/14[b]	28	52[g]	15	42[g]	15	38[g]	15	45[g,h]	29	12	34[g]
24[c]/26[d]	33	60[e]					21	54[g,h]	42		
48	43	63[g]						49[i]	40		
ACR70 (% of patients)											
12[a]/14[b]	14	32[g]	3	23[g]	6	21[g]	5	25[g,h]	13	7	12
24[c]/26[d]	18	44[g]					10	35[g,h]	23		
48	29	51[g]						36[h]	23		
CDAI ≤10 (% of patients)											
12[a]/14[b]	30	46[g]	25	35[l]	19	40[e]	16	40[e,h]	30	14	32[g]

24[c]/26[d]	38	56[g]					22	53[g,h]	38		
48	43	60[g]						47[h]	34		

Abbreviations: ACR20 (or 50 or 70) = American College of Rheumatology ≥20% (or ≥50% or ≥70%) improvement; ADA = adalimumab; CDAI = Clinical Disease Activity Index; CR = Clinical Remission; CRP = C-Reactive Protein, DAS28 = Disease Activity Score 28 joints; IR = inadequate responder; LDA = Low Disease Activity; MTX = methotrexate; PBO = placebo; UPA= upadacitinib
[a] SELECT-NEXT, SELECT-EARLY, SELECT-COMPARE, SELECT-BEYOND
[b] SELECT-MONOTHERAPY
[c] SELECT-EARLY
[d] SELECT-COMPARE
[e] multiplicity-controlled p≤0.001upadacitinib vs placebo or MTX comparison
[f] multiplicity-controlled p≤0.01 upadacitinib vs placebo or MTX comparison
[g] nominal p≤0.001 upadacitinib vs placebo or MTX comparison
[h] nominal p≤0.001upadacitinib vs adalimumab comparison
[i] nominal p≤0.01 upadacitinib vs adalimumab comparison
[j] nominal p<0.05 upadacitinib vs adalimumab comparison
[k] nominal p≤0.01 upadacitinib vs placebo or MTX comparison
[l] nominal p<0.05 upadacitinib vs MTX comparison
Note: Week 48-data derived from analysis on Full Analysis set (FAS) by randomised group using Non-Responder Imputation

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 weeks 24/26 and week 48 in SELECT-EARLY and SELECT-COMPARE.

Treatment with upadacitinib 15 mg resulted in significantly greater inhibition of the progression of structural joint damage compared to placebo in combination with MTX in SELECT-COMPARE and as monotherapy compared to MTX in SELECT-EARLY (Table 5). Analyses of erosion and joint space narrowing scores were consistent with the overall scores. The proportion of patients with no radiographic progression (mTSS change ≤ 0) was significantly higher with upadacitinib 15 mg in both studies.

Table 5: Radiographic changes

Study	SELECT EARLY MTX-Naïve		SELECT COMPARE MTX-IR		
Treatment Group	MTX	UPA 15 mg	PBO[a]	UPA 15 mg	ADA 40 mg
Modified Total Sharp Score, mean change from baseline					
Week 24[b]/26[c]	0.7	0.1[f]	0.9	0.2[g]	0.1
Week 48	1.0	0.03[e]	1.7	0.3[e]	0.4
Proportion of patients with no radiographic progression[d]					
Week 24[b]/26[c]	77.7	87.5[f]	76.0	83.5[f]	86.8
Week 48	74.3	89.9[e]	74.1	86.4[e]	87.9

Abbreviations: ADA = adalimumab; IR = inadequate responder; MTX = methotrexate; PBO = placebo; UPA= upadacitinib
[a] All placebo data at week 48 derived using linear extrapolation
[b] SELECT-EARLY
[c] SELECT-COMPARE
[d] No progression defined as mTSS change ≤ 0
[e] nominal p≤0.001 upadacitinib vs placebo or MTX comparison
[f] multiplicity-controlled p≤0.01 upadacitinib vs placebo or MTX comparison
[g] multiplicity-controlled p≤0.001 upadacitinib vs placebo or MTX comparison

Physical function response and health-related outcomes

Treatment with upadacitinib 15 mg, alone or in combination with csDMARDs, resulted in a significantly greater improvement in physical function compared to all comparators as measured by HAQ-DI (see Table 6).

Table 6: Mean change from baseline in HAQ-DI[a,b]

Study	SELECT EARLY MTX-Naïve		SELECT MONO MTX-IR		SELECT NEXT csDMARD-IR		SELECT COMPARE MTX-IR			SELECT BEYOND BIO-IR	
Treatment group	MTX	UPA 15mg	MTX	UPA 15mg	PBO	UPA 15mg	PBO	UPA 15mg	ADA 40mg	PBO	UPA 15mg
N	313	317	216	216	220	216	648	644	324	165	163
Baseline score, mean	1.6	1.6	1.5	1.5	1.4	1.5	1.6	1.6	1.6	1.6	1.7
Week 12[c]/14[d]	-0.5	-0.8[h]	-0.3	-0.7[g]	-0.3	-0.6[g]	-0.3	-0.6[g,i]	-0.5	-0.2	-0.4[g]
Week 24[e]/26[f]	-0.6	-0.9[g]					-0.3	-0.7[h,i]	-0.6		

Abbreviations: ADA = adalimumab; HAQ-DI = Health Assessment Questionnaire-Disability Index; IR = inadequate responder; MTX = methotrexate; PBO = placebo; UPA = upadacitinib
[a] Data shown are mean
[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] SELECT-EARLY, SELECT-NEXT, SELECT-COMPARE, SELECT-BEYOND
[d] SELECT-MONOTHERAPY
[e] SELECT-EARLY
[f] SELECT-COMPARE
[g] multiplicity-controlled p≤0.001 upadacitinib vs placebo or MTX comparison
[h] nominal p≤0.001 upadacitinib vs placebo or MTX comparison

[i] nominal p≤0.01 upadacitinib vs adalimumab comparison

In the studies SELECT-MONOTHERAPY, SELECT-NEXT, and SELECT-COMPARE, treatment with upadacitinib 15 mg resulted in a significantly greater improvement in the mean duration of morning joint stiffness compared to placebo or MTX.

In the clinical studies, upadacitinib treated patients reported significant improvements in patient-reported quality of life, as measured by the Short Form (36) Health Survey (SF-36) Physical Component Summary compared to placebo and MTX. Moreover, upadacitinib treated patients reported significant improvements in fatigue, as measured by the Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F) compared to placebo.

Psoriatic arthritis

The efficacy and safety of upadacitinib 15 mg once daily were assessed in two Phase 3 randomised, double-blind, multicenter, placebo-controlled studies in patients 18 years of age or older with moderately to severely active psoriatic arthritis. 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.

SELECT-PsA 1 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 upadacitinib 15 mg or 30 mg once daily, adalimumab, or placebo. At week 24, all patients randomised to placebo were switched to upadacitinib 15 mg or 30 mg once daily in a blinded manner. SELECT-PsA 1 included a long-term extension for up to 5 years.

SELECT-PsA 2 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 upadacitinib 15 mg or 30 mg once daily or placebo. At week 24, all patients randomised to placebo were switched to upadacitinib 15 mg or 30 mg once daily in a blinded manner. SELECT-PsA 2 included a long-term extension for up to 3 years.

Clinical response

In both studies, a statistically significant greater proportion of patients treated with upadacitinib 15 mg achieved ACR20 response compared to placebo at week 12 (Table 7). Time to onset of efficacy was rapid across measures with greater responses seen as early as week 2 for ACR20.

Treatment with upadacitinib 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.

In SELECT-PsA 1, upadacitinib 15 mg achieved non-inferiority compared to adalimumab in the proportion of patients achieving ACR20 response at week 12; however, superiority to adalimumab could not be demonstrated.

In both studies, consistent responses were observed alone or in combination with methotrexate for primary and key secondary endpoints.

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

Table 7: Clinical response in SELECT-PsA 1 and SELECT-PsA 2

Study	SELECT-PsA 1 non-biologic DMARD-IR			SELECT-PsA 2 bDMARD-IR	
Treatment Group	PBO	UPA 15 mg	ADA 40 mg	PBO	UPA 15 mg
N	423	429	429	212	211
ACR20, % of patients (95% CI)					
Week 12	36 (32, 41)	71 (66, 75)[f]	65 (61, 70)	24 (18, 30)	57 (50, 64)
Difference from placebo (95% CI)	35 (28, 41)[d,e]		-	33 (24, 42)[d,e]	
Week 24	45 (40, 50)	73 (69, 78)	67 (63, 72)	20 (15, 26)	59 (53, 66)
Week 56		74 (70, 79)	69 (64, 73)		60 (53, 66)
ACR50, % of patients (95% CI)					
Week 12	13 (10, 17)	38 (33, 42)	38 (33, 42)	5 (2, 8)	32 (26, 38)
Week 24	19 (15, 23)	52 (48, 57)	44 (40, 49)	9 (6, 13)	38 (32, 45)
Week 56		60 (55, 64)	51 (47, 56)		41 (34, 47)
ACR70, % of patients (95% CI)					
Week 12	2 (1, 4)	16 (12, 19)	14 (11, 17)	1 (0, 1)	9 (5, 12)
Week 24	5 (3, 7)	29 (24, 33)	23 (19, 27)	1 (0, 2)	19 (14, 25)
Week 56		41 (36, 45)	31 (27, 36)		24 (18, 30)
MDA, % of patients (95% CI)					
Week 12	6 (4, 9)	25 (21, 29)	25 (21, 29)	4 (2, 7)	17 (12, 22)
Week 24	12 (9, 15)	37 (32, 41)[e]	33 (29, 38)	3 (1, 5)	25 (19, 31)[e]
Week 56		45 (40, 50)	40 (35, 44)		29 (23, 36)
Resolution of enthesitis (LEI=0), % of patients (95% CI)[a]					
Week 12	33 (27, 39)	47 (42, 53)	47 (41, 53)	20 (14, 27)	39 (31, 47)
Week 24	32 (27, 39)	54 (48, 60)[e]	47 (42, 53)	15 (9, 21)	43 (34, 51)
Week 56		59 (53, 65)	54 (48, 60)		43 (34, 51)
Resolution of dactylitis (LDI=0), % of patients (95% CI)[b]					
Week 12	42 (33, 51)	74 (66, 81)	72 (64, 80)	36 (24, 48)	64 (51, 76)
Week 24	40 (31, 48)	77 (69, 84)	74 (66, 82)	28 (17, 39)	58 (45, 71)
Week 56		75 (68, 82)	74 (66, 82)		51 (38, 64)
PASI75, % of patients (95% CI)[c]					
Week 16	21 (16, 27)	63 (56, 69)[e]	53 (46, 60)	16 (10, 22)	52 (44, 61)[e]
Week 24	27 (21, 33)	64 (58, 70)	59 (52, 65)	19 (12, 26)	54 (45, 62)
Week 56		65 (59, 72)	61 (55, 68)		52 (44, 61)
PASI90, % of patients (95% CI)[c]					
Week 16	12 (8, 17)	38 (32, 45)	39 (32, 45)	8 (4, 13)	35 (26, 43)
Week 24	17 (12, 22)	42 (35, 48)	45 (38, 52)	7 (3, 11)	36 (28, 44)
Week 56		49 (42, 56)	47 (40, 54)		41 (32, 49)

Abbreviations: ACR20 (or 50 or 70) = American College of Rheumatology ≥20% (or ≥50% or ≥70%) improvement, ADA = adalimumab; bDMARD = biologic disease-modifying anti-rheumatic drug; IR = inadequate responder; MDA = minimal disease activity; PASI75 (or 90) = ≥75% (or ≥90%) improvement in Psoriasis Area and Severity Index; PBO = placebo; UPA= upadacitinib

Patients who discontinued randomised 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 24/56, 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, for SELECT-PsA 1 and n=144 and 133, respectively, for SELECT-PsA 2)

[b] In patients with dactylitis at baseline (n=126, 136, and 127, respectively, for SELECT-PsA 1 and n=64 and 55, respectively, for SELECT-PsA 2)
[c] In patients with ≥ 3% BSA psoriasis at baseline (n=211, 214, and 211, respectively, for SELECT-PsA 1 and n=131 and 130, respectively, for SELECT-PsA 2)
[d] primary endpoint
[e] multiplicity-controlled p≤0.001 upadacitinib vs placebo comparison
[f] multiplicity-controlled p≤0.001 upadacitinib vs adalimumab comparison (non-inferiority test)

Radiographic response

In SELECT-PsA 1, inhibition of progression of structural damage was assessed radiographically and expressed as the change from baseline in modified Total Sharp Score (mTSS) and its components, the erosion score and the joint space narrowing score, at week 24.

Treatment with upadacitinib 15 mg resulted in statistically significant greater inhibition of the progression of structural joint damage compared to placebo at week 24 (Table 8). Erosion and joint space narrowing scores were consistent with the overall scores. The proportion of patients with no radiographic progression (mTSS change ≤ 0.5) was higher with upadacitinib 15 mg compared to placebo at week 24.

Table 8: Radiographic changes in SELECT-PsA 1

Treatment Group	PBO	UPA 15 mg	ADA 40 mg
Modified Total Sharp Score, mean change from baseline (95% CI)			
Week 24	0.25 (0.13, 0.36)	-0.04 (-0.16, 0.07)[c]	0.01 (-0.11, 0.13)
Week 56[a]	0.44 (0.29, 0.59)	-0.05 (-0.20, 0.09)	-0.06 (-0.20, 0.09)
Proportion of patients with no radiographic progression[b], % (95% CI)			
Week 24	92 (89, 95)	96 (94, 98)	95 (93, 97)
Week 56[a]	89 (86, 92)	97 (96, 99)	94 (92, 97)

Abbreviations: ADA = adalimumab; PBO = placebo; UPA= upadacitinib
[a] All placebo data at week 56 derived using linear extrapolation
[b] No progression defined as mTSS change ≤0.5
[c] multiplicity-controlled p≤0.001 upadacitinib vs placebo comparison

Physical function response and health-related outcomes

In SELECT-PsA 1, patients treated with upadacitinib 15 mg showed statistically significant improvement from baseline in physical function as assessed by HAQ-DI at week 12 (-0.42 [95% CI: -0.47, -0.37]) compared to placebo (-0.14 [95% CI: -0.18, -0.09]); improvement in patients treated with adalimumab was -0.34 (95% CI: -0.38, -0.29). In SELECT-PsA 2, patients treated with upadacitinib 15 mg showed statistically significant improvement from baseline in HAQ-DI at week 12 (-0.30 [95% CI: -0.37, -0.24]) compared to placebo (-0.10 [95% CI: -0.16, -0.03]). Improvement in physical function was maintained through week 56 in both studies.

Health-related quality of life was assessed by SF-36v2. In both studies, patients receiving upadacitinib 15 mg experienced statistically significant 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 upadacitinib 15 mg experienced statistically significant 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.

At baseline, psoriatic spondylitis was reported in 31% and 34% of patients in SELECT-PsA 1 and SELECT-PsA 2, respectively. Patients with psoriatic spondylitis treated with upadacitinib 15 mg showed improvements from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores compared to placebo at week 24. Improvements from baseline were maintained through week 56 in both studies.

Ankylosing spondylitis

The efficacy and safety of upadacitinib 15 mg once daily were assessed in a randomised, double-blind, multicenter, placebo-controlled study in patients 18 years of age or older with active ankylosing spondylitis based upon the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 and Patient's Assessment of Total Back Pain score ≥4. The study included a long-term extension for up to 2 years.

SELECT-AXIS 1 was a 14-week trial in 187 ankylosing spondylitis patients with an inadequate response to at least two Nonsteroidal Anti-inflammatory Drugs (NSAIDs) or intolerance to or contraindication for NSAIDs and had no previous exposure to biologic DMARDs. At baseline, patients had symptoms of ankylosing spondylitis for an average of 14.4 years and approximately 16% of the patients were on a concomitant csDMARD. Patients received upadacitinib 15 mg once daily or placebo. At week 14, all patients randomised to placebo were switched to upadacitinib 15 mg once daily. The primary endpoint was the proportion of patients achieving an Assessment of SpondyloArthritis international Society 40 (ASAS40) response at week 14.

Clinical response

In SELECT-AXIS 1, a significantly greater proportion of patients treated with upadacitinib 15 mg achieved an ASAS40 response compared to placebo at week 14 (Table 9). A numerical difference between treatment groups was observed at week 2 and response was maintained through week 64.

Treatment with upadacitinib 15 mg resulted in improvements in individual ASAS components (patient global assessment of disease activity, total back pain assessment, inflammation, and function) and other measures of disease activity, including hsCRP, at week 14 compared to placebo.

The efficacy of upadacitinib 15 mg was demonstrated regardless of subgroups evaluated including gender, baseline BMI, symptom duration of AS, and baseline hsCRP.

Table 9: Clinical response in SELECT-AXIS 1

Treatment Group	**PBO**	**UPA 15 mg**
N	94	93
ASAS40, % of patients (95% CI)[a]		
Week 14	25.5 (16.7, 34.3)	51.6 (41.5, 61.8)
Difference from placebo (95% CI)	26.1 (12.6, 39.5)[b,c]	
ASAS20, % of patients (95% CI)[a]		
Week 14	40.4 (30.5, 50.3)	64.5 (54.8, 74.2)[e]
ASAS Partial Remission, % of patients (95% CI)		
Week 14	1.1 (0.0, 3.1)	19.4 (11.3, 27.4)[c]
BASDAI 50, % of patients (95% CI)		
Week 14	23.4 (14.8, 32.0)	45.2 (35.0, 55.3)[d]
Change from baseline in ASDAS-CRP (95% CI)		
Week 14	-0.54 (-0.71, -0.37)	-1.45 (-1.62, -1.28)[c]
ASDAS Inactive Disease, % of patients (95% CI)		
Week 14	0	16.1 (8.7, 23.6)[e]
ASDAS Low Disease Activity, % of patients (95% CI)[f]		
Week 14	10.6 (4.4, 16.9)	49.5 (39.3, 59.6)[e]

ASDAS Major Improvement, % of patients (95% CI)		
Week 14	5.3 (0.8, 9.9)	32.3 (22.8, 41.8)[e]

Abbreviations: ASAS20 (or ASAS40) = Assessment of SpondyloArthritis international Society ≥20% (or ≥40%) improvement; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score C-Reactive Protein; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; PBO = placebo; UPA= upadacitinib
[a] An ASAS20 (ASAS40) response is defined as a ≥20% (≥40%) improvement and an absolute improvement from baseline of ≥1 (≥2) unit(s) (range 0 to 10) in ≥3 of 4 domains (Patient Global, Total Back Pain, Function, and Inflammation), and no worsening in the potential remaining domain (defined as worsening ≥20% and ≥1 unit for ASAS20 or defined as worsening of > 0 units for ASAS40).
[b] primary endpoint
[c] multiplicity-controlled p≤0.001 upadacitinib vs placebo comparison
[d] multiplicity-controlled p≤0.01 upadacitinib vs placebo comparison
[e] comparison not multiplicity-controlled
[f] post-hoc analysis, not multiplicity-controlled
For binary endpoints, week 14 results are based on non-responder imputation analysis. For continuous endpoints, week 14 results are based on the least squares mean change from baseline using mixed models for repeated measures analysis.

Physical function response

Patients treated with upadacitinib 15 mg showed significant improvement in physical function from baseline compared to placebo as assessed by the BASFI at week 14.

Objective measure of inflammation

Signs of inflammation were assessed by MRI and expressed as change from baseline in the SPARCC score for spine. At week 14, significant improvement of inflammatory signs in the spine was observed in patients treated with upadacitinib 15 mg compared to placebo.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with RINVOQ in one or more subsets of the paediatric population in chronic idiopathic arthritis (including rheumatoid arthritis, psoriatic arthritis, spondyloarthritis and juvenile idiopathic arthritis) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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 prolonged-release formulation, upadacitinib is absorbed with a median T_{max} of 2 to 4 hours. Coadministration of upadacitinib with a high-fat meal had no clinically relevant effect on upadacitinib exposures (increased AUC by 29% and C_{max} by 39%). In clinical trials, upadacitinib was administered without regard to meals (see section 4.2). *In vitro*, upadacitinib is a substrate for the efflux transporters P-gp and BCRP.

Distribution

Upadacitinib is 52% bound to plasma proteins. Upadacitinib partitions similarly between plasma and blood cellular components, as indicated by the blood to plasma ratio of 1.0.

Metabolism

Upadacitinib metabolism is mediated by 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 (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 faeces (38%). Approximately 34% of upadacitinib dose was excreted as metabolites. Upadacitinib mean terminal elimination half-life ranged from 9 to 14 hours.

Renal impairment

Renal impairment has no clinically relevant effect on upadacitinib exposure. Upadacitinib AUC was 18%, 33%, and 44% higher in subjects with mild (estimated glomerular filtration rate 60 to 89 mL/min/1.73 m^2), moderate (estimated glomerular filtration rate 30 to 59 mL/min/1.73 m^2), and severe (estimated glomerular filtration rate 15 to 29 mL/min/1.73 m^2) 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 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 (Child-Pugh C) hepatic impairment.

Paediatric population

The pharmacokinetics of upadacitinib have not yet been evaluated in a paediatric population (see section 4.2).

Intrinsic factors

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology.

Upadacitinib, at exposures (based on AUC) approximately 4 and 10 times the clinical dose of 15 mg in male and female Sprague-Dawley rats, respectively, was not carcinogenic in a 2-year carcinogenicity study in Sprague-Dawley rats. Upadacitinib was not carcinogenic in a 26-week carcinogenicity study in CByB6F1-Tg(HRAS)2Jic transgenic mice.

Upadacitinib was not mutagenic or genotoxic based on the results of *in vitro* and *in vivo* tests for gene mutations and chromosomal aberrations.

Upadacitinib had no effect on fertility in male or female rats at doses up to 50 mg/kg/day in males and 75 mg/kg/day in females in a fertility and early embryonic development study. Dose related increases in foetal resorptions associated with post-implantation losses at 25 and 75 mg/kg/day in this study in rats were attributed to the developmental/teratogenic effects of upadacitinib. Upadacitinib was teratogenic in both rats and rabbits. In a pre-/postnatal development study in rats, there were no maternal effects, no effects on parturition, lactation or maternal behaviour and no effects on their offspring.

Following administration of upadacitinib to lactating rats, the concentrations of upadacitinib in milk over time generally paralleled those in plasma, with approximately 30-fold higher exposure in milk relative to maternal plasma. Approximately 97% of drug-related material in milk was parent drug.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet contents:

Microcrystalline cellulose
Hypromellose
Mannitol
Tartaric acid
Silica, colloidal anhydrous
Magnesium stearate

Film coating:

Poly(vinyl alcohol)
Macrogol
Talc
Titanium dioxide (E171)
Iron oxide black (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Prolonged-release tablets in blisters: 2 years
Prolonged-release tablets in bottles: 3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Store in the original blister or bottle in order to protect from moisture. Keep the bottle tightly closed.

6.5 Nature and contents of container

Polyvinylchloride/polyethylene/polychlorotrifluoroethylene - aluminium calendar blisters in packs containing 28 or 98 prolonged-release tablets, or multipacks containing 84 (3 packs of 28) prolonged-release tablets.

HDPE bottles with desiccant and polypropylene cap in carton containing 30 prolonged-release tablets.
Pack size: 1 bottle (30 prolonged-release tablets) or 3 bottles (90 prolonged-release tablets).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1404/001
EU/1/19/1404/002
EU/1/19/1404/003
EU/1/19/1404/004
EU/1/19/1404/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 December 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

AbbVie S.r.l.
148, Pontina Km 52 snc
04011
Campoverde di Aprilia (LT)
ITALY

And

AbbVie Logistics B.V
Zuiderzeelaan 53
8017 JV Zwolle
NETHERLANDS

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of RINVOQ in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including

communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The objective of the programme is to increase awareness of HCPs and patients on the risks of serious and opportunistic infections including TB, herpes zoster, foetal malformation (pregnancy risk), MACE, and VTEs and how to manage these risks.

The MAH shall ensure that in each Member State where RINVOQ is marketed, all healthcare professionals and patients/carers who are expected to prescribe, dispense or use RINVOQ have access to/are provided with the following educational package:

The physician educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals
- Patient Alert Card (PAC)

The Guide for healthcare professionals shall contain the following key elements:

- General introductory language that the HCP measure contains important information to assist the discussion with patients when prescribing upadacitinib. The brochure also informs on steps which can be taken to reduce a patient's risk for key safety aspects of upadacitinib.
- Language for HCPs to inform patients of the importance of the PAC
- *Risk of serious and opportunistic infections including TB*
    - Language on the risk of infections during treatment with upadacitinib
    - Details on how to reduce the risk of infection with specific clinical measures (what laboratory parameters should be used to initiate upadacitinib, screening for TB, and getting patients immunised as per local guidelines, and interruption of upadacitinib if an infection develops)
    - Language on avoidance of live vaccines (i.e., Zostavax) prior to and during upadacitinib treatment
    - Details to advise patients on signs/symptoms of infection to be aware of, so that patients can seek medical attention quickly.
- *Risk of herpes zoster*
    - Language on the risk of herpes zoster during treatment with upadacitinib
    - Details to advise patients on signs/symptoms of infection to be aware of, so that patients can seek medical attention quickly.
- *Risk of foetal malformation*
    - Language on teratogenicity of upadacitinib in animals
    - Details on how to reduce the risk of exposure during pregnancy for women of childbearing potential based on the following: upadacitinib is contraindicated during pregnancy, women of childbearing potential should be advised to use effective contraception both during treatment and for 4 weeks after the final dose of upadacitinib treatment, and to advise patients to inform their HCP immediately if they think they could be pregnant or if pregnancy is confirmed.
- *Risk of MACE*
    - Language on the increased risk of MACE in patients with immune-mediated inflammatory diseases and the need to consider typical CV risk factors (e.g., hypertension, hyperlipidaemia) when treating patients
    - Language on the risk of MACE during treatment with upadacitinib
    - Language on the risk of hyperlipidaemia during upadacitinib therapy
    - Details on monitoring of lipid levels and management of elevated lipid levels per clinical guidelines

- *Risk of VTE*
    - Examples of the risk factors which may put a patient at higher risk for VTE and in whom caution is needed when using upadacitinib.
    - Language on the risk of VTE during treatment with upadacitinib
    - Language on need for discontinuation of upadacitinib, evaluation, and appropriate treatment for VTE if clinical features of deep venous thrombosis or pulmonary embolism develop
- Instructions for how to access digital HCP information
- Instructions on where to report AEs

The patient information pack should contain:

- Patient information leaflet
- A patient alert card

- **The patient alert card** shall contain the following key messages:
    - Contact details of the upadacitinib prescriber
    - Language that the PAC should be carried by the patient at any time and to share it with HCPs involved in their care (i.e., non-upadacitinib prescribers, emergency room HCPs, etc.)
    - Description of signs/symptoms of infections the patient needs to be aware of, so that they can seek attention from their HCP:
        - Language to advise patients and their HCPs about the risk of live vaccinations when given during upadacitinib therapy
    - Description of targeted risks for awareness by the patient and for HCPs involved in their care including:
        - Elevations in plasma lipids and the need for monitoring and lipid lowering treatment
        - A reminder to use contraception, that upadacitinib is contraindicated during pregnancy, and to notify their HCPs if they become pregnant while taking upadacitinib
    - Description of signs/symptoms of deep venous thrombosis or pulmonary embolism which the patient needs to be aware of, so that they can seek attention from an HCP.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Blister Carton (Individual carton)

1. NAME OF THE MEDICINAL PRODUCT

RINVOQ 15 mg prolonged-release tablets
upadacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains upadacitinib hemihydrate, equivalent to 15 mg upadacitinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Do not chew, crush or break the tablet. Swallow whole.

QR code to be included
For more information and support on taking RINVOQ go to www.rinvoq.eu

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1404/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rinvoq

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for 84 tablet multipack (with Blue Box)

1. NAME OF THE MEDICINAL PRODUCT

RINVOQ 15 mg prolonged-release tablets
upadacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains upadacitinib hemihydrate, equivalent to 15 mg upadacitinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 84 (3 packs of 28) prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Do not chew, crush or break the tablet. Swallow whole.

QR code to be included
For more information and support on taking RINVOQ go to www.rinvoq.eu

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1404/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rinvoq

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Intermediate carton of 84 tablet multipack (without Blue Box)

1. NAME OF THE MEDICINAL PRODUCT

RINVOQ 15 mg prolonged-release tablets
upadacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains upadacitinib hemihydrate, equivalent to 15 mg upadacitinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 prolonged-release tablets.
Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Do not chew, crush or break the tablet. Swallow whole.

QR code to be included
For more information and support on taking RINVOQ go to www.rinvoq.eu

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1404/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rinvoq

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton of 98 tablets

1. NAME OF THE MEDICINAL PRODUCT

RINVOQ 15 mg prolonged-release tablets
upadacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains upadacitinib hemihydrate, equivalent to 15 mg upadacitinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

98 prolonged-release tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Do not chew, crush or break the tablet. Swallow whole.

QR code to be included
For more information and support on taking RINVOQ go to www.rinvoq.eu

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1404/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rinvoq

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Inner carton of 49 tablets (for the 98 pack)

1. NAME OF THE MEDICINAL PRODUCT

RINVOQ 15 mg prolonged-release tablets
upadacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains upadacitinib hemihydrate, equivalent to 15 mg upadacitinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

49 prolonged-release tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Do not chew, crush or break the tablet. Swallow whole.

QR code to be included
For more information and support on taking RINVOQ go to www.rinvoq.eu

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1404/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rinvoq

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

RINVOQ 15 mg prolonged-release tablets
upadacitinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AbbVie (as logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon. Tue. Wed. Thu. Fri. Sat. Sun.

PC

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Bottle Carton (30 and 90 pack)

1. NAME OF THE MEDICINAL PRODUCT

RINVOQ 15 mg prolonged-release tablets
upadacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains upadacitinib hemihydrate, equivalent to 15 mg upadacitinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 prolonged-release tablets
90 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use
Do not chew, crush or break the tablet. Swallow whole. Do not swallow the desiccant.

QR code to be included
For more information and support on taking RINVOQ go to www.rinvoq.eu

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle and keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1404/002
EU/1/19/1404/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rinvoq

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

This Information is Confidential

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

Bottle Label

1. NAME OF THE MEDICINAL PRODUCT

RINVOQ 15 mg prolonged-release tablets
upadacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains upadacitinib hemihydrate, equivalent to 15 mg upadacitinib

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Do not chew, crush or break the tablet. Swallow whole. Do not swallow the desiccant.

Important to open

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle and keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie (as logo)

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

RINVOQ 15 mg prolonged-release tablets
upadacitinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What RINVOQ is and what it is used for
2. What you need to know before you take RINVOQ
3. How to take RINVOQ
4. Possible side effects
5. How to store RINVOQ
6. Contents of the pack and other information

1. What RINVOQ is and what it is used for

RINVOQ contains the active substance upadacitinib. It belongs to a group of medicines called Janus kinase inhibitors. RINVOQ works by reducing the activity of an enzyme called 'Janus kinase' in the body, which helps to reduce inflammation.

RINVOQ is used for the treatment of the following inflammatory diseases:

- Rheumatoid Arthritis
- Psoriatic Arthritis
- Ankylosing Spondylitis

Rheumatoid Arthritis
RINVOQ is used to treat adults with rheumatoid arthritis. Rheumatoid arthritis is a disease that causes inflamed joints. If you have moderate to severe active rheumatoid arthritis, you may first be given other medicines, one of which will usually be methotrexate. If these medicines do not work well enough, you will be given RINVOQ either alone or in combination with methotrexate to treat your rheumatoid arthritis.

RINVOQ can help to reduce pain, stiffness and swelling in your joints, reduce tiredness and it can slow down damage to the bone and cartilage in your joints. These effects can ease your normal daily activities and so improve your quality of life.

Psoriatic Arthritis
RINVOQ is used to treat adults with psoriatic arthritis. Psoriatic arthritis is a disease that causes inflamed joints and psoriasis. If you have active psoriatic arthritis, you may first be given other medicines. If these medicines do not work well enough, you will be given RINVOQ either alone or in combination with methotrexate to treat your psoriatic arthritis.

RINVOQ can help to reduce pain, stiffness, and swelling in and around your joints, pain and stiffness in your spine, psoriatic skin rash, and tiredness, and it can slow down damage to the bone and cartilage in your joints. These effects can ease your normal daily activities and so improve your quality of life.

Ankylosing Spondylitis
RINVOQ is used to treat adults with ankylosing spondylitis. Ankylosing spondylitis is a disease that primarily causes inflammation in the spine. If you have active ankylosing spondylitis, you may first be given other medicines. If these medicines do not work well enough, you will be given RINVOQ to treat your ankylosing spondylitis.

RINVOQ can help to reduce back pain, stiffness, and inflammation in your spine. These effects can ease your normal daily activities and so improve your quality of life.

2. What you need to know before you take RINVOQ

Do not take RINVOQ
- if you are allergic to upadacitinib or any of the other ingredients of this medicine (listed in section 6)
- if you have a severe infection (such as pneumonia or bacterial skin infection)
- if you have active tuberculosis (TB)
- if you have severe liver problems
- if you are pregnant (see section Pregnancy, breast-feeding and contraception)

Warnings and precautions
Talk to your doctor or pharmacist before and during treatment with RINVOQ if:
- you have an infection (fever, sweating, or chills, shortness of breath, warm, red, or painful skin or sores on your body, feeling tired, cough, burning sensation when you pass urine or passing urine more often than normal, severe headache with stiff neck), or if you have ever had an infection that keeps coming back – RINVOQ can reduce your body's ability to fight infections and so may worsen an infection that you already have, or make it more likely for you to get a new infection
- you have had tuberculosis or have been in close contact with someone with tuberculosis. Your doctor will test you for tuberculosis before starting RINVOQ and may retest during treatment
- you have had a herpes zoster infection (shingles), because RINVOQ may allow it to come back. Tell your doctor if you get a painful skin rash with blisters as these can be signs of shingles
- you have ever had hepatitis B or C
- you have recently had or plan to have a vaccination (immunisation) - this is because live vaccines are not recommended while using RINVOQ
- you have cancer - because your doctor will have to decide if you can still be given RINVOQ
- you are at high risk of developing skin cancer, your doctor may recommend preventive measures such as regular skin examinations while taking RINVOQ. Talk to your doctor if you develop a new lesion or any change in the appearance of an area on the skin. Some patients receiving RINVOQ have developed skin cancers
- you have heart problems, high blood pressure, or high cholesterol
- your liver does not work as well as it should
- you have had blood clots in the veins of your legs (deep vein thrombosis) or lungs (pulmonary embolism). Tell your doctor if you get a painful swollen leg, chest pain, or shortness of breath as these can be signs of blood clots in the veins.

Blood tests
You will need blood tests before you start taking RINVOQ, or while you are taking it. This is to check for a low red blood cell count (anaemia), low white blood cell count (neutropaenia or lymphopaenia), high blood fat (cholesterol) or high levels of liver enzymes. The tests are to check that treatment with RINVOQ is not causing problems.

Children and adolescents
RINVOQ is not recommended for use in children and adolescents under 18 years of age. This is because it has not been studied in this age group.

Other medicines and RINVOQ
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because some medicines may reduce how well RINVOQ works or may increase the risk of getting side effects. It is very important to talk to your doctor or pharmacist if you are taking any of the following:

- medicines to treat fungal infections (such as itraconazole, posaconazole or voriconazole)
- medicines to treat bacterial infections (such as clarithromycin)
- medicines to treat Cushing's syndrome (such as ketoconazole)
- medicines to treat tuberculosis (such as rifampicin)
- medicines to treat seizures or fits (such as phenytoin)
- medicines that affect your immune system (such as azathioprine, ciclosporin and tacrolimus)

If any of the above apply to you or you are not sure, talk to your doctor or pharmacist before taking RINVOQ.

Pregnancy, breast-feeding and contraception

Pregnancy
RINVOQ must not be used during pregnancy.

Breast-feeding
If you are breast-feeding or are planning to breast-feed, talk to your doctor before taking this medicine. You should not use RINVOQ while breast-feeding as it is not known if this medicine passes into breast milk. You and your doctor should decide if you will breast-feed or use RINVOQ. You should not do both.

Contraception
If you are a woman of child-bearing potential, you must use effective contraception to avoid becoming pregnant while taking RINVOQ and for at least 4 weeks after your last dose of RINVOQ. If you become pregnant during this time, you must talk to your doctor straight away.

Driving and using machines
RINVOQ has no effect on the ability to drive and use machines.

3. How to take RINVOQ

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one 15 mg tablet once a day.

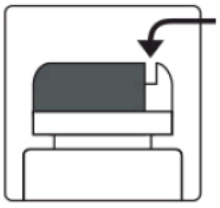
- Swallow the tablet whole with water. Do not split, crush, chew or break the tablet before swallowing as it may change how much medicine gets into your body.
- To help you remember to take RINVOQ, take it at the same time every day.
- The tablets can be taken with or without food.
- Do not swallow the desiccant.

If you take more RINVOQ than you should
If you take more RINVOQ than you should, contact your doctor. You may get some of the side effects listed in section 4.

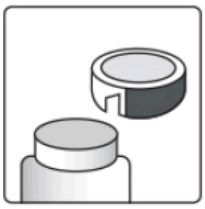
If you forget to take RINVOQ
- If you miss a dose, take it as soon as you remember.
- If you forget your dose for an entire day, just skip the missed dose and take only a single dose as usual the following day.
- Do not take a double dose to make up for a forgotten tablet.

If you stop taking RINVOQ
Do not stop taking RINVOQ unless your doctor tells you to stop taking it.

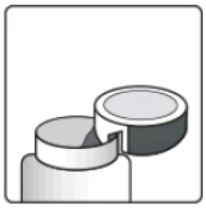
How to open the bottle



Foil Cutting Tool - on the cap of the bottle



1. How to puncture the foil
1a. Remove the cap from the bottle by pushing down and while still pushing, turn the cap anti-clockwise.
1b. Turn the cap over and place the cutting tool near the edge of the foil seal.



2. Push down to make a hole in the foil and move the cutting tool round the edge of the foil to continue cutting the foil.



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

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, RINVOQ can cause side effects, although not everybody gets them.

Serious side effects
Talk to your doctor or get medical help straight away if you get any signs of infection such as:
- shingles or painful skin rash with blisters (herpes zoster) – common (may affect up to 1 in 10 people)

- infection of the lung (pneumonia), which may cause shortness of breath, fever, and a cough with mucus – uncommon (may affect up to 1 in 100 people)

Other side effects
Talk to your doctor if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people)
- throat and nose infections

Common (may affect up to 1 in 10 people)
- cough
- fever
- cold sores (herpes simplex)
- feeling sick in the stomach (nausea)
- increase in an enzyme called creatine kinase, shown by blood tests
- low white blood cell counts shown in blood tests
- increased levels of cholesterol (a type of fat in the blood) as shown in tests
- increased levels of liver enzymes, shown by blood tests (sign of liver problems)
- weight gain
- acne

Uncommon (may affect up to 1 in 100 people)
- thrush in the mouth (white patches in the mouth)
- increased levels of triglycerides (a type of fat) in the blood, as shown in tests

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store RINVOQ

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister label and carton after 'EXP'.

This medicine does not require any special temperature storage conditions.

Store in original blister or bottle with the lid tightly closed to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What RINVOQ contains
- The active substance is upadacitinib. Each prolonged-release tablet contains 15 mg of upadacitinib (as upadacitinib hemihydrate).
- The other ingredients are:
  - Core tablet: microcrystalline cellulose, mannitol, tartaric acid, hypromellose, silica colloidal anhydrous, magnesium stearate.

- Film coating: poly(vinyl alcohol), macrogol, talc, titanium dioxide, iron oxide red (E172), iron oxide black (E172).

What RINVOQ looks like and contents of the pack
RINVOQ 15 mg prolonged-release tablets are purple, oblong, biconvex tablets imprinted on one side with 'a15'.

The tablets are provided in blisters or bottles.

RINVOQ is available in packs containing 28 or 98 prolonged-release tablets and in multipacks of 84 comprising 3 cartons, each containing 28 prolonged-release tablets.
Each calendar blister contains 7 tablets.

RINVOQ is available in bottles with desiccant containing 30 prolonged-release tablets, each pack contains 1 bottle (30 tablet pack) or 3 bottles (90 tablet pack).

Not all pack sizes may be marketed.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Detailed and updated information on this product is available by scanning the QR code included below or on the outer carton with a smart phone. The same information is also available on the following URL: www.rinvoq.eu.

QR code to be included

To listen to or request a copy of this leaflet in <Braille>, <large print> or <audio>, please contact the local representative of the Marketing Authorisation Holder.