q This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PI – RINVOQ®

UPADACITINIB - TABLET

1 NAME OF THE MEDICINE

Upadacitinib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

RINVOQ contains upadacitinib hemihydrate, equivalent to 15 mg of upadacitinib, a Janus Kinase (JAK) inhibitor.

The tablets do not contain gluten or lactose.

For the full list of excipients, see Section **6.1 LIST OF EXCIPIENTS**.

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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 or other conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs).

4.2 Dose and method of administration

Therapy with RINVOQ should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.

The recommended oral dose of RINVOQ is 15 mg once daily with or without food.

RINVOQ should not be initiated in patients with an absolute lymphocyte count (ALC) less than 500 cells/mm^3, an absolute neutrophil count (ANC) less than 1000 cells/mm^3 or who have haemoglobin levels less than 8 g/dL (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.8 ADVERSE EFFECTS**).

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

Combination with other JAK inhibitors or potent immunosuppressants has not been studied and is not recommended.

RINVOQ tablets should be swallowed whole. RINVOQ should not be split, crushed, or chewed.

Dose Interruption

RINVOQ treatment should be interrupted if a patient develops a serious infection until the infection is controlled (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

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 <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 <500 cells/mm^3 and may be restarted once ALC return above this value
Haemoglobin (Hb)	Treatment should be interrupted if Hb is <8 g/dL and may be restarted once Hb return above this value
Hepatic transaminases	Treatment should be temporarily interrupted if drug-induced liver injury is suspected

Missed dose

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

Dosing in Special Populations:

Paediatric 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.

Use in the Elderly

No dose adjustment is required in patients aged 65 years and older.

Use in renal impairment

No dose adjustment is required in patients with mild, moderate or severe renal impairment. There are limited data on the use of upadacitinib in subjects with severe renal impairment (see **5.2 PHARMACOKINETIC PROPERTIES**). Upadacitinib should be used with caution in patients with severe renal impairment. The use of RINVOQ has not been studied in subjects with end stage renal disease. Haemodialysis is not expected to have a clinically relevant effect on upadacitinib plasma exposures due to the major contribution of non-renal clearance to upadacitinib overall elimination (see **5 PHARMACOLOGICAL PROPERTIES**).

Use in 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 **5 PHARMACOLOGICAL PROPERTIES**).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

RINVOQ must not be used in combination with biologic disease-modifying anti-rheumatic drugs (bDMARDs).

4.4 Special warnings and precautions for use

Therapy with RINVOQ should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.

Combination with other potent immunosuppressants such as azathioprine, cyclosporine, tacrolimus, and biologic DMARDs or other JAK inhibitors has not been evaluated in clinical

studies and is not recommended as a risk of additive immunosuppression cannot be excluded (see **4.3 CONTRAINDICATIONS**).

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 **4.8 ADVERSE EFFECTS**). Cases of bacterial meningitis have been reported in patients receiving upadacitinib. Among opportunistic infections, tuberculosis, multi-dermatomal herpes zoster, oral/oesophageal candidiasis, cryptococcosis and pneumocystosis were reported with RINVOQ.

Avoid use of RINVOQ in patients with an active, serious infection, including localised 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 travelled 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.

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes.

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 (see **4.8 ADVERSE EFFECTS**). 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.

Vaccination

No data are available on the response to vaccination with live or inactivated vaccines in patients receiving RINVOQ. 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 immunisations, including prophylactic zoster vaccinations, in agreement with current immunisation guidelines.

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, upadacitinib treatment should be temporarily interrupted and patients should be evaluated promptly, followed by appropriate treatment.

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.

Malignancy

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

Malignancies (including lymphomas) have been observed in clinical studies of RINVOQ (see **4.8 ADVERSE EFFECTS**). 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.

Use in Hepatic Impairment

See **4.2 DOSE AND METHOD OF ADMINISTRATION** and **5 PHARMACOLOGICAL PROPERTIES**.

Use in Renal Impairment

See **4.2 DOSE AND METHOD OF ADMINISTRATION** and **5 PHARMACOLOGICAL PROPERTIES**.

Use in the elderly

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. 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. There are limited data in patients aged 75 years and older.

Paediatric 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.

Effects on laboratory tests

Neutropaenia

Treatment with RINVOQ was associated with an increased incidence of neutropaenia (ANC <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 **4.2 DOSE AND METHOD OF ADMINISTRATION**].

Lymphopaenia

ALCs <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 **4.2 DOSE AND METHOD OF ADMINISTRATION**].

Anaemia

Decreases in haemoglobin levels to <8 g/dL were reported in RINVOQ clinical studies.

Evaluate haemoglobin at baseline and thereafter according to routine patient management. Avoid initiation of or interrupt RINVOQ treatment in patients with a low haemoglobin level (i.e., less than 8 g/dL) [see **4.2 DOSE AND METHOD OF ADMINISTRATION**].

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 **4.8 ADVERSE EFFECTS**). 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 international clinical guidelines for hyperlipidaemia.

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.

4.5 Interactions with other medicines and other forms of interactions

Strong CYP3A4 Inhibitors

Upadacitinib exposure is increased when co-administered with strong CYP3A4 inhibitors (such as ketoconazole, itraconazole, posaconazole, voriconazole and clarithromycin) (see **5 PHARMACOLOGICAL PROPERTIES**). RINVOQ should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors.

Strong CYP3A4 Inducers

Upadacitinib exposure is decreased when co-administered with strong CYP3A4 inducers (such as rifampicin and phenytoin), which may lead to reduced therapeutic effect of RINVOQ (see **5 PHARMACOLOGICAL PROPERTIES**). Patients should be monitored for changes in disease activity if RINVOQ is co-administered with strong CYP3A4 inducers.

Potential for Other Drugs to Affect the Pharmacokinetics of Upadacitinib

Upadacitinib is metabolised *in vitro* by CYP3A4 with a minor contribution from CYP2D6. The effect of co-administered drugs on upadacitinib plasma exposures is provided in Table 2.

Upadacitinib is a substrate of P-glycoprotein and BCRP. The clinical relevance of this is unknown.

Table 2. Change in Pharmacokinetics of Upadacitinib in the Presence of Co-administered Drugs

		Ratio (90% CI)[a]	
Co-administered Drug	**Regimen of Co-administered Drug**	**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: Rifampicin	600 mg once daily x 9 days	0.49 (0.44-0.55)	0.39 (0.37-0.42)
OATP1B inhibitor: Rifampiciin	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.

Methotrexate, inhibitors of OATP1B transporters, and pH modifying medications (e.g., antacids or proton pump inhibitors) have no effect on upadacitinib plasma exposures. CYP2D6 metabolic phenotype had no effect on upadacitinib pharmacokinetics, indicating that inhibitors of CYP2D6 have no clinically relevant effect on upadacitinib exposures.

Potential for Upadacitinib to Affect 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, BSEP, 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 plasma exposures of other drugs is provided in Table 3.

Table 3. Change in Pharmacokinetics of Co-administered Drugs or In Vivo Markers of CYP Activity in the Presence of Upadacitinib

		Ratio (90% CI)[a]	
Co-administered Drug or CYP Activity Marker	**Multiple-Dose Regimen of Upadacitinib**	**C_{max}**	**AUC**
Methotrexate	6 mg to 24 mg twice daily[b]	1.03 (0.86-1.23)	1.14 (0.91-1.43)
Sensitive CYP1A2 Substrate: Caffeine	30 mg once daily[c]	1.13 (1.05-1.22)	1.22 (1.15-1.29)
Sensitive CYP2D6 Substrate: Dextromethorphan	30 mg once daily[c]	1.09 (0.98-1.21)	1.07 (0.95-1.22)
Sensitive CYP2C9 Substrate: S-Warfarin	30 mg once daily[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 once daily[c]	--	1.09 (1.00-1.19)
CYP2B6 Substrate: Buproprion	30 mg once daily[c]	0.87 (0.79-0.96)	0.92 (0.87-0.98)
Sensitive CYP3A Substrate: Midazolam	30 mg once daily[c]	0.74 (0.68-0.80)	0.74 (0.68-0.80)
Rosuvastatin	30 mg once daily[c]	0.77 (0.63-0.94)	0.67 (0.56-0.82)
Atorvastatin	30 mg once daily[c]	0.88 (0.79-0.97)	0.77 (0.70-0.85)
Ethinylestradiol	30 mg once daily[c]	0.96 (0.89-1.02)	1.11 (1.04-1.19)
Levonorgestrel	30 mg once daily[c]	0.96 (0.87-1.06)	0.96 (0.85-1.07)

CYP: cytochrome P450; CI: Confidence interval
[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]Modified-release formulation

4.6 Fertility, pregnancy and lactation

Effects on fertility

Based on findings in rats, treatment with upadacitinib does not reduce fertility in males or females of reproductive potential.

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, respectively (approximately 46 and 132 times the clinical dose of 15 mg on an AUC basis for males and females, respectively).

Use in pregnancy (Pregnancy Category D)

RINVOQ should not be used during pregnancy. There are limited human data on the use of upadacitinib in pregnant women. Based on findings in animal studies, RINVOQ may cause foetal harm when administered to a pregnant woman. Administration of upadacitinib to rats and rabbits during organogenesis caused increases in foetal malformations. Pregnant women should be advised of the potential risk to a foetus.

Advise females of reproductive potential that effective contraception should be used during treatment and for 4 weeks following the final dose of RINVOQ.

Upadacitinib crossed the placenta in both rats (significantly) and rabbits (to a lesser degree). Teratogenicity was seen in both species when pregnant animals received upadacitinib during the period of organogenesis. In rats, an increased incidence of skeletal malformations (misshapen humerus, bent scapula and bent bones of the fore- and hind-limbs) and variations (bent ribs) was seen at doses greater than or equal to 4 mg/kg/day. No adverse embryofoetal effects were seen at 1.5 mg/kg/day (exposures below the AUC from a clinical dose of 15 mg). In rabbits, an increased incidence of foetal cardiac malformations (dilated aortic arch, discontinuous interventricular septum, constricted or smaller pulmonary trunk, absent pulmonary valve and a larger ventricle) was seen following maternal exposure to 25 mg/kg/day. Embryofoetal lethality and abortions were also seen at this dose. Exposures at the no effect level were marginally above the AUC from a clinical dose of 15 mg.

Use in lactation

It is unknown whether upadacitinib/metabolites are excreted in human milk. Data in animals have shown excretion of upadacitinib in milk. Following administration of upadacitinib to

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

A risk to newborns/infants cannot be excluded. RINVOQ should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (Undesirable effects)

Adverse Events Reported in Clinical Trials

A total of 4443 patients with rheumatoid arthritis were treated with upadacitinib in clinical studies representing 5263 patient-years of exposure, of whom 2972 were exposed for at least one year. In the Phase 3 studies, 2630 patients (2655.1 patient-years of drug exposure) received at least 1 dose of RINVOQ 15 mg, of whom 1607 were exposed for at least one year.

Three placebo-controlled studies were integrated (1035 patients on RINVOQ 15 mg once daily and 1042 patients on placebo) to evaluate the safety of RINVOQ 15 mg in combination with csDMARDs in comparison to placebo for up to 12/14 weeks after treatment initiation. Two methotrexate (MTX)-controlled studies were integrated (534 patients on RINVOQ 15 mg and 530 patients on MTX) to evaluate the safety of RINVOQ 15 mg as monotherapy in comparison to MTX monotherapy for up to 12/14 weeks.

Table 4

Gastroenteritis	16 (1.5)	7 (0.7)	0	1 (0.2)	7 (1.3)
Influenza	11 (1.1)	5 (0.5)	2 (0.6)	0	3 (0.6)
Nasopharyngitis	46 (4.4)	33 (3.2)	8 (2.4)	15 (2.8)	13 (2.5)
Pharyngitis	15 (1.4)	8 (0.8)	7 (2.1)	5 (0.9)	4 (0.8)
Sinusitis	15 (1.4)	7 (0.7)	4 (1.2)	6 (1.1)	8 (1.5)
Upper respiratory tract infection	53 (5.1)	38 (3.6)	6 (1.8)	17 (3.2)	23 (4.3)
Urinary tract infection	42 (4.1)	34 (3.3)	13 (4.0)	23 (4.3)	17 (3.2)
Blood and lymphatic system disorders					
Anaemia	10 (1.0)	16 (1.5)	4 (1.2)	5 (0.9)	5 (0.9)
Leukopenia	16 (1.5)	5 (0.5)	2 (0.6)	7 (1.3)	5 (0.9)
Lymphopenia	13 (1.3)	11 (1.1)	2 (0.6)	2 (0.4)	4 (0.8)
Neutropenia	19 (1.8)	2 (0.2)	1 (0.3)	6 (1.1)	2 (0.4)
Metabolism and nutrition disorders					
Hypercholesterolemia	11 (1.1)	2 (0.2)	4 (1.2)	2 (0.4)	0
Nervous system disorders					
Headache	33 (3.2)	38 (3.6)	4 (1.2)	9 (1.7)	7 (1.3)
Dizziness	10 (1.0)	8 (0.8)	5 (1.5)	6 (1.1)	6 (1.1)
Vascular disorders					
Hypertension	24 (2.3)	22 (2.1)	4 (1.2)	9 (1.7)	9 (1.7)
Respiratory, thoracic and mediastinal disorders					
Cough	23 (2.2)	10 (1.0)	4 (1.2)	9 (1.7)	5 (0.9)

Gastrointestinal disorders					
Constipation	11 (1.1)	5 (0.5)	2 (0.6)	5 (0.9)	2 (0.4)
Diarrhoea	30 (2.9)	26 (2.5)	10 (3.1)	8 (1.5)	9 (1.7)
Nausea	36 (3.5)	23 (2.2)	8 (2.4)	17 (3.2)	13 (2.5)
Vomiting	11 (1.1)	7 (0.7)	4 (1.2)	3 (0.6)	2 (0.4)
Musculoskeletal and connective tissue disorders					
Back pain	21 (2.0)	14 (1.3)	4 (1.2)	4 (0.7)	1 (0.2)
Rheumatoid arthritis (worsening)	11 (1.1)	36 (3.5)	5 (1.5)	4 (0.7)	18 (3.4)
General disorders and administration site conditions					
Pyrexia	12 (1.2)	0	1 (0.3)	3 (0.6)	5 (0.9)
Injury, poisoning and procedural complications					
Fall	10 (1.0)	5 (0.5)	2 (0.6)	4 (0.7)	4 (0.8)
Investigations					
Alanine aminotransferase increased	28 (2.7)	27 (2.6)	5 (1.5)	14 (2.6)	7 (1.3)
Aspartate aminotransferase increased	21 (2.0)	21 (2.0)	6 (1.8)	10 (1.9)	6 (1.1)
Blood creatine phosphokinase increased	26 (2.5)	9 (0.9)	1 (0.3)	11 (2.1)	1 (0.2)
Weight increased	10 (1.0)	3 (0.3)	1 (0.3)	2 (0.4)	4 (0.8)

Adverse Drug Reactions

The frequency of adverse reactions listed below is defined using the following

to < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Very Common: Upper respiratory tract infections (URTI)*
Uncommon: Pneumonia, Herpes zoster, Herpes simplex**, Oral candidiasis

Common: Neutropenia

Common: Hypercholesterolemia
Uncommon: Hypertriglyceridemia

Common: Cough

Common: Nausea

Common: Pyrexia

Common: Blood creatine phosphokinase (CPK) increased, ALT increased, AST increased, weight increased

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

Specific Adverse Reactions

Infections

In placebo-controlled clinical studies with background DMARDs, the frequency of infection over 12/14 weeks in the RINVOQ 15 mg group was 27.4% compared to 20.9% in the placebo group. In MTX-controlled studies, the frequency of infection over 12/14 weeks in the RINVOQ 15 mg monotherapy group was 19.5% compared to 24.0% in the MTX group. The overall long-term rate of infections for the RINVOQ 15 mg group across all five Phase 3 clinical studies (2630 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 RINVOQ 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 RINVOQ 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 RINVOQ 15 mg group across all five Phase 3 clinical studies was 3.8 events per 100 patient-years. The most frequently reported serious infections were pneumonia and cellulitis. The rate of serious infections remained stable with long-term exposure.

limited.

The frequencies of infection Adverse Drug Reactions (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.

Tuberculosis

In placebo-controlled clinical studies with background DMARDs, there were no active cases of tuberculosis reported in any treatment group. In MTX-controlled studies, there were no cases over 12/14 weeks in either the RINVOQ 15 mg monotherapy group or the MTX group. The overall long-term rate of active tuberculosis for the RINVOQ 15 mg group across all five Phase 3 clinical studies was 0.1 events per 100 patient-years.

Opportunistic Infections (excluding tuberculosis)

In placebo-controlled clinical studies with background DMARDs, the frequency of opportunistic infections over 12/14 weeks in the RINVOQ 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 RINVOQ 15 mg monotherapy group and 0.2% in the MTX group. The

overall long-term rate of opportunistic infections for the RINVOQ 15 mg group across all five Phase 3 clinical studies was 0.6 events per 100 patient-years.

Malignancy

In placebo-controlled clinical studies with background DMARDs, the frequency of malignancies excluding NMSC over 12/14 weeks in the RINVOQ 15 mg group was <0.1% compared to <0.1% in the placebo group. In MTX-controlled studies, the frequency of malignancies excluding NMSC over 12/14 weeks in the RINVOQ 15 mg monotherapy group was 0.6% compared to 0.2% in the MTX group. The overall long-term incidence rate of malignancies excluding NMSC for the RINVOQ 15 mg group in the clinical trial program was 0.8 per 100 patient-years.

Gastrointestinal Perforations

In placebo-controlled clinical studies with background DMARDs, the frequency of gastrointestinal perforations in the RINVOQ 15 mg group was 0.2% compared to 0% in the placebo group. In MTX-controlled studies, there were no gastrointestinal perforations over 12/14 weeks in either the RINVOQ 15 mg monotherapy group or the MTX group. The overall long-term rate of gastrointestinal perforation for the RINVOQ 15 mg group across all five Phase 3 clinical studies was 0.08 events per 100 patient-years.

Thrombosis

In placebo-controlled studies with background DMARDs, there were two (0.2%) venous thrombosis events (pulmonary embolism or deep vein thrombosis) in the RINVOQ 15 mg group compared to one event (0.1%) in the placebo group. In MTX-controlled studies, there was one VTE event (0.2%) over 12/14 weeks in the RINVOQ 15 mg monotherapy group and there were no events in the MTX group. The overall long-term incidence rate of VTE for the RINVOQ 15 mg group across all five Phase 3 clinical studies was 0.6 per 100 patient-years.

Hepatic transaminase elevations

In placebo-controlled studies with background DMARDs, for up to 12/14 weeks, alanine

(ULN) in at least one measurement were observed in 2.1% and 1.5% of patients treated with RINVOQ 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-
least one measurement were observed in 0.8% and 0.4% of patients treated with RINVOQ 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 15mg 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 controlled studies with baseline values below the specified limits, the following frequencies of patients were observed to shift 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 elevations

In placebo-controlled studies with background DMARDs, for up to 12/14 weeks, 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. 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 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 clinical studies,

treatment was interrupted in response to ANC <1000 cells/mm^3. The pattern and incidence of decreases in neutrophil counts remained stable at a lower value than baseline over time including with extended therapy.

Lymphopaenia

In placebo-controlled studies with background DMARDs, for up to 12/14 weeks, 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.

Anaemia

In placebo-controlled studies with background DMARDs, for up to 12/14 weeks, haemoglobin 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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

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

For information on the management of overdose in Australia contact the Poisons Information Centre on 131126.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: not yet assigned.

Mechanism of action

Janus Kinases (JAKs) are important intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, haematopoiesis 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 inhibitor of JAK1. Upadacitinib more potently inhibits JAK1 compared to JAK2 and JAK3. In cellular potency assays that correlated with the *in vivo* pharmacodynamic responses, upadacitinib demonstrated 33-197-fold greater selectivity for JAK1-associated signalling over JAK2-JAK2 signalling. In enzyme assays, upadacitinib had >50-fold selectivity for JAK1 over JAK3.

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.

High-Sensitivity (hs) CRP

Treatment with upadacitinib was associated with significant decreases from baseline in mean hsCRP levels as early as Week 1 which were maintained with continued treatment.

Cardiac electrophysiology

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

Clinical trials

The efficacy and safety of RINVOQ 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 5). 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 (currently ongoing for up to 5 years).

Table 5. Clinical Trial Summary

Study Name	Population (n)	Treatment Arms	Key Outcome Measures
SELECT EARLY 24-week monotherapy trial	MTX-naive[a] (947)	Upadacitinib 15 mg Upadacitinib 30 mg MTX Monotherapy	Primary Endpoint: ACR 50 at Week 12
			Key Secondary Endpoints: Low Disease Activity (DAS28-3.2) at Week 12 Clinical Remission (DAS28-CRP <2.6) at Week 24 •Δ Physical Function (HAQ-DI) at Week 12 Radiographic progression (ΔmTSS) at Week 24 ΔSF-36 PCS at Week 12
SELECT MONOTHERAPY 14-week monotherapy trial	MTX-IR[b] (648)	Upadacitinib 15 mg Upadacitinib 30 mg MTX Monotherapy	Primary Endpoint: ACR20 at Week 14
			Key Secondary Endpoints: Low Disease Activity (DAS28-CRP ≤ 3.2) at Week 14 Clinical Remission (DAS 28-CRP <2.6) at Week 14 Δ Physical Function (HAQ-DI) at Week 14 ΔSF-36 PCS at Week 14 Morning stiffness at Week 14
SELECT NEXT 12-week trial	csDMARD IR[c] (661)	Upadacitinib 15 mg Upadacitinib 30 mg Placebo On background csDMARDs	Primary Endpoint: ACR20 at Week 12
			Key Secondary Endpoints: Clinical Remission (DAS28- CRP <2.6) at Week 12 Δ Physical Function HAQ-DI at Week 12 Low Disease Activity (DAS28-CRP ≤ 3.2) at Week 12 ΔSF-36 PCS at Week 12 ΔMorning stiffness at Week 12 ΔFACIT-F at Week 12
SELECT COMPARE 48-week trial	MTX-IR[d] (1629)	Upadacitinib 15 mg Placebo Adalimumab 40 mg On background MTX	Primary Endpoint: ACR20 at Week 12
			Key Secondary Endpoints: Low Disease Activity (DAS28-CRP ≤3.2) at Week 12 Clinical Remission (DAS28-CRP <2.6) at Week 12;

			ACR50 vs adalimumab at Week 12; Δ Physical Function (HAQ-DI) vs adalimumab at Week 12; Δ Patient's Assessment of Pain vs adalimumab at Week 12 Radiographic progression (ΔmTSS) at Week 26 ΔSF-36 PCS at Week 12 Δ Morning stiffness at Week 12 ΔFACIT-F at Week 12
SELECT BEYOND 12-week trial	bDMARD-IR[e] (499)	Upadacitinib 15 mg Upadacitinib 30 mg Placebo On background csDMARDs	Primary Endpoint: ACR20 at Week 12
			Key Secondary Endpoint: Low Disease Activity (DAS28-CRP ≤3.2) at Week 12 Δ Physical Function (HAQ-DI) at Week 12 Δ SF-36 PCS at Week 12

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
FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue
mTSS = modified Total Sharp Score
csDMARD = conventional synthetic disease-modifying anti-rheumatic drug
HAQ-DI = Health Assessment Questionnaire Disability Index
IR = inadequate responder
MTX = methotrexate
SF-36 = Short Form (36) Health Survey
PCS = Physical Component Summary

[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

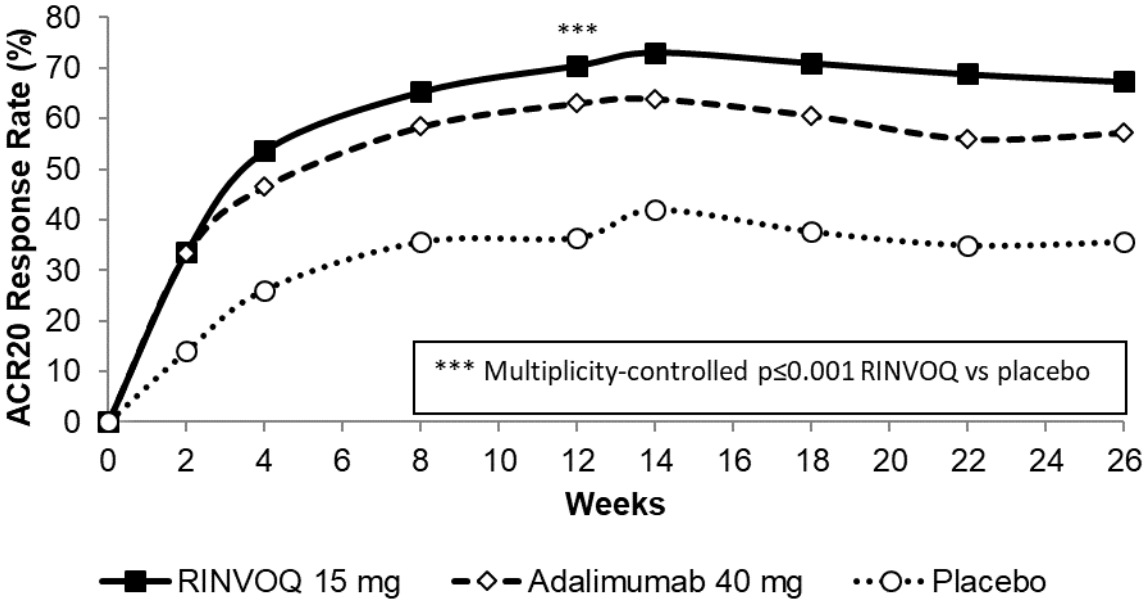
Clinical Response

ACR Response

In all studies, significantly more patients treated with RINVOQ 15 mg achieved ACR20, ACR50, and ACR70 responses at 12/14 weeks compared to placebo or MTX except for ACR70 in SELECT-BEYOND (Table 6). Time to onset of efficacy was rapid across measures with greater responses seen as early as Week 1 for ACR20. In SELECT-COMPARE, a higher proportion of patients treated with RINVOQ 15 mg achieved ACR20 (Figure 1) and ACR70 at Week12 compared to placebo or adalimumab. In a multiplicity-controlled comparison, RINVOQ was superior to adalimumab for ACR50 at Week 12.

Treatment with RINVOQ 15 mg, alone or in combination with csDMARDs, resulted in greater improvements in individual ACR components, including tender and swollen joint counts, patient and physician global assessments, HAQ-DI, pain assessment, and hsCRP, compared to placebo or MTX monotherapy at Week 12/14. In SELECT-COMPARE at Week 12, RINVOQ was superior to adalimumab for pain reduction in a multiplicity-controlled comparison. Greater pain reduction was seen as early as Week 1 compared to placebo and as early as Week 4 compared to adalimumab.

Figure 1. Percent of Patients Achieving ACR20 in SELECT COMPARE



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 <2.6) compared to placebo, or MTX (Table 6). Overall, both low disease activity and clinical remission rates were consistent across patient populations, with or without MTX.

Table 6. Response and Remission

Study	SELECT EARLY MTX-Naive		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											
ACR20 (% of patients)											
12[a]/14[b]	54	76[g]	41	68[e]	36	64[e]	36	71[e,i]	63	28	65[e]
24[c]/26[d]	59	79[g]					36	67[g,i]	57		
ACR50 (% of patients)											
12[a]/14[b]	28	52[e]	15	42[g]	15	38[g]	15	45[g,h,]	29	12	34[g]
24[c]/26[d]	33	60[g]					21	54[g,i]	42		
ACR70 (% of patients)											
12[a]/14[b]	14	32[g]	3	23[g]	6	21[g]	5	25[g,i]	13	7	12
24[c]/26[d]	18	44[g]					10	35[g,i]	23		
LDA DAS28-CRP ≤3.2 (% of patients)											
12[a]/14[b]	28	53[f]	19	45[e]	17	48[e]	14	45[e,i]	29	14	43[e]
24[c]/26[d]	32	60[g]					18	55[g,i]	39		
CR DAS28-CRP <2.6 (% of patients)											
12[a]/14[b]	14	36[g]	8	28[e]	10	31[e]	6	29[e,i]	18	9	29[g]
24[c]/26[d]	18	48[f]					9	41[g,i]	27		
SDAI ≤3.3 (% of patients)											
12[a]/14[b]	6	16[g]	1	14[g]	3	10[g]	3	12[g,i]	7	5	9
24[c]/26[d]	9	28[g]					5	24[g,i]	14		
SDAI ≤2.8 (% of patients)											
12[a]/14[b]	6	16[g]	1	13[g]	3	9[g]	3	13[g,i]	8	5	8
24[c]/26[d]	11	28[g]					6	23[g,i]	14		

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
LDA = Low Disease Activity
MTX = methotrexate
PBO = placebo
SDAI = Simple Disease Activity Index
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≤0.05 upadacitinib vs placebo or MTX comparison
h multiplicity-controlled p≤0.001 upadacitinib vs adalimumab comparison
i nominal p≤0.05 upadacitinib vs adalimumab comparison

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 (SELECT-COMPARE) and Week 24 (SELECT-EARLY).

Treatment with RINVOQ 15 mg resulted in significantly greater inhibition of the progression of structural joint damage compared to placebo at Week 26 in SELECT-COMPARE and as monotherapy compared to MTX at Week 24 in SELECT-EARLY (Table 7). Analyses of erosion and joint space narrowing scores were consistent with the overall scores. The proportion of patients with no radiographic progression (mTS
RINVOQ 15 mg in both studies.

Table 7: Radiographic Changes

Study	**SELECT EARLY MTX-Naive**		**SELECT COMPARE MTX-IR**		
Treatment Group	MTX	UPA 15 mg	PBO	UPA 15mg	ADA 40mg
Modified Total Sharps Score, mean change from baseline					
Week 24[a]/26[b]	0.7	0.1[e]	0.9	0.2[d]	0.1
Erosion Score, mean change from baseline					
Week 24[a]/26[b]	0.3	0.1[d]	0.4	0[d]	0
Joint Space Narrowing Score, mean change from baseline					
Week 24[a]/26[b]	0.3	0.1[f]	0.6	0.2[d]	0.1
Proportion of patients with no radiographic progression[c]					
Week 24[a]/26[b]	77.7	87.5[e]	76.0	83.5[e]	86.8

Abbreviations:
ADA = adalimumab
IR = inadequate responder MTX = methotrexate PBO = placebo
UPA= upadacitinib

[a] SELECT-EARLY
[b] SELECT-COMPARE
c No progression defined as mTSS change ≤0.
d p≤0.001 upadacitinib vs placebo or MTX comparison
ep≤0.01 upadacitinib vs placebo or MTX comparison
f p≤0.05 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 at Week 12/14 (Table 8) with RINVOQ being superior to adalimumab in a multiplicity-controlled comparison.

Table 8: Mean change from baseline in HAQ-DI [a,b]

Study	SELECT EARLY MTX-		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[g]	-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[h]					-0.3	-0.7[h,j]	-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 multiplicity-controlled p≤0.01 upadacitinib vs adalimumab comparison

j 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 at Week 12/14.

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 Score compared to placebo and MTX. Moreover, upadacitinib treated patients reported significant improvements in fatigue at Week 12, as measured by the Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F) compared to placebo.

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. The pharmacokinetic properties of RINVOQ are provided in Table 9.

Table 9. Pharmacokinetic Properties of RINVOQ

Absorption	
T_{max} (h)	2-4
Effect of high-fat meal (relative to fasting)	No clinically relevant effect AUC: ↑ 29%, Cmax ↑ C_{max} 39%
Distribution	
% Bound to human plasma proteins	59
Blood-to-plasma ratio	1.0
Metabolism	
Metabolism	CYP3A4, CYP2D6 (minor) No active metabolites
Elimination	
Terminal phase elimination $t_{1/2}$ (h)	9-14
% of dose excreted unchanged in urine[a]	24
% of dose excreted unchanged in faeces[a]	38
% of dose excreted as metabolites[a]	34
[a]Based on single dose administration of [^{14}C] upadacitinib immediate-release solution in a mass balance study.	

Pharmacokinetics in special populations

Renal Impairment

Renal impairment has no clinically relevant effect on upadacitinib exposure. Upadacitinib AUC 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 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).

Other Intrinsic Factors

Age, sex, body weight, race, and ethnicity did not have a clinically meaningful effect on upadacitinib exposure.

5.3 Preclinical safety data

Upadacitinib is teratogenic in both rats and rabbits (see **4.6 Fertility, Pregnancy and Lactation**)

Genotoxicity

Upadacitinib was not mutagenic in a bacterial mutagenicity assay or clastogenic in an *in vitro* chromosomal aberration assay (human peripheral blood lymphocytes) or an *in vivo* rat bone marrow micronucleus assay.

Carcinogenicity

The carcinogenic potential of upadacitinib was evaluated in Sprague-Dawley rats and Tg.rasH2 mice. No evidence of tumourigenicity 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 5 and 12 times the clinical dose of 15 mg on an AUC basis for males and females, respectively). No evidence of tumourigenicity was observed in Tg.rasH2 mice that received upadacitinib for 26 weeks at oral doses up to 20 mg/kg/day in male or female mice (approximately 3 times the clinical dose of 15 mg on an AUC basis).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each tablet contains the following inactive ingredients: microcrystalline cellulose, hypromellose, mannitol, tartaric acid, colloidal anhydrous silica, and magnesium stearate.

Film coating contains polyvinyl alcohol, macrogol 3350, talc, titanium dioxide (E171), ferrosoferric oxide (E172) and iron oxide red (E172).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

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

6.5 Nature and contents of container

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

The following presentations are available:

Starter Pack 15 mg (7 tablets) - 1 carton containing one PVC/PE/PCTFE/Aluminium blister with 7 tablets.

Monthly Pack 15 mg (28 tablets) - 1 carton containing four PVC/PE/PCTFE/Aluminium blisters with 7 tablets in each blister. Not all presentations may be marketed.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

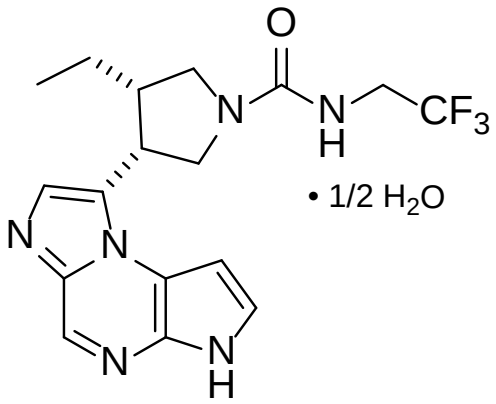
Upadacitinib is a white to light brown powder with the following chemical name: (3S,4R)-3-Ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrate (2:1).

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 37ºC.

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.

Chemical structure

The chemical structure of upadacitinib is:



CAS number

1310726-60-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine – Schedule 4

8 SPONSOR

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www.abbvie.com.au

9 DATE OF FIRST APPROVAL

17 January 2020

10 DATE OF REVISION

N/A

Summary table of changes

Section Changed	Summary of new information
All	New document