# NEW ZEALAND DATA SHEET

# 1 RINVOQ® UPADACITINIB 15 MG MODIFIED RELEASE TABLETS

# 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

RINVOQ contains upadacitinib hemihydrate, equivalent to 15 mg of upadacitinib, a 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 adults with moderately to severely active rheumatoid arthritis.

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

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

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

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

**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.

**Dose Interruption**

It is recommended that RINVOQ 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 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**).

**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 |

**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. 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.

## 4.4 Special warnings and precautions for use

**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**). Among opportunistic infections, tuberculosis, multi-dermatomal herpes zoster, oral/oesophageal candidiasis, and cryptococcosis 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.

**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.

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), were reported in clinical studies (see **4.8 ADVERSE EFFECTS**). The risk of herpes zoster appears to be higher in patients treated with RINVOQ in Japan. If a patient develops herpes zoster, consider temporarily interrupting RINVOQ until the episode resolves.

Screening for viral hepatitis and monitoring for reactivation should be performed in accordance with clinical guidelines before starting and during therapy with RINVOQ. Patients who were positive for hepatitis C antibody and hepatitis C virus RNA, were excluded from clinical 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 RINVOQ, a liver specialist should be consulted.

**Vaccination**

No data are available on the response to vaccination with live 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 (see **5 PHARMACOLOGICAL PROPERTIES** for data on inactivated pneumococcal 13-valent conjugate vaccine and concomitant use with RINVOQ).

**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 effect of RINVOQ treatment on malignancies is not known.

Malignancies were 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.

**Venous thromboembolism**

Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving JAK inhibitors including RINVOQ. If clinical features of DVT/PE occur, patients should be evaluated promptly, followed by appropriate treatment.

**Immunosuppressive medicinal products**

Combination with other potent immunosuppressants such as azathioprine, cyclosporine, 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.

**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.

**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**

## Neutropenia

Treatment with RINVOQ was associated with an increased incidence of neutropenia (ANC <1000 cells/$mm^3$). There was no clear association between low neutrophil counts and the occurrence of serious infections.

## Lymphopenia

ALCs <500 cells/$mm^3$ were reported in RINVOQ clinical studies. There was no clear association between low lymphocyte counts and the occurrence of serious infections.

## Anaemia

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

The majority of the above haematologic laboratory changes were transient and resolved with temporary treatment interruption.

Evaluate at baseline and thereafter according to routine patient management. Treatment should not be initiated or should be temporarily interrupted in patients who meet the criteria described in Table 1 (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) (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), 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.

**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** | **Regimen of Upadacitinib** | **N** | **$C_{max}$** | **AUC** | **Clinical Impact** |
| Ketoconazole | 400 mg once daily x 6 days | 3 mg single dose[b] | 11 | 1.70 (1.55-1.89) | 1.75 (1.62-1.88) | Use with caution if used chronically. |
| Rifampicin | 600 mg once daily x 9 days | 12 mg single dose[b] | 12 | 0.49 (0.44-0.55) | 0.39 (0.37-0.42) | May decrease efficacy |
| CI: Confidence interval | | | | | | |

| | | | | Ratio (90% CI)[a] | | |
|---|---|---|---|---|---|---|
| **Co-administered Drug** | **Regimen of Co-administered Drug** | **Regimen of Upadacitinib** | **N** | **$C_{max}$** | **AUC** | **Clinical Impact** |
| Ketoconazole | 400 mg once daily x 6 days | 3 mg single dose[b] | 11 | 1.70 (1.55-1.89) | 1.75 (1.62-1.88) | Use with caution if used chronically. |
| [a] Ratios for $C_{max}$ and AUC compare co-administration of the medication with upadacitinib vs. administration of upadacitinib alone.<br>[b] Upadacitinib was administered as an immediate-release formulation. | | | | | | |

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**

The effect of upadacitinib on plasma exposures of other drugs is provided in Table 3.

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

| | | | | Ratio (90% CI)[a] | | |
|---|---|---|---|---|---|---|
| **Co-administered Drug** | **Regimen of Co-administered Drug** | **Regimen of Upadacitinib** | **N** | **$C_{max}$** | **AUC** | **Clinical Impact** |
| Midazolam | 5 mg single dose | 30 mg once daily x 10 days | 20 | 0.74 (0.68-0.80) | 0.74 (0.68-0.80) | No dose adjustment |
| Rosuvastatin | 5 mg single dose | 30 mg once daily x 10 days | 12 | 0.77 (0.63-0.94) | 0.67 (0.56-0.82) | No dose adjustment |
| Atorvastatin | 10 mg single dose | 30 mg once daily x 10 days | 24 | 0.88 (0.79-0.97) | 0.77 (0.70-0.85) | No dose adjustment |
| CI: Confidence interval<br>[a] Ratios for $C_{max}$ and AUC compare co-administration of the medication with upadacitinib vs. administration of medication alone | | | | | | |

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

## 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. Dose related increases in foetal resorptions associated with post-implantation losses at 25 and 75 mg/kg/day in this study were attributed to the developmental/teratogenic effects of upadacitinib in rats.

### Use in pregnancy (Pregnancy Category D)

The limited human data with RINVOQ in pregnant women are not sufficient to inform drug-associated risk for major birth defects and miscarriage.

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

Based on animal studies, upadacitinib has the potential to affect a developing foetus.

In animal embryo-foetal development studies, upadacitinib was teratogenic in rats and rabbits when pregnant animals received upadacitinib during the period of organogenesis at exposure multiples of 1.6 and 15 times the clinical dose of 15 mg for rats and rabbits, respectively. Further, in a pre-/postnatal development study in rats, upadacitinib administration resulted in no drug-related effects in the mothers or pups.

Upadacitinib has been shown to be teratogenic in rats and rabbits when given at exposures of 1.6 and 15 times the clinical dose of 15 mg (on an AUC basis at maternal oral doses of 4 mg/kg/day and 25 mg/kg/day, respectively).

In two rat embryo-foetal development studies, pregnant animals were dosed during the period of organogenesis from gestation day (GD) 6 to GD 17. Upadacitinib was teratogenic at all dose levels studied in rats except the lowest dose of 1.5 mg/kg/day. At doses of 4, 5, 25, and 75 mg/kg/day, upadacitinib-related effects included an increase in two particular skeletal malformations (i.e., misshapen humerus and bent scapula) and, at 75 mg/kg/day, an increase

in bent bones of the fore- and hind-limbs. Additionally, at 25 and 75 mg/kg/day, there was an increase in bent ribs, a skeletal variation, which was also considered upadacitinib-related.

In a rabbit embryo-foetal development study, pregnant animals were dosed during the period of organogenesis from GD 7 to GD 19. Upadacitinib was teratogenic when given at doses of 25 mg/kg/day. Developmental effects observed at 25 mg/kg/day in rabbits included an increase in post-implantation losses, increase in total and early resorptions, lower foetal body weights, and increased incidence of cardiac malformations. In addition, maternal toxicity was evident within the 25 mg/kg/day dose group as weight loss, lower food consumption, and the increased occurrence of aborted pregnancies.

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

**Use in lactation**

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

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

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.

## 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)

### Clinical trials experience

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 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 comparison to placebo for up to 12-14 weeks after treatment initiation.

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 4. Adverse Drug Reactions**

| System Organ Class | Very Common | Common | Uncommon |
|---|---|---|---|
| **Infections and infestations** | Upper respiratory tract infections (URTI)* | | Pneumonia<br>Herpes zoster<br>Herpes simplex**<br>Oral candidiasis |
| **Blood and lymphatic system disorders** | | Neutropenia | |
| **Metabolism and nutrition disorders** | | Hypercholesterolaemia | Hypertriglyceridemia |
| **Respiratory, thoracic and mediastinal disorders** | | Cough | |
| **Gastrointestinal disorders** | | Nausea | |
| **General disorders and administration site conditions** | | Pyrexia | |
| **Investigations** | | Blood creatine phosphokinase (CPK) increased<br>ALT increased<br>AST increased<br>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.

***Tuberculosis***

In placebo-controlled clinical studies with background DMARDs, there were no active cases of TB 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 TB 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 venous thrombosis 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 venous thrombosis events 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 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, 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 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***

RINVOQ 15mg treatment was associated with increases in lipid parameters including total cholesterol, triglycerides, LDL cholesterol, and 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 15mg are summarized below:

- Mean LDL cholesterol increased by 0.38 mmol/L.
- Mean HDL cholesterol increased by 0.21 mmol/L.
- The mean LDL/HDL ratio remained stable.
- Mean triglycerides increased by 0.15 mmol/L.

***Creatinine phosphokinase (CPK)***

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 and then remained stable at the increased value thereafter including with extended therapy.

***Neutropenia***

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.

***Lymphopenia***

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. In New Zealand, healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

### 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 advice on the management of overdose in New Zealand, please contact the National Poisons Centre on 0800 POISON (0800 764 766).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

ATC code: L04AA44.

**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 50–70-fold greater selectivity for JAK1 over JAK2 and >100-fold 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.

Vaccine Study

The influence of RINVOQ on the humoral response following the administration of inactivated pneumococcal 13-valent conjugate vaccine was evaluated in 111 patients with rheumatoid arthritis under stable treatment with upadacitinib 15 mg (n = 87) or 30 mg (n = 24). 97% of patients (n = 108) were on concomitant methotrexate. Vaccination resulted in a satisfactory humoral response

in 67.5% (95% CI: 57.4, 77.5) and 56.5% (95% CI: 36.3, 76.8) of patients treated with upadacitinib 15 mg and 30 mg, respectively.

### 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. Four studies included long-term extensions for up to 5 years and one study (SELECT-COMPARE) included a long-term extension for up to 10 years.

**Table 5. Clinical Trial Summary**

| **Study Name** | **Population**<br><br>**(n)** | **Treatment Arms** | **Key Outcome Measures** |
|---|---|---|---|
| SELECT EARLY | MTX-naive[a]<br><br>(947) | • Upadacitinib 15 mg<br>• Upadacitinib 30 mg<br>• MTX<br><br>Monotherapy | Primary Endpoint:<br>• ACR 50 at Week 12 |
| | | | Key Secondary Endpoints:<br>• Low Disease Activity (DAS28-CRP ≤ 3.2) at Week 12<br>• Clinical Remission (DAS28-CRP <2.6) at Week 24<br>• Δ Physical Function (HAQ-DI) at Week 12<br>• Radiographic progression (ΔmTSS) at Week 24<br>• SF-36 PCS |
| SELECT MONOTHERAPY | MTX-IR[b]<br><br>(648) | • Upadacitinib 15 mg<br>• Upadacitinib 30 mg<br>• MTX<br><br>Monotherapy | Primary Endpoint:<br>• ACR20 at Week 14 |
| | | | Key Secondary Endpoints:<br>• Low Disease Activity (DAS28-CRP ≤ 3.2) at Week 14<br>• Clinical Remission (DAS 28-CRP <2.6) at Week 14<br>• Δ Physical Function (HAQ-DI) at Week 14<br>• SF-36 PCS<br>• Morning stiffness |

| | | | |
|---|---|---|---|
| SELECT NEXT | csDMARD IR[c]<br><br>(661) | • Upadacitinib 15 mg<br>• Upadacitinib 30 mg<br>• Placebo<br><br>On background csDMARDs | Primary Endpoint:<br>• ACR20 at Week 12<br><br>Key Secondary Endpoints:<br>• Clinical Remission (DAS28- CRP <2.6) at Week 12<br>• Δ Physical Function HAQ-DI at Week 12<br>• Low Disease Activity (DAS28-CRP ≤ 3.2) at Week 12<br>• SF-36 PCS<br>• Morning stiffness<br>• FACIT-F |
| SELECT COMPARE | MTX-IR[d]<br><br>(1629) | • Upadacitinib 15 mg<br>• Placebo<br>• Adalimumab 40 mg<br><br>On background MTX | Primary Endpoint:<br>• ACR20 at Week 12<br><br>Key Secondary Endpoints:<br>• Low Disease Activity (DAS28-CRP ≤3.2) at Week 12<br>• Clinical Remission (DAS28-CRP <2.6) at Week 12<br>• ACR50 vs adalimumab at Week 12<br>• Δ Physical Function (HAQ-DI) at Week 12<br>• Radiographic progression (ΔmTSS) at Week 26<br>• SF-36 PCS<br>• Morning stiffness<br>• FACIT-F |
| SELECT BEYOND | bDMARD-IR[e]<br><br>(499) | • Upadacitinib 15 mg<br>• Upadacitinib 30 mg<br>• Placebo<br><br>On background csDMARDs | Primary Endpoint:<br>• ACR20 at Week 12<br><br>Key Secondary Endpoint:<br>• Low Disease Activity (DAS28-CRP ≤3.2) at Week 12<br>• Δ Physical Function (HAQ-DI) at Week 12<br>• SF-36 PCS |
| **Abbreviations:**<br>ACR20 (or 50) = American College of Rheumatology ≥20% (or ≥50%) improvement<br>bDMARD = biologic disease-modifying anti-rheumatic drug | | | |

CR = Clinical Response

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

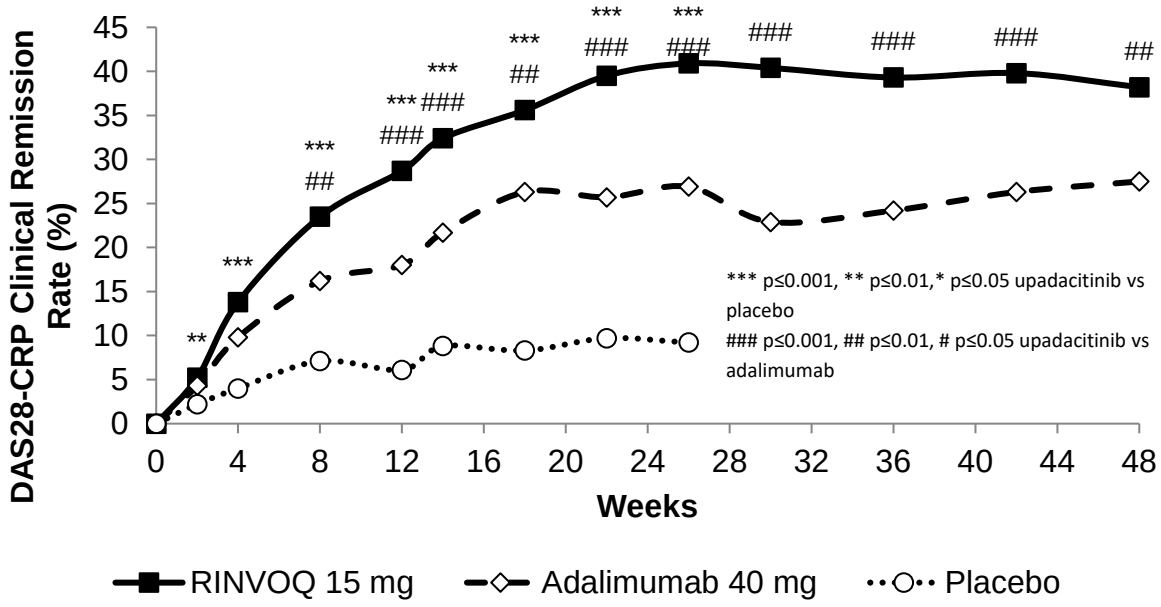
[e] Patients who had an inadequate response or intolerance to at least one bDMARD

## Clinical Response

### *Remission and low disease activity*

In all studies, a significantly higher proportion of patients treated with RINVOQ 15 mg achieved both low disease activity (DAS28-CRP ≤3.2) and clinical remission (DAS28-CRP <2.6) compared to placebo, MTX, or adalimumab (Table 6). Compared to adalimumab, significantly higher responses were achieved as early as Week 8 and maintained through Week 48 (Figure 1). Significantly higher responses were also observed for other disease activity outcomes including CDAI ≤2.8, SDAI ≤3.3, and Boolean remission. Overall, both low disease activity and clinical remission rates were consistent across patient populations, with or without MTX.

**Figure 1. Clinical Remission (DAS28-CRP) over time in SELECT COMPARE**




**ACR Response**

In all studies, significantly more patients treated with RINVOQ 15 mg achieved ACR20, ACR50, and ACR70 responses at 12 weeks compared to placebo or MTX except for ACR70 in SELECT-BEYOND (Table 6). Time to onset of efficacy was rapid across measures with significantly 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. The percentage of patients who achieved ACR20/50/70 responses at each visit in SELECT-COMPARE are shown in Figure 2, Figure 3 and Figure 4.

Treatment with RINVOQ 15 mg, alone or in combination with csDMARDs, resulted in significant 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 (Table 7).

In SELECT-COMPARE, a significantly higher proportion of patients treated with RINVOQ 15 mg achieved ACR20/50/70 at Weeks 12 through 48 compared to adalimumab. In addition, greater improvements were observed for individual ACR components (Table 7).

**Figure 2. Percent of Patients Achieving ACR20 in SELECT COMPARE**

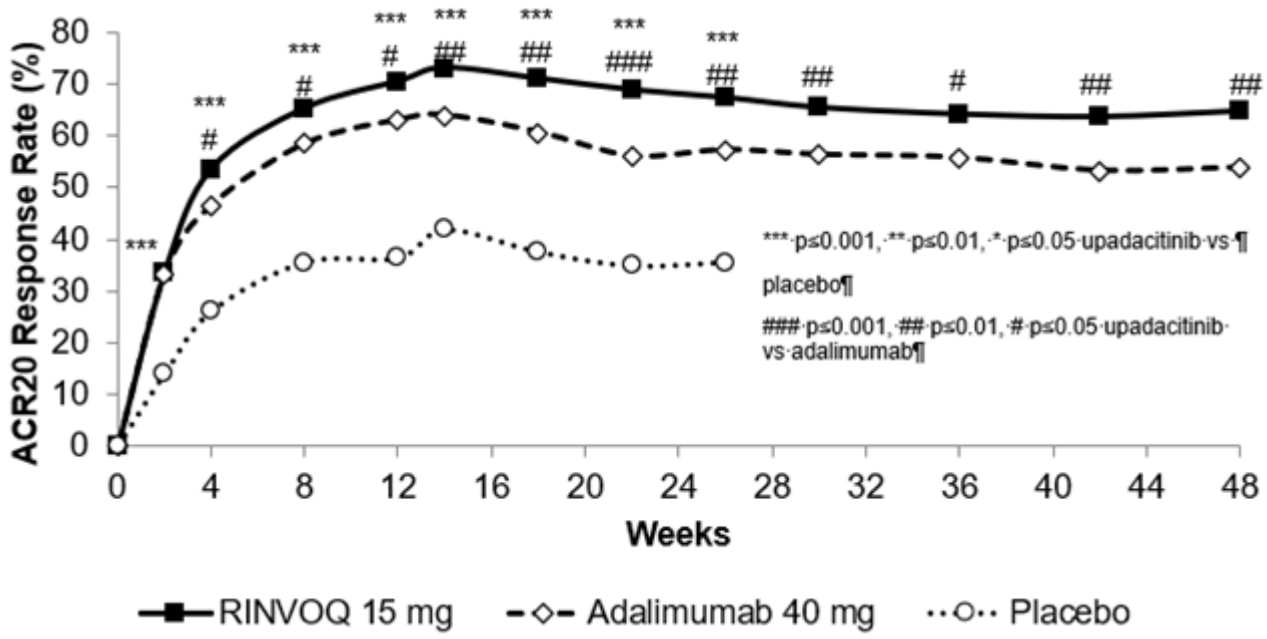



**Figure 3. Percent of Patients Achieving ACR50 in SELECT COMPARE**

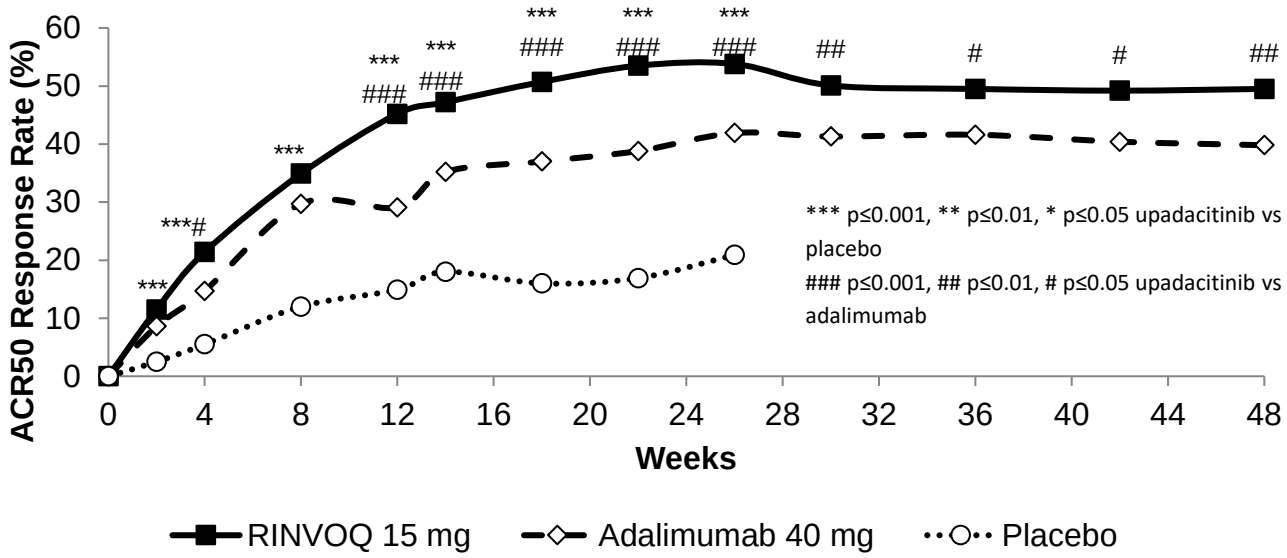


**Figure 4. Percent of Patients Achieving ACR70 in SELECT COMPARE**

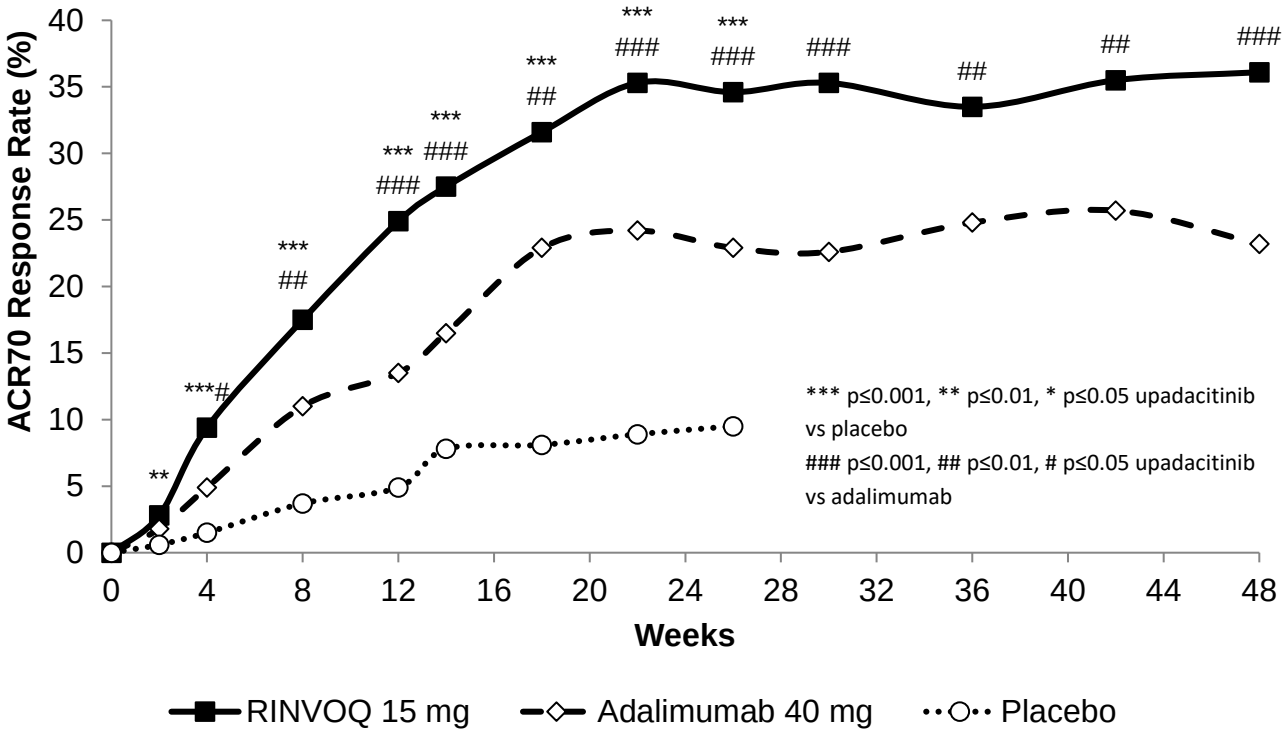



**Table 6. Response and Remission**

| 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[e] | 41 | 68[e] | 36 | 64[e] | 36 | 71[e,j] | 63 | 28 | 65[e] |
| 24[c]/26[d] | 59 | 79[e] | | | | | 36 | 67[e,i] | 57 | | |
| 48 | 57 | 74[e] | | | | | | 65[j] | 54 | | |
| **ACR50 (% of patients)** | | | | | | | | | | | |
| 12[a]/14[b] | 28 | 52[e] | 15 | 42[e] | 15 | 38[e] | 15 | 45[e,h] | 29 | 12 | 34[e] |
| 24[c]/26[d] | 33 | 60[e] | | | | | 21 | 54[e,h] | 42 | | |
| 48 | 43 | 63[e] | | | | | | 49[j] | 40 | | |
| **ACR70 (% of patients)** | | | | | | | | | | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 12[a]/14[b] | 14 | 32[e] | 3 | 23[e] | 6 | 21[e] | 5 | 25[e,h] | 13 | 7 | 12 |
| 24[c]/26[d] | 18 | 44[e] | | | | | 10 | 35[e,h] | 23 | | |
| 48 | 29 | 51[e] | | | | | | 36[h] | 23 | | |
| **LDA DAS28-CRP ≤3.2 (% of patients)** | | | | | | | | | | | |
| 12[a]/14[b] | 28 | 53[e] | 19 | 45[e] | 17 | 48[e] | 14 | 45[e,h] | 29 | 14 | 43[e] |
| 24[c]/26[d] | 32 | 60[e] | | | | | 18 | 55[e,h] | 39 | | |
| 48 | 39 | 59[e] | | | | | | 50[h] | 35 | | |
| **CR DAS28-CRP <2.6 (% of patients)** | | | | | | | | | | | |
| 12[a]/14[b] | 14 | 36[e] | 8 | 28[e] | 10 | 31[e] | 6 | 29[e,h] | 18 | 9 | 29[e] |
| 24[c]/26[d] | 18 | 48[e] | | | | | 9 | 41[e,h] | 27 | | |
| 48 | 29 | 49[e] | | | | | | 38[j] | 28 | | |
| **SDAI ≤3.3 (% of patients)** | | | | | | | | | | | |
| 12[a]/14[b] | 6 | 16[e] | 1 | 14[e] | 3 | 10[f] | 3 | 12[e,j] | 7 | 5 | 9 |
| 24[c]/26[d] | 9 | 28[e] | | | | | 5 | 24[e,h] | 14 | | |
| 48 | 16 | 32[e] | | | | | | 25[j] | 17 | | |
| **CDAI ≤2.8 (% of patients)** | | | | | | | | | | | |
| 12[a]/14[b] | 6 | 16[e] | 1 | 13[e] | 3 | 9[f] | 3 | 13[e,i] | 8 | 5 | 8 |
| 24[c]/26[d] | 11 | 28[e] | | | | | 6 | 23[e,h] | 14 | | |
| 48 | 17 | 32[e] | | | | | | 25[j] | 17 | | |
| **Boolean Remission (% of patients)** | | | | | | | | | | | |
| 12[a]/14[b] | 6 | 13[f] | 1 | 9e | 4 | 10[f] | 2 | 10[e,i] | 4 | 2 | 7[g] |
| 24[c]/26[d] | 7 | 24[e] | | | | | 4 | 18[e,h] | 10 | | |
| 48 | 13 | 28[e] | | | | | | 21[j] | 15 | | |

**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; CDAI = Clinical Disease Activity Index; CR = Clinical Remission; CRP = c-reactive protein, csDMARD = conventional synthetic disease modifying anti-rheumatic drug; DAS28 = Disease Activity Score 28 joints; IR = inadequate responder; 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] p≤0.001 upadacitinib vs placebo or MTX comparison
[f] p≤0.01 upadacitinib vs placebo or MTX comparison
[g] p<0.05 upadacitinib vs placebo or MTX comparison
[h] p≤0.001 upadacitinib vs adalimumab comparison
[i] p≤0.01 upadacitinib vs adalimumab comparison
[j] p<0.05 upadacitinib vs adalimumab comparison

## Table 7: Components of ACR Response (mean change from baseline)[a]

| **Study** | **SELECT EARLY MTX-Naive** | | **SELECT MONO MTX-IR** | | **SELECT NEXT csDMARD-IR** | | **SELECT COMPARE MTX-IR** | | | **SELECT BEYOND bDMARD-IR** | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | MTX | UPA | MTX | UPA | PBO | UPA 15mg | PBO | UPA 15mg | ADA 40mg | PBO | UPA |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 15mg | | 15mg | | | | | | | 15mg |
| N | 314 | 317 | 216 | 217 | 221 | 221 | 651 | 651 | 327 | 169 | 164 |
| **Week** | | | | | | | | | | | |
| **Number of tender joints (0-68)** | | | | | | | | | | | |
| 12[b]/14[c] | -13 | -17[h] | -11 | -15[h] | -8 | -14[h] | -10 | -16[h,k] | -14 | -8 | -16[h] |
| 24[d]/26[e] | -16 | -19[h] | | | | | -9 | -18[h,j] | -15 | | |
| **Number of swollen joints (0-66)** | | | | | | | | | | | |
| 12[b]/14[c] | -10 | -12[h] | -8 | -11[h] | -6 | -9[h] | -7 | -11[h] | -10 | -6 | -11[h] |
| 24[d]/26[e] | -12 | -14 | | | | | -6 | -12[h] | -11 | | |
| **Pain[f]** | | | | | | | | | | | |
| 12[b]/14[c] | -25 | -36[h] | -14 | -26[h] | -10 | -30[h] | -15 | -32[h,i] | -25 | -10 | -26[h] |
| 24[d]/26[e] | -28 | -40[h] | | | | | -19 | -37[hj] | -32 | | |
| **Patient global assessment[f]** | | | | | | | | | | | |
| 12[b]/14[c] | -25 | -35[h] | -11 | -23[h] | -10 | -30[h] | -15 | -30[h,i] | -24 | -10 | -26[h] |
| 24[d]/26[e] | -28 | -39[h] | | | | | -18 | -36[h,j] | -30 | | |
| **Disability Index (HAQ-DI)[g]** | | | | | | | | | | | |
| 12[b]/14[c] | -0.5 | -0.8[h] | -0.3 | -0.7[h] | -0.3 | -0.6[h] | -0.3 | -0.6[h,j] | -0.5 | -0.2 | -0.4[h] |
| 24[d]/26[e] | -0.6 | -0.9[h] | | | | | -0.3 | -0.7[h,j] | -0.6 | | |
| **Physician global assessment[f]** | | | | | | | | | | | |
| 12[b]/14[c] | -35 | -46[h] | -26 | -40[h] | -23 | -38[h] | -25 | -39[h] | -36 | -26 | -39[h] |
| 24[d]/26[e] | -45 | -50[h] | | | | | -27 | -45[h,j] | -41 | | |
| **CRP (mg/L)** | | | | | | | | | | | |
| 12[b]/14[c] | -10.6 | -17.5[h] | -1.1 | -10.2[h] | -0.4 | -10.1[h] | -1.7 | -12.5[h,j] | -9.2 | -1.1 | -11.0[h] |
| 24[d]/26[e] | -11.6 | -18.4[h] | | | | | -1.5 | -13.5[h,j] | -10.3 | | |

**Abbreviations:**
ACR = American College of Rheumatology
ADA = adalimumab
bDMARD = biologic disease-modifying anti rheumatic drug
CRP = c-reactive protein
csDMARD = conventional synthetic disease-modifying anti-rheumatic drug
HAQ-DI = Health Assessment Questionnaire Disability Index
IR = inadequate responder
MTX = methotrexate
PBO = placebo
UPA = upadacitinib
[a] Data shown are mean
[b] SELECT-NEXT, SELECT-EARLY, SELECT-COMPARE, SELECT-BEYOND
[c] SELECT-MONOTHERAPY
[d] SELECT-EARLY
[e] SELECT-COMPARE
[f] Visual analog scale: 0 = best, 100 = worst
[g] Health Assessment Questionnaire-Disability Index: 0=best, 3=worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
[h] p≤0.001 upadacitinib vs placebo or MTX comparison
[i] p≤0.001 upadacitinib vs adalimumab comparison
j p≤0.01 upadacitinib vs adalimumab comparison

[k] 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 Weeks 26 and 48 (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 Weeks 26 and 48 in SELECT-COMPARE and as monotherapy compared to MTX at Week 24 in SELECT-EARLY (Table 8). Statistically significant results were also achieved for both erosion and joint space narrowing scores. The proportion of patients with no radiographic progression (mTSS change ≤ 0) was significantly higher with RINVOQ 15 mg compared to placebo at Weeks 26 and 48 (SELECT-COMPARE) and compared to MTX at Week 24 (SELECT-EARLY).

**Table 8: Radiographic Changes**

| **Study** | **SELECT EARLY MTX-Naive** | | **SELECT COMPARE MTX-IR** | | |
|---|---|---|---|---|---|
| Treatment Group | MTX | UPA 15 mg | PBO[a] | UPA 15mg | ADA 40mg |
| **Modified Total Sharps Score, mean change from baseline** | | | | | |
| Week 24[b]/26[c] | 0.7 | 0.1[f] | 0.9 | 0.2[e] | 0.1 |
| Week 48 | | | 1.7 | 0.3[e] | 0.4 |
| **Erosion Score, mean change from baseline** | | | | | |
| Week 24[b]/26[c] | 0.3 | 0.1[e] | 0.4 | 0[e] | 0 |
| Week 48 | | | 0.8 | 0.1[e] | 0.2 |
| **Joint Space Narrowing Score, mean change from baseline** | | | | | |
| Week 24[b]/26[c] | 0.3 | 0.1[g] | 0.6 | 0.2[e] | 0.1 |

| | | | | | |
|---|---|---|---|---|---|
| Week 48 | | | 0.8 | 0.2[e] | 0.2 |
| **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 | | | 74.1 | 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] p≤0.001 upadacitinib vs placebo or MTX comparison
[f] p≤0.01 upadacitinib vs placebo or MTX comparison
[g] p<0.05 upadacitinib vs placebo or MTX comparison

**Physical function response and health-related outcomes**

Treatment with RINVOQ 15 mg, alone or in combination with csDMARDs, resulted in a significant improvement in physical function compared to all comparators (placebo, MTX, adalimumab) as measured by HAQ-DI. Improvements were seen as early as Week 1 compared to placebo in SELECT-NEXT and SELECT-BEYOND and were maintained for up to 60 weeks. In SELECT-COMPARE, patients treated with RINVOQ 15 mg had significantly greater improvement in physical function compared to adalimumab as early as Week 8 and maintained through Week 48.

In all studies, treatment with RINVOQ 15 mg, alone or in combination with csDMARDs, resulted in a significantly greater improvement in pain compared to all comparators, as measured on a 0-100 visual analogue scale, at 12/14 weeks, with responses maintained for up to 48-60 weeks. Significantly greater pain reduction was seen as early as Week 1 compared to placebo and as early as Week 4 compared to adalimumab.

In all studies, treatment with RINVOQ 15 mg resulted in a significantly greater improvement in the mean duration and severity of morning joint stiffness compared to placebo or MTX. In SELECT-COMPARE, patients treated with RINVOQ 15mg had significantly greater improvement in severity of morning joint stiffness compared to adalimumab.

Across all studies, patients receiving RINVOQ 15 mg experienced significantly greater improvement from baseline in physical component summary (PCS) score of the Short Form Health Survey (SF-

36) compared to placebo, adalimumab, or MTX. In SELECT-EARLY, SELECT-MONOTHERAPY, and SELECT-COMPARE patients receiving RINVOQ 15 mg experienced significantly greater improvement from baseline in mental component summary (MCS) scores and in all 8 domains of SF-36 compared to placebo or MTX.

Fatigue was assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F) in SELECT-EARLY, SELECT-NEXT, SELECT-EARLY and SELECT- COMPARE studies. Treatment with RINVOQ 15 mg resulted in significant improvement in fatigue compared to placebo, MTX, or adalimumab.

RA-associated work instability was assessed by the Rheumatoid Arthritis-Work Instability Scale (RA-WIS) in employed patients in SELECT-NEXT and SELECT-COMPARE. Treatment with RINVOQ 15mg resulted in significantly greater reduction in work instability 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<br>AUC: ↑ 29%, $C_{max}$ ↑ 39% |
| **Distribution** | |
| % Bound to human plasma proteins | 52 |
| Blood-to-plasma ratio | 1.0 |
| **Metabolism** | |
| Metabolism | CYP3A4, CYP2D6 (minor)<br>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 Pre-clinical safety data

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

**Genotoxicity**

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

**Carcinogenicity**

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

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

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

Film coating contains polyvinyl alcohol, macrogol, 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

RINVOQ 15 mg modified release tablets: 24 months

## 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 blister with 7 tablets.

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

## 6.6 Special precautions for disposal

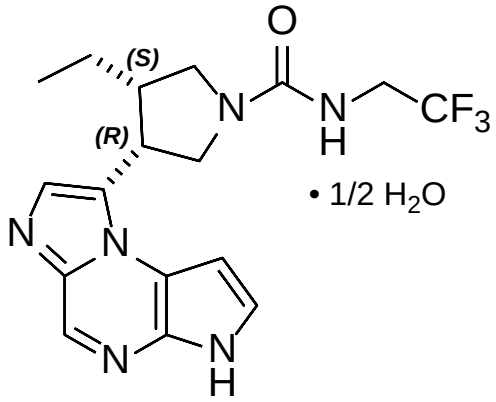
Any unused medicine or waste material should be disposed of in accordance with local requirements.

### 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 37°C.

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:




**CAS number**

1310726-60-3

## 7 MEDICINE SCHEDULE

Prescription Only Medicine

## 8 SPONSOR

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# 9 DATE OF FIRST APPROVAL

19 November 2020

# 10 DATE OF REVISION

14 January 2021

**Summary table of changes**

| Section Changed | Summary of new information |
|---|---|
| 4.4 Special Warnings and Precautions for Use | Update to viral reactivation and vaccination section |
| 5 Pharmacological Properties | Inclusion of Vaccine Study and update to Clinical Trials |