APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

RINVOQ 15 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

This professional information has been checked for grammatical and typographical errors.

CCDS0520 v3.0

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

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.

4.2 Posology and method of administration

Treatment with RINVOQ should be initiated and supervised by medical practitioners experienced in the diagnosis and treatment of rheumatoid arthritis.

Posology

The recommended dose of RINVOQ is 15 mg once daily.

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

Dose interruption

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

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

Table 1. Laboratory measures and monitoring guidance

Laboratory measure	**Action**	**Monitoring guidance**
Absolute Neutrophil Count (ANC)	Treatment should be interrupted if ANC is < 1,000 cells/mm^3 and may be	Evaluate at baseline and thereafter

	restarted once ANC returns above this value	according to routine patient management
Absolute Lymphocyte Count (ALC)	Treatment should be interrupted if ALC is < 500 cells/mm^3 and may be restarted once ALC returns above this value	
Haemoglobin (Hb)	Treatment should be interrupted if Hb is < 8 g/dL and may be restarted once Hb returns above this value	
Hepatic transaminases	Treatment should be temporarily interrupted if drug-induced liver injury is suspected	

Lipids	Patients should be managed according to international clinical guidelines for hyperlipidaemia	12 weeks after initiation of treatment and thereafter according to international clinical guidelines for hyperlipidaemia

Special populations

Elderly

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

Renal impairment

No dose adjustment is required in patients with mild or moderate renal impairment. There are limited data on the use of RINVOQ in subjects with severe renal impairment (see section 5.2).

RINVOQ 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.

Hepatic impairment

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

Paediatric population

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

Method of administration

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Immunosuppressive medicinal products

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

Serious infections

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

RINVOQ should not be initiated 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.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with RINVOQ. RINVOQ therapy should be interrupted 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 therapy should be interrupted if the patient is not responding to antimicrobial therapy. RINVOQ therapy may be resumed once the infection is controlled.

As there is a higher incidence of infections in the elderly ≥ 75 years of age, caution should be used when treating this population.

Tuberculosis

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

Consultation with a medical practitioner with expertise in the treatment of TB is recommended to aid in the decision about whether initiating anti-TB therapy is appropriate for an individual patient.

Patients should be monitored for the development of signs and symptoms of TB, including patients who tested negative for latent TB infection prior to initiating therapy.

Viral reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), was reported in clinical studies (see section 4.8). If a patient develops herpes zoster, interruption of RINVOQ therapy should be considered until the episode resolves.

Screening for viral hepatitis and monitoring for reactivation should be performed before starting and during therapy with 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 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.

Malignancy

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

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

Haematological abnormalities

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

Cardiovascular risk

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

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 section 4.8). Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy, although evidence is limited. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined (see section 4.2 for monitoring guidance).

Hepatic transaminase elevations

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

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

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

Venous thromboembolism

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

4.5 Interaction with other medicines and other forms of interaction

Potential for other medicinal products to affect the pharmacokinetics of RINVOQ

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

Coadministration with CYP3A4 inhibitors

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

Coadministration with CYP3A4 inducers

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

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

Potential for RINVOQ to affect the pharmacokinetics of other medicinal products

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

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

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

RINVOQ is contraindicated during pregnancy (see section 4.3).

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

Breastfeeding

Mothers taking RINVOQ should not breast-feed their babies (see section 4.3).

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

A risk to newborns/infants cannot be excluded.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse drug reactions (ADRs) are upper respiratory tract infections (13.5%), nausea (3.5%), blood creatine phosphokinase (CPK) increased (2.5%) and cough (2.2%). The most common serious adverse reactions were serious infections (see section 4.4).

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from registrational clinical studies.

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

Table 2. Adverse reactions

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System Organ Class	**Very common**	**Common**	**Uncommon**
Infections and infestations	Upper respiratory tract infections (URTI)*		Pneumonia Herpes zoster Herpes simplex** Oral candidiasis
Blood and lymphatic system disorders		Neutropaenia	
Metabolism and nutrition disorders		Hypercholesterolaemia	Hypertriglyceridaemia
Respiratory, thoracic and mediastinal disorders		Cough	
Gastrointestinal disorders		Nausea	

This professional information has been checked for grammatical and typographical errors.

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General disorders and administration site conditions		Pyrexia	
Investigations		Blood 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			

Description of selected 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 methotrexate (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 (2,630 patients) was 93.7 events per 100 patient-years.

In placebo-controlled clinical studies with background DMARDs, the frequency of serious infection over 12/14 weeks in the 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 common serious infection was pneumonia. The rate of serious infections remained stable with long-term exposure.

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

The frequencies of infection ADRs for RINVOQ compared to placebo were: URTI (13.5% vs 9.5%), pneumonia (0.5% vs 0.3%), herpes zoster (0.7% vs 0.2%), herpes simplex (0.8% v 0.5%), and oral candidiasis (0.4% vs. <0.1%). Most of the herpes zoster events involved a single dermatome and were non-serious.

Opportunistic infections (excluding tuberculosis)

In placebo-controlled clinical studies with background DMARDs, the frequency of opportunistic infections over 12/14 weeks in the 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.

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 15 mg treatment was associated with dose-dependent increases in lipid parameters including total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol. There was no change in the LDL/HDL ratio. Elevations were observed at 2 to 4 weeks of treatment and remained stable with longer-term treatment. Among patients in the controlled studies with baseline values below the specified limits, the following frequencies of patients were observed

to shift to above the specified limits on at least one occasion during 12/14 weeks (including patients who had an isolated elevated value):

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

Creatine phosphokinase

In placebo-controlled studies with background DMARDs, for up to 12/14 weeks, increases in CPK values were observed. CPK elevations > 5 x upper limit of normal (ULN) were reported in 1.0% and 0.3% of patients over 12/14 weeks in the 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 1,000 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 < 1,000 cells/mm^3 (see section 4.2). Mean neutrophil counts decreased over 4 to 8 weeks. The decreases in neutrophil counts remained stable at a lower value than baseline over time including with extended therapy.

<u>Reporting of suspected adverse reactions</u>

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug**

Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

RINVOQ was administered in clinical studies up to doses equivalent in daily AUC to 60 mg prolonged-release once daily. Adverse reactions were comparable to those seen at lower doses and no specific toxicities were identified. Approximately 90% of RINVOQ 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 supportive and symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 3.1 Antirheumatics (anti-inflammatory agents)

Mechanism of action

Janus Kinases (JAKs) are intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, 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 JAK inhibitor. In human cellular assays, upadacitinib preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2.

Pharmacodynamic effects

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

In healthy volunteers, the administration of upadacitinib (immediate release formulation) resulted in a dose- and concentration-dependent inhibition of IL-6 (JAK1/JAK2) - induced

STAT3 and IL-7 (JAK1/JAK3)-induced STAT5 phosphorylation in whole blood. The maximal inhibition was observed 1 hour after dosing which returned to near baseline by the end of dosing interval.

Lymphocytes

Treatment with upadacitinib was associated with a small, transient increase in mean ALC from baseline up to week 36 which gradually returned to at or near baseline levels with continued treatment.

hsCRP

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

Clinical efficacy and safety

Rheumatoid Arthritis

Upadacitinib was compared to placebo in SELECT-COMPARE, SELECT-NEXT, and SELECT-BEYOND; to MTX in SELECT-EARLY and SELECT-MONOTHERAPY; and to adalimumab in SELECT-COMPARE. The studied population included:

- patients naïve to MTX (SELECT-EARLY)
- patients who had inadequate response to MTX (SELECT-MONOTHERAPY and SELECT-COMPARE)
- patients who had inadequate response to csDMARDs (SELECT-NEXT)
- patients who had inadequate response or intolerance to at least one bDMARD (SELECT-BEYOND).

Across all studies, a significantly higher proportion of patients treated with upadacitinib 15 mg (alone or in combination with csDMARDs) achieved:

- both low disease activity (DAS28-CRP ≤3.2) and clinical remission (DAS28-CRP <2.6) compared to placebo, MTX, or adalimumab. Compared to adalimumab, significantly higher responses were achieved as early as Week 8 and maintained through Week 48. Significantly higher responses were also observed for other disease activity outcomes including CDAI ≤2.8, SDAI ≤3.3, and Boolean remission compared to placebo, MTX, or adalimumab. Overall, both low disease activity and clinical remission rates were consistent across patient populations.

- ACR20, ACR50, and ACR70 responses at 12 weeks compared to all comparators (placebo, MTX, and adalimumab) except for ACR70 compared to placebo in SELECT-BEYOND. 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.
- 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.
- ACR20/50/70 responses at Weeks 12 through 48 compared to adalimumab
- greater inhibition of the progression of structural joint damage compared to placebo at Weeks 26 and 48 and as monotherapy compared to MTX at Week 24. 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 upadacitinib 15 mg compared to placebo at Weeks 26 and 48 and compared to MTX at Week 24.
- 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 which were maintained for up to 60 weeks, and as early as Week 8 compared to adalimumab which were maintained through Week 48.

- greater improvement in pain compared to all comparators (placebo, MTX, and adalimumab) 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.
- greater improvement in the mean duration and severity of morning joint stiffness compared to placebo or MTX. Greater improvement in severity of morning joint stiffness was seen also compared to adalimumab.

Paediatric population

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

5.2 Pharmacokinetic properties

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

Absorption

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

Distribution

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

Metabolism

Upadacitinib metabolism is mediated by CYP3A4 with a potential minor contribution from CYP2D6. The pharmacologic activity of upadacitinib is attributed to the parent molecule. In a human radiolabeled study, unchanged upadacitinib accounted for 79% of the total radioactivity in plasma while the main metabolite (product of monooxidation followed by glucuronidation) accounted for 13% of the total plasma radioactivity. No active metabolites have been identified for upadacitinib.

Elimination

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

Renal impairment

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

and severe (estimated glomerular filtration rate 15 to 29 mL/min/1.73 m^2) renal impairment, respectively, compared to subjects with normal renal function. Upadacitinib C_{max} was similar in subjects with normal and impaired renal function.

Hepatic impairment

Mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment has no clinically relevant effect on upadacitinib exposure. Upadacitinib AUC was 28% and 24% higher in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal liver function. Upadacitinib C_{max} was unchanged in subjects with mild hepatic impairment and 43% higher in subjects with moderate hepatic impairment compared to subjects with normal liver function. Upadacitinib was not studied in patients with severe (Child-Pugh C) hepatic impairment.

Paediatric population

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

Intrinsic factors

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

5.3 Preclinical safety data

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

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

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

Upadacitinib had no effect on fertility in male or female rats at doses up to 50 mg/kg/day in males and 75 mg/kg/day in females in a fertility and early embryonic development study. Dose

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet contents:

Microcrystalline cellulose

Hypromellose

Mannitol

Tartaric acid

Silica, colloidal anhydrous

Magnesium stearate

Film coating:

Poly(vinyl alcohol)

Macrogol

Talc

Titanium dioxide (E171)

Iron oxide black (E172)

Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

This professional information has been checked for grammatical and typographical errors.

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6.3 Shelf life

2 years

6.4 Special precautions for storage

Store RINVOQ at or below 25 °C

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

6.5 Nature and contents of container

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

HDPE bottles with desiccant and polypropylene cap in carton containing 30 prolonged-release tablets.

This professional information has been checked for grammatical and typographical errors.

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Pack size: 1 bottle (30 prolonged-release tablets) or 3 bottles (90 prolonged-release tablets).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

AbbVie (Pty) Ltd

Abbott Place, 219 Golf Club Terrace

1709, Constantia Kloof

Republic of South Africa

Tel No: (011) 831 3200

This professional information has been checked for grammatical and typographical errors.

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8 REGISTRATION NUMBER(S)

54/3.1/0187

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

06 April 2022

10 DATE OF REVISION OF THE TEXT

Original application

This professional information has been checked for grammatical and typographical errors.

CCDS0520 v3.0