SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

RINVOQ 15 mg prolonged-release tablets

RINVOQ 30 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

RINVOQ 15 mg prolonged-release tablets

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

Sugar free.

For full list of excipients, see section 6.1.

RINVOQ 30 mg prolonged-release tablets

Each prolonged-release tablet contains upadacitinib hemihydrate, equivalent to 30 mg of upadacitinib.

Contains Mannitol 100,6 mg

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

RINVOQ 15 mg prolonged-release tablets

Prolonged-release tablet.

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

RINVOQ 30 mg prolonged-release tablets

Red 14 x 8 mm, oblong biconvex prolonged-release tablets imprinted on one side with ‘a30’.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

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

Psoriatic arthritis

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

Axial spondyloarthritis

Non-radiographic axial spondyloarthritis (nr-axSpA)

RINVOQ is indicated for the treatment of active non-radiographic axial spondyloarthritis in adult patients with objective signs of inflammation as indicated by elevated C-reactive protein (CRP)

and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs).

Ankylosing spondylitis (AS, radiographic axial spondyloarthritis)

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

Giant cell arteritis

RINVOQ is indicated for the treatment of giant cell arteritis in adult patients.

Atopic dermatitis

RINVOQ is indicated for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.

Ulcerative colitis

RINVOQ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent.

Crohn's Disease

RINVOQ is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response or were intolerant to either conventional therapy or biologic agent.

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 conditions for which RINVOQ is indicated.

Posology

Rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis

The recommended dose of RINVOQ is 15 mg once daily.

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

Giant cell arteritis

The recommended dose of RINVOQ is 15 mg once daily in combination with a tapering course of corticosteroids. Upadacitinib monotherapy should not be used for the treatment of acute relapses (see section 4.4).

Based upon the chronic nature of giant cell arteritis, RINVOQ 15 mg once daily can be continued as monotherapy following discontinuation of corticosteroids. Treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient choice.

Atopic dermatitis

The recommended dose of RINVOQ is 15 mg or 30 mg once daily based on individual patient presentation.

- A dose of 15 mg is recommended for patients at higher risk of venous thromboembolism (VTE), major adverse cardiovascular events (MACE) and malignancy (see section 4.4).

- A dose of 30 mg once daily may be appropriate for patients with high disease burden who are not at higher risk of VTE, MACE and malignancy (see section 4.4) or patients with an inadequate response to 15 mg once daily.
- In adolescents (12 to 17 years of age) weighing at least 30 kg, a dose of 15 mg is recommended. If the patient does not respond adequately to 15 mg once daily, the dose can be increased to 30 mg once daily.
- The lowest effective dose to maintain response should be used.

For patients 65 years of age and older, the recommended dose is 15 mg once daily (see section 4.4).

Concomitant topical therapies

RINVOQ can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used for sensitive areas such as the face, neck, and intertriginous and genital areas.

Consideration should be given to discontinuing RINVOQ treatment in any patient who shows no evidence of therapeutic benefit after 12 weeks of treatment.

Ulcerative colitis

Induction

The recommended induction dose of RINVOQ is 45 mg once daily for 8 weeks. For patients who do not achieve adequate therapeutic benefit by week 8, RINVOQ 45 mg once daily may be continued for an additional 8-week period (see section 5.1). RINVOQ should be discontinued in any patient who shows no evidence of therapeutic benefit by week 16.

Maintenance

The recommended maintenance dose of RINVOQ is 15 mg or 30 mg once daily based on individual patient presentation:

- A dose of 15 mg is recommended for patients at higher risk of VTE, MACE and malignancy (see section 4.4).
- A dose of 30 mg once daily may be appropriate for some patients, such as those with high disease burden or requiring 16-week induction treatment who are not at higher risk of VTE, MACE and malignancy (see section 4.4) or who do not show adequate therapeutic benefit to 15 mg once daily.
- The lowest effective dose to maintain response should be used.

For patients 65 years of age and older, the recommended dose is 15 mg once daily (see section 4.4).

In patients who have responded to treatment with RINVOQ, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

Crohn's disease

Induction

The recommended induction dose of RINVOQ is 45 mg once daily for 12 weeks. For patients who have not achieved adequate therapeutic benefit after the initial 12-week induction, prolonged induction for an additional 12 weeks with a dose of 30 mg once daily may be considered. For these patients RINVOQ should be discontinued if there is no evidence of therapeutic benefit after 24 weeks of treatment.

Maintenance

The recommended maintenance dose of RINVOQ is 15 mg or 30 mg once daily based on individual patient presentation:

- A dose of 15 mg is recommended for patients at higher risk of VTE, MACE and malignancy (see section 4.4).
- A dose of 30 mg once daily may be appropriate for patients with high disease burden who are not at higher risk of VTE, MACE and malignancy (see section 4.4) or who do not show adequate therapeutic benefit to 15 mg once daily.
- The lowest effective dose to maintain response should be used.

For patients 65 years of age and older, the recommended maintenance dose is 15 mg once daily (see section 4.4).

In patients who have responded to treatment with upadacitinib, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

Interactions

For patients with ulcerative colitis and Crohn's disease receiving strong inhibitors of cytochrome P450 (CYP) 3A4 (e.g., ketoconazole, clarithromycin), the recommended induction dose is 30 mg once daily and the recommended maintenance dose is 15 mg once daily (see section 4.5).

Dose initiation

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

Dose interruption

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

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

Table 1. Laboratory measures and monitoring guidance

Laboratory measure	**Action**	**Monitoring guidance**
Absolute Neutrophil Count (ANC)	Treatment should be interrupted if ANC is < 1,000 cells/mm^3 and may be restarted once ANC returns above this value	Evaluate at baseline and then no later than 12 weeks after initiation of treatment. Thereafter evaluate 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	Evaluate at baseline and thereafter according to routine patient management.
Lipids	Patients should be managed according to international clinical guidelines for hyperlipidaemia	Evaluate 12 weeks after initiation of treatment and thereafter according to international clinical guidelines for hyperlipidaemia

Special populations

Elderly

Rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis

There are limited data in patients aged 75 years and older (see section 4.4).

Atopic dermatitis

For atopic dermatitis, doses higher than 15 mg once daily are not recommended in patients 65 years of age and older (see sections 4.4 and 4.8).

Ulcerative colitis and Crohn's disease

For ulcerative colitis and Crohn's disease doses higher than 15 mg once daily for maintenance therapy are not recommended in patients 65 years of age and older (see sections 4.4 and 4.8). The

safety and efficacy of upadacitinib in patients 75 years of age and older have not yet been established.

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 as described in Table 2. The use of RINVOQ has not been studied in subjects with end stage renal disease and is therefore not recommended for use in these patients.

Table 2 Recommended dose for severe renal impairment[a]

Therapeutic indication	**Recommended once daily dose**
Rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, giant cell arteritis, atopic dermatitis	15 mg
Ulcerative colitis, Crohn's disease	Induction: 30 mg Maintenance: 15 mg
[a]estimated glomerular filtration rate (eGFR) 15 to < 30 ml/min/1.73m^2	

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 with atopic dermatitis below the age of 12 years have not been established. No data are available.

The safety and efficacy of RINVOQ in children and adolescents with rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, ulcerative colitis and Crohn's disease, aged 0 to less than 18 years have not yet been established. No data are available.

There is no relevant use of RINVOQ in the paediatric population in the indication giant cell arteritis. .

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 in order to ensure the entire dose is delivered correctly.

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

RINVOQ should only be used if no suitable treatment alternatives are available in patients:

- 65 years of age and older;
- patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers);

- patients with malignancy risk factors (e.g. current malignancy or history of malignancy)

Use in patients 65 years of age and older

Considering the increased risk of MACE, malignancies, serious infections, and all-cause mortality in patients 65 years of age and older, as observed in a large, randomised study of tofacitinib (another Janus Kinase (JAK) inhibitor), RINVOQ should only be used in these patients if no suitable treatment alternatives are available.

In patients 65 years of age and older, there is an increased risk of adverse reactions with RINVOQ 30 mg once daily. Consequently, the recommended dose for long-term use in this patient population is 15 mg once daily (see sections 4.2 and 4.8).

Immunosuppressive medicinal products

Combination with other potent immunosuppressants such as azathioprine, 6-mercaptopurine, 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 (see section 4.8) and cellulitis. Cases of bacterial meningitis and sepsis 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 (see section 4.3).

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.

A higher rate of serious infections was observed with RINVOQ 30 mg compared to RINVOQ 15 mg.

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. In patients 65 years of age and older, RINVOQ should only be used if no suitable treatment alternatives are available (see section 4.2).

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). The risk of herpes zoster appears to be higher in Japanese patients treated with RINVOQ. 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 vaccines in patients receiving RINVOQ. Use of live, attenuated vaccines during or immediately prior to RINVOQ therapy is not recommended. Prior to initiating RINVOQ treatment, it is recommended that patients be brought up

to date with all immunisations, including prophylactic zoster vaccinations, in agreement with current immunisation guidelines. (see section 5.1).

Malignancy

Lymphoma and other malignancies have been reported in patients receiving JAK inhibitors, including RINVOQ.

In a large randomised active controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of malignancies, particularly lung cancer, lymphoma and non-melanoma skin cancer (NMSC) was observed with tofacitinib compared to tumour necrosis factor (TNF) inhibitors.
A higher rate of malignancies was observed with RINVOQ 30 mg compared to RINVOQ 15 mg.

In patients 65 years of age and older, patients who are current or past long-time smokers, or with other malignancy risk factors (e.g., current malignancy or history of malignancy) RINVOQ should only be used if no suitable treatment alternatives are available.

Non-melanoma skin cancer (NMSC)

NMSCs have been reported in patients treated with RINVOQ (see section 4.8). A higher rate of NMSC was observed with RINVOQ 30 mg compared to RINVOQ 15 mg. Periodic skin examination is recommended for all patients, particularly those with risk factors 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).

Gastrointestinal perforations

Events of diverticulitis and gastrointestinal perforations have been reported in clinical trials and from post-marketing sources (see section 4.8).

RINVOQ should be used with caution in patients who may be at risk for gastrointestinal perforation (e.g., patients with diverticular disease, a history of diverticulitis, or who are taking nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or opioids). Patients with active Crohn's disease are at increased risk for developing intestinal perforation. Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of diverticulitis or gastrointestinal perforation.

Major adverse cardiovascular events

Events of MACE were observed in clinical studies of RINVOQ.

In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a higher rate of MACE, defined as cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal stroke, was observed with tofacitinib compared to TNF inhibitors.

Therefore, in patients 65 years of age and older, patients who are current or past long-time smokers, and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, RINVOQ should only be used if no suitable treatment alternatives are available.

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 (see section 4.8).

Hepatic transaminases must be evaluated 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) were observed in clinical trials for RINVOQ.

In a large randomised active-controlled study of tofacitinib (another JAK inhibitor) in rheumatoid arthritis patients 50 years and older with at least one additional cardiovascular risk factor, a dose dependent higher rate of VTE including DVT and PE was observed with tofacitinib compared to TNF inhibitors.

In patients with cardiovascular or malignancy risk factors (see also section 4.4 “Major adverse cardiovascular events” and “Malignancy”) RINVOQ should only be used if no suitable treatment alternatives are available.

In patients with known VTE risk factors other than cardiovascular or malignancy risk factors, RINVOQ should be used with caution. VTE risk factors other than cardiovascular or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy, and inherited coagulation disorder. Patients should be re-evaluated periodically during RINVOQ treatment to assess for changes in VTE risk. Patients with signs and symptoms of VTE should be promptly evaluated and treatment should be discontinued in patients with suspected VTE, regardless of dose.

Hypersensitivity reactions

Serious hypersensitivity reactions such as anaphylaxis and angioedema have been reported in patients receiving RINVOQ. If a clinically significant hypersensitivity reaction occurs, treatment with RINVOQ must be discontinued and ~~institute~~ appropriate therapy must be instituted (see sections 4.3 and 4.8).

Hypoglycaemia in patients treated for diabetes

There have been reports of hypoglycaemia following initiation of JAK inhibitors, including RINVOQ, in patients receiving treatment for diabetes. Dose adjustment of anti-diabetic medicinal products may be necessary in the event that hypoglycaemia occurs.

Medication Residue in Stool

Reports of medication residue in stool or ostomy output have occurred in patients taking RINVOQ. Most reports described anatomic (e.g., ileostomy, colostomy, intestinal resection) or functional gastrointestinal conditions with shortened gastrointestinal transit times. Patients should be instructed to contact their healthcare professional if medication residue is observed repeatedly. Patients should be clinically monitored, and alternative treatment should be considered if there is an inadequate therapeutic response.

Giant Cell Arteritis

RINVOQ monotherapy should not be used for the treatment of acute relapses as efficacy in this setting has not been established. Corticosteroids should be given according to medical judgement and practice guidelines.

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, clarithromycin and grapefruit). In a clinical study, coadministration of RINVOQ with ketoconazole resulted in 70% and 75% increases in RINVOQ C_{max} and AUC, respectively. RINVOQ 15 mg once daily should be used with caution in patients receiving chronic treatment with strong CYP3A4 inhibitors. RINVOQ 30 mg once daily dose

is not recommended for patients with atopic dermatitis receiving chronic treatment with strong CYP3A4 inhibitors. For patients with ulcerative colitis or Crohn's disease using strong CYP3A4 inhibitors, the recommended induction dose is 30 mg once daily and the recommended maintenance dose is 15 mg once daily (see section 4.2). Alternatives to strong CYP3A4 inhibitors should be considered when used in the long-term. Food or drink containing grapefruit should be avoided during treatment with RINVOQ.

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 or 45 mg once daily doses of RINVOQ to healthy subjects had a limited effect on midazolam (sensitive substrate for CYP3A) plasma exposures (24 - 26 % decrease in midazolam AUC and C_{max}), indicating that RINVOQ 30 mg or 45 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). Administration of multiple 45 mg once daily doses of RINVOQ to healthy subjects led to a limited increase in AUC and C_{max} of dextromethorphan (sensitive CYP2D6 substrate) by 30% and 35%, respectively, indicating that RINVOQ 45 mg once daily has a weak inhibitory effect on CYP2D6. No dose adjustment is recommended for CYP3A substrates, CYP2D6 substrates , 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, or CYP2C19.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraception during treatment and for 4 weeks following the final dose of RINVOQ. Female paediatric patients and/or their parents/caregivers should be informed about the need to contact the treating medical practitioner once the patient experiences menarche while taking 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 may have a minor influence on the ability to drive and use machines because dizziness and vertigo may occur during treatment with RINVOQ (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

In the placebo-controlled clinical trials for rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis, the most commonly reported adverse reactions (≥ 2 % of patients in at least one of the indications with the highest rate among indications presented) with RINVOQ 15 mg were upper respiratory tract infections (19,5 %), blood creatine phosphokinase (CPK) increased (8,6 %), alanine transaminase increased (4,3 %), bronchitis (3,9 %), nausea (3,5 %), neutropenia (2,8 %), cough (2,2 %), aspartate transaminase increased (2,2 %), and hypercholesterolaemia (2,2 %).

In the placebo-controlled atopic dermatitis clinical trials, the most commonly reported adverse reactions (≥ 2 % of patients) with RINVOQ 15 mg or 30 mg were upper respiratory tract infection (25,4 %), acne (15,1 %), herpes simplex (8,4 %), headache (6,3 %), blood CPK increased (5,5 %), cough (3,2 %), folliculitis (3,2 %), abdominal pain (2,9 %), nausea (2,7 %), neutropenia (2,3 %), pyrexia (2,1 %), and influenza (2,1 %).

In the placebo-controlled ulcerative colitis and Crohn's disease induction and maintenance clinical trials, the most commonly reported adverse reactions (≥3% of patients) with RINVOQ 45 mg, 30 mg or 15 mg were upper respiratory tract infection (19.9%), pyrexia (8.7%), blood CPK increased (7.6%), anemia (7.4%), headache (6.6%), acne (6.3%), herpes zoster (6.1%), neutropenia (6.0%), rash (5.2%), pneumonia (4.1%), hypercholesterolemia (4.0%), bronchitis (3.9%), aspartate transaminase increased (3.9%), fatigue (3.9%), folliculitis (3.6%), alanine transaminase increased (3.5%),herpes simplex (3.2%), and influenza (3.2%).

The most common serious adverse reactions were serious infections (see section 4.4).

The safety profile of RINVOQ with long term treatment was generally similar to the safety profile during the placebo-controlled period across indications.

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical studies and post-marketing experience. 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 to decrease seriousness.

The frequencies in Table 3 are based on the higher of the rates for adverse reactions reported with RINVOQ in clinical trials of rheumatologic disease (15 mg) and atopic dermatitis (15 mg and 30 mg), ulcerative colitis (15 mg, 30 mg and 45 mg) or Crohn's disease (15 mg, 30 mg and 45 mg). When notable differences in frequency were observed between indications, these are presented in the footnotes below the table.

Table 3. Adverse reactions

System Organ Class	Very common	Common	Uncommon
Infections and infestations	Upper respiratory tract infections (URTI)[a]	Bronchitis[a,b] Herpes zoster[a] Herpes simplex[a] Folliculitis Influenza Urinary tract infection Pneumonia [a,h]	Oral candidiasis Diverticulitis Sepsis
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Non-melanoma skin cancer[f]	
Blood and lymphatic system disorders		Anaemia[a] Neutropenia[a] Lymphopenia	
Immune system disorders		Urticaria[c,g]	Serious hypersensitivity reactions[a,e]

Metabolism and nutrition disorders		Hypercholesterolaemia[a,b] Hyperlipidaemia[a,b]	Hypertriglyceridaemia
Nervous system disorders		Headache[a,j] Dizziness	
Ear and labyrinth disorders		Vertigo[a]	
Respiratory, thoracic and mediastinal disorders		Cough	
Gastrointestinal disorders		Abdominal pain[a,d] Nausea	Gastrointestinal perforation[i]
Skin and subcutaneous tissue disorders	Acne[a,c,d,g]	Rash[a]	
General disorders and administration site conditions		Fatigue Pyrexia Peripheral oedema[a,k]	
Investigations		Blood CPK increased ALT increased[b] AST increased[b] Weight increased[g]	

[a] Presented as grouped term

[b] In atopic dermatitis trials, the frequency of bronchitis, hypercholesterolaemia, hyperlipidaemia ALT increased and AST increased was uncommon.

[c] In rheumatologic disease trials, the frequency was common for acne and uncommon for urticaria.

[d] In ulcerative colitis trials, the frequency was common for acne.

[e] Serious hypersensitivity reactions including anaphylactic reaction and angioedema

[f] Most events reported as basal cell carcinoma and squamous cell carcinoma of skin

[g] In Crohn's disease, the frequency was common for acne, and uncommon for urticaria and weight increased.

[h]Pneumonia was common in Crohn's disease and uncommon across other indications.

[i] Frequency is based on Crohn's disease clinical trials.

[j] Headache was very common in the giant cell arteritis trial.

[k] Frequency is based on the giant cell arteritis trial.

Description of selected adverse reactions

Rheumatoid arthritis

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.

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.

The long-term rate of herpes zoster for the RINVOQ 15 mg group across all five Phase 3 clinical studies was 3,7 events per 100 patient-years. Most of the herpes zoster events involved a single dermatome and were non-serious.

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. Of the 22 cases of hepatic transaminase elevations, most 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.

Neutropenia

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.

Psoriatic arthritis

Overall, the safety profile observed in patients with active psoriatic arthritis treated with RINVOQ 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis. A higher rate of serious infections (2,6 events per 100 patient- years and 1,3 events per 100 patient- years, respectively) and hepatic transaminase elevations (ALT elevations Grade 3 and higher rates 1,4 % and 0,4 %, respectively) was observed in patients treated with RINVOQ in combination with MTX therapy compared to patients treated with monotherapy.

Axial spondyloarthritis

Overall, the safety profile observed in patients with active axial spondyloarthritis treated with RINVOQ 15 mg was consistent with the safety profile observed in patients with rheumatoid arthritis. No new safety findings were identified.

Giant cell arteritis

Overall, the safety profile observed in patients with giant cell arteritis treated with RINVOQ 15 mg was generally consistent with the known safety profile for RINVOQ.

Serious Infections

In the placebo-controlled clinical study, the frequency of serious infections over 52 weeks was 5,7% in the RINVOQ 15 mg group and 10,7% in the placebo group. The long-term rate of serious infections for the RINVOQ 15 mg group was 2,9 events per 100 patient-years.

Opportunistic infections (excluding tuberculosis)

In the placebo-controlled clinical study, the frequency of opportunistic infection (excluding tuberculosis and herpes zoster) over 52 weeks was 1,9% in the RINVOQ 15 mg group and 0,9% in the placebo group. The long-term rate of opportunistic infections (excluding tuberculosis and herpes zoster) for the RINVOQ 15 mg group was 0,6 events per 100 patient-years.

In the placebo-controlled clinical study, the frequency of herpes zoster over 52 weeks was 5,3% in the RINVOQ 15 mg group and 2,7% in the placebo group. The long-term rate of herpes zoster for the RINVOQ 15 mg group was 4,1 events per 100 patient-years.

Atopic dermatitis

Infections

In the placebo-controlled period of the clinical studies, the frequency of infection over 16 weeks in the RINVOQ 15 mg and 30 mg groups was 39 % and 43 % compared to 30 % in the placebo group, respectively. The long-term rate of infections for the RINVOQ 15 mg and 30 mg groups was 98,5 and 109,6 events per 100 patient-years, respectively.

In placebo-controlled clinical studies, the frequency of serious infection over 16 weeks in the RINVOQ 15 mg and 30 mg groups was 0,8 % and 0,4 % compared to 0,6 % in the placebo group, respectively. The long-term rate of serious infections for the RINVOQ 15 mg and 30 mg groups was 2,3 and 2,8 events per 100 patient-years, respectively.

Opportunistic infections (excluding tuberculosis)

In the placebo-controlled period of the clinical studies, all opportunistic infections (excluding TB and herpes zoster) reported were eczema *herpeticum*. The frequency of eczema *herpeticum* over 16 weeks in the RINVOQ 15 mg and 30 mg groups was 0,7 % and 0,8 % compared to 0,4 % in the placebo group, respectively. The long-term rate of eczema *herpeticum* for the RINVOQ 15 mg and 30 mg groups was 1,6 and 1,8 events per 100 patient-years, respectively. One case of oesophageal candidiasis was reported with RINVOQ 30 mg.

The long-term rate of herpes zoster for the RINVOQ 15 mg and 30 mg groups was 3,5 and 5,2 events per 100 patient-years, respectively. Most of the herpes zoster events involved a single dermatome and were non-serious.

Laboratory abnormalities

Dose-dependent changes in ALT increased and/or AST increased ≥ 3 x ULN), lipid parameters, CPK values (> 5 x ULN), and neutropenia (ANC < 1 x 10^9 cells/L) associated with 15 and 30 mg RINVOQ treatment were similar to what was observed in the rheumatologic disease clinical studies.

Small increases in LDL cholesterol were observed after week 16 in atopic dermatitis studies. At week 52, the mean increase in LDL cholesterol from baseline was 0,41 mmol/L for RINVOQ 15 mg and 0.56 mmol/L RINVOQ 30 mg.

Ulcerative colitis

The overall safety profile observed in patients with ulcerative colitis was generally consistent with that observed in patients with rheumatoid arthritis.

A higher rate of herpes zoster was observed with an induction treatment period of 16 weeks vs 8 weeks.

Infections

In the placebo-controlled induction studies, the frequency of infection over 8 weeks in the RINVOQ 45 mg group compared to the placebo group was 20.7% and 17.5%, respectively. In the placebo-controlled maintenance study, the frequency of infection over 52 weeks in the RINVOQ 15 mg and 30 mg groups was 40.4% and 44.2%, respectively, compared to 38.8% in the placebo group. The long-term rate of infections for RINVOQ 15 mg and 30 mg was 64.5 and 77.8 events per 100 patient-years, respectively.

In the placebo-controlled induction studies, the frequency of serious infection over 8 weeks in both the RINVOQ 45 mg group and the placebo group was 1.3%. No additional serious infections were observed over 8-week extended treatment with RINVOQ 45 mg. In the placebo-controlled

maintenance study, the frequency of serious infection over 52 weeks in the RINVOQ 15 mg and 30 mg groups was 3.6% and 3.2%, respectively, compared to 3.3% in the placebo group. The long-term rate of serious infections for the RINVOQ 15 mg and 30 mg groups was 3.0 and 4.6 events per 100 patient-years, respectively. The most frequently reported serious infection in the induction and maintenance phases was COVID-19 pneumonia

Opportunistic infections (excluding tuberculosis)

In the placebo-controlled induction studies over 8 weeks, the frequency of opportunistic infection (excluding tuberculosis and herpes zoster) in the RINVOQ 45 mg group was 0.4% and 0.3% in the placebo group. No additional opportunistic infections (excluding tuberculosis and herpes zoster) were observed over 8-week extended treatment with RINVOQ 45 mg. In the placebo-controlled maintenance study over 52 weeks, the frequency of opportunistic infection (excluding tuberculosis and herpes zoster) in the RINVOQ 15 mg and 30 mg groups was 0.8% and 0.8%, respectively, compared to 0.8% in the placebo group. The long-term rate of opportunistic infections (excluding tuberculosis and herpes zoster) for the upadacitinib 15 mg and 30 mg groups was 0.3 and 0.6 events per 100 patient-years, respectively.

In the placebo-controlled induction studies over 8 weeks, the frequency of herpes zoster in the RINVOQ 45 mg group was 0.6% and 0% in the placebo group. The frequency of herpes zoster was 3.9% over 16-week treatment with RINVOQ 45 mg. In the placebo-controlled maintenance study over 52 weeks, the frequency of herpes zoster in the RINVOQ 15 mg and 30 mg groups was 4.8% and 5.6%, respectively, compared to 0% in the placebo group. The long-term rate of herpes zoster for the RINVOQ 15 mg and 30 mg groups was 4.5 and 7.2 events per 100 patient-years, respectively.

Gastrointestinal perforations

In the placebo-controlled maintenance period, gastrointestinal perforation was reported in 1 patient treated with placebo (1.5 per 100 patient-years) and no patients treated with RINVOQ 15 mg or 30 mg. In the long-term extension study, 1 patient treated with RINVOQ 15 mg (0.1 per 100 patient-years) and 1 patient treated with RINVOQ 30 mg (<0.1 per 100 patient-years) reported events.

Laboratory abnormalities

In the induction and maintenance clinical studies, the laboratory changes in ALT increased and/or AST increased (≥ 3 x ULN), CPK values (> 5 x ULN), and neutropaenia (ANC < 1 x 10^9 cells/L) associated with RINVOQ treatment were generally similar to what was observed in the rheumatologic disease and atopic dermatitis clinical studies. Dose-dependent changes for these laboratory parameters associated with 15 mg and 30 mg RINVOQ treatment were observed.

In the placebo-controlled induction studies for up to 8 weeks, decreases in lymphocyte counts below 0.5 x 10^9 cells/L in at least one measurement occurred in 2.0% and 0.8% of patients in the RINVOQ 45 mg and placebo groups, respectively. In the placebo-controlled maintenance study, for up to 52 weeks, decreases in lymphocyte counts below 0.5 x 10^9 cells/L in at least one measurement occurred in 1.6%, 1.2% and 0.8% of patients in the RINVOQ 15 mg 30 mg and placebo groups, respectively. In clinical studies, treatment was interrupted in response to ALC < 0.5 x 10^9 cells/L (see section 4.2). No notable mean changes of lymphocyte counts were observed during RINVOQ treatment over time.

Elevations in lipid parameters were observed at 8 weeks of treatment with RINVOQ 45 mg and remained generally stable with longer-term treatment with RINVOQ 15 mg and 30 mg. Among patients in the placebo-controlled induction 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 8 weeks (including patients who had an isolated elevated value):

- Total cholesterol ≥ 5.17 mmol/L (200 mg/dL): 49% vs. 11%, in the upadacitinib 45 mg and placebo groups, respectively
- LDL cholesterol ≥ 3.36 mmol/L (130 mg/dL): 27% vs. 9%, in the upadacitinib 45 mg and placebo groups, respectively
- HDL cholesterol ≥ 1.03 mmol/L (40 mg/dL): 79% vs. 36%, in the upadacitinib 45 mg and placebo groups, respectively
- Triglycerides ≥ 2.26 mmol/L (200 mg/dL): 6% vs 4% in the upadacitinib 45 mg and placebo groups, respectively

Crohn's disease

Overall, the safety profile observed in patients with Crohn's disease treated with RINVOQ was consistent with the known safety profile for RINVOQ.

Serious infections

In the placebo-controlled induction studies, the frequency of serious infection over 12 weeks in the RINVOQ 45 mg group and the placebo group was 1.9% and 1.7%, respectively. In the placebo-controlled maintenance study, the frequency of serious infection over 52 weeks in the RINVOQ 15 mg and 30 mg groups was 3.2% and 5.7%, respectively, compared to 4.5% in the

placebo group. The long-term rate of serious infections for the RINVOQ 15 mg and 30 mg groups in patients who responded to RINVOQ 45 mg as induction treatment was 5.1 and 7.3 events per 100 patient-years, respectively. The most frequently reported serious infection in the induction and maintenance studies was gastrointestinal infections.

Gastrointestinal perforations

During the placebo-controlled period in the Phase 3 induction clinical studies, gastrointestinal perforation was reported in 1 patient (0.1%) treated with RINVOQ 45 mg and no patients on placebo through 12 weeks. In all patients treated with RINVOQ 45 mg (n=938) during the induction studies, gastrointestinal perforation was reported in 4 patients (0.4%).

In the long-term placebo-controlled period, gastrointestinal perforation was reported in 1 patient each treated with placebo (0.7 per 100 patient-years), upadacitinib 15 mg (0.4 per 100 patient-years), and RINVOQ 30 mg (0.4 per 100 patient-years). In all patients treated with rescue RINVOQ 30 mg (n=336), gastrointestinal perforation was reported in 3 patients (0.8 per 100 patient-years) through long-term treatment.

Laboratory abnormalities

In the induction and maintenance clinical studies, the laboratory changes in ALT increased and/or AST increased (≥ 3 x ULN), CPK values (> 5 x ULN), neutropaenia (ANC < 1 x 10^9 cells/L), and lipid parameters associated with RINVOQ treatment were generally similar to what was observed in the rheumatologic disease, atopic dermatitis and ulcerative colitis clinical studies. Dose-dependent

changes for these laboratory parameters associated with 15 mg and 30 mg RINVOQ treatment were observed.

In the placebo-controlled induction studies for up to 12 weeks, decreases in lymphocyte counts below 0.5 x 10^9 cells/L in at least one measurement occurred in 2.2% and 2.0% of patients in the RINVOQ 45 mg and placebo groups, respectively. In the placebo-controlled maintenance study, for up to 52 weeks, decreases in lymphocyte counts below 0.5 x 10^9 cells/L in at least one measurement occurred in 4.6%, 5.2% and 1.8% of patients in the upadacitinib 15 mg, 30 mg and placebo groups, respectively. In clinical studies, treatment was interrupted in response to ALC < 0.5 x 10^9 cells/L (see section 4.2). No notable mean changes of lymphocyte counts were observed during RINVOQ treatment over time.

In the placebo-controlled induction studies for up to 12 weeks, decreases in haemoglobin concentration to below 8 g/dL in at least one measurement occurred in 2.7% and 1.4% of patients in the RINVOQ 45 mg and placebo groups, respectively. In the placebo-controlled maintenance study, for up to 52 weeks, decreases in haemoglobin concentration below 8 g/dL in at least one measurement occurred in 1.4%, 4.4% and 2.8% of patients in the RINVOQ 15 mg, 30 mg and placebo groups, respectively. In clinical studies, treatment was interrupted in response to Hb < 8 g/dL (see section 4.2). No notable mean changes of haemoglobin concentration were observed during RINVOQ treatment over time.

Elderly

Based on the limited data from patients 65 years and older with atopic dermatitis, ulcerative colitis and Crohn's disease, there was a higher rate of overall adverse reactions with the RINVOQ 30 mg dose compared to the 15 mg dose (see section 4.4).

Paediatric population

A total of 541 adolescents aged 12 to 17 years with atopic dermatitis were treated in the global Phase 3 studies (n=343) and the supplemental adolescent substudies (n=198), of whom 264 were exposed to 15 mg and 265 were exposed to 30 mg. The safety profile for RINVOQ 15 mg and RINVOQ 30 mg in adolescents was similar to that in adults. With long-term exposure, the adverse drug reaction of skin papilloma was reported in 3,4% and 6,8% of adolescent patients with atopic dermatitis in the RINVOQ 15 mg and 30 mg groups, respectively.

Reporting of suspected adverse reactions

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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

You can also report side effects to AbbVie (Pty) Ltd via this e-mail address: MEAPV@abbvie.com

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

Upadacitinib is a selective and reversible Janus Kinases (JAK) inhibitor. 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.

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.

Atopic dermatitis is driven by pro-inflammatory cytokines (including IL-4, IL-13, IL-22, TSLP, IL-31 and IFN-γ) that transduce signals via the JAK1 pathway. Inhibiting JAK1 with upadacitinib reduces the signaling of many mediators which drive the signs and symptoms of atopic dermatitis such as eczematous skin lesions and pruritus.

Pro-inflammatory cytokines (primarily IL-6, IL-7, IL-15 and IFNγ) transduce signals via the JAK1 pathway and are involved in the pathology of inflammatory bowel diseases. JAK1 inhibition with

upadacitinib modulates the signalling of the JAK-dependent cytokines underlying the inflammatory burden and signs and symptoms of inflammatory bowel diseases.

Pharmacodynamic effects

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

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

Lymphocytes

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

hsCRP

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

Vaccine studies

The influence of upadacitinib on the humoral response following administration of adjuvanted recombinant glycoprotein E herpes zoster vaccine was evaluated in 93 patients with rheumatoid arthritis under stable treatment with upadacitinib 15 mg. 98% of patients were on concomitant methotrexate. 49% of patients were on oral corticosteroids at baseline. The primary endpoint was the proportion of patients with a satisfactory humoral response defined as ≥ 4-fold increase in pre-

vaccination concentration of anti-glycoprotein E titer levels at week 16 (4 weeks post-dose 2 vaccination). Vaccination of patients treated with upadacitinib 15 mg resulted in a satisfactory humoral response in 79/90 (88% [95% CI: 81.0, 94.5]) of patients at week 16.

The influence of upadacitinib on the humoral response following the administration of inactivated pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) 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. The primary endpoint was the proportion of patients with satisfactory humoral response defined as ≥ 2-fold increase in antibody concentration from baseline to Week 4 in at least 6 out of the 12 pneumococcal antigens (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F). Results at Week 4 demonstrated 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 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 and were maintained through 3 years.
- 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 through 3 years among the patients who remained on their originally allocated treatment.
- 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. Inhibition of progression of structural joint damage was

maintained through Week 96 in both studies for patients who remained on their originally allocated treatment with upadacitinib 15 mg.

- 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. Improvement in HAQ-DI was maintained through 3 years for patients who remained on their originally allocated treatment with upadacitinib 15 mg based on available results from SELECT COMPARE and SELECT EARLY.
- 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.

Psoriatic Arthritis

Upadacitinib was compared to placebo in SELECT-PsA 1 (non-biologic DMARD-IR population) and SELECT-PsA 2 (biologic DMARD-IR population) studies, and to adalimumab in SELECT-PsA 1 study. In SELECT-PsA 1, upadacitinib 15 mg achieved non-inferiority compared to adalimumab in the proportion of patients achieving ACR20 response at Week 12.

A significantly higher proportion of patients treated with upadacitinib 15 mg compared to placebo achieved:

- ACR20 response and HAQ-DI improvement at Week 12
- minimal disease activity (MDA) and resolution of enthesitis at Week 24
- PASI75 and sIGA responses at Week 16.

A higher proportion (nominal $p < 0.05$) of patients treated with upadacitinib 15 mg achieved:

- ACR50, ACR70 responses at week 12, and resolution of dactylitis at Week 24 compared to placebo
- ACR20, ACR50, and ACR70 responses compared to adalimumab at Week 24
- PASI90/100 responses compared to placebo at Week 16
- improvements in individual ACR components, including tender/painful and swollen joint counts, patient and physician global assessments, HAQ-DI, pain assessment, and hsCRP compared to placebo at Weeks 12 and 24.

Greater improvements compared to adalimumab were observed in pain and patient global assessment at Week 24, and HAQ-DI at Weeks 12 and 24.

Significantly greater improvement from baseline in the Physical Component of SF-36 quality of life score compared to placebo at Week 12 was achieved. Greater improvement was observed in the Mental Component Summary score and all 8 domains of SF-36 (Physical Functioning, Bodily Pain, Vitality, Social Functioning, Role Physical, General Health, Role Emotional, and Mental Health) compared to placebo. Greater improvement of Physical component SF-36 score was also observed compared to adalimumab. Significantly greater improvement from baseline in fatigue, as measured by Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score, at Week 12 compared to placebo was also demonstrated.

Improvements from baseline in the symptoms of psoriatic spondylitis were observed as assessed by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity (ASDAS) scores compared to placebo at Week 24. Greater improvements were also observed compared to adalimumab at Week 24.

Significantly greater inhibition of the progression of structural joint damage compared to placebo at Week 24 was observed. 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 higher with upadacitinib 15 mg compared to placebo at Week 24.

Response rates for all measures were maintained through Week 56. Time to onset of efficacy was rapid across measures with greater responses seen as early as Week 2 for ACR20.
Consistent responses were observed alone or in combination with non-biologic DMARDs for primary and key secondary endpoints. The efficacy of upadacitinib 15 mg was demonstrated regardless of subgroups evaluated including baseline BMI, baseline hsCRP, and number of prior non-biologic DMARDs (≤ 1 or >1).

Axial spondyloarthritis

Non-radiographic axial spondyloarthritis

upadacitinib 15 mg was studied in patients who had an inadequate response to at least two NSAIDs or had intolerance to or contraindication for NSAIDs, and patients with inadequate response or intolerance to bDMARD therapy. Patients must have had objective signs of inflammation indicated by elevated CRP (defined as > upper limit of normal), and/or sacroiliitis on MRI, and no definitive radiographic evidence of structural damage on sacroiliac joints.

By Week 14, a significantly higher proportion of patients treated with upadacitinib 15 mg achieved ASAS40, ASAS20 responses, ASAS Partial Remission, BASDAI50, ASDAS Inactive Disease, and ASDAS Low Disease Activity; there was also a significant improvement from baseline in ASDAS-CRP compared to placebo.

By Week 14, a higher proportion (nominal p value ≤0.001) of patients treated with upadacitinib 15 mg achieved

- ASDAS Major Improvement.
- improvements in individual ASAS components, including patient global assessment of disease activity and inflammation (captured as part of BASDAI) compared to placebo.

Significant improvements in physical function as assessed by the BASFI were achieved compared to placebo.

Patients showed significant improvements in total back pain and nocturnal back pain compared to placebo. Improvements were observed as early as Week 2 for total back pain and Week 4 for nocturnal back pain.

Significant improvements in health-related quality of life and overall health as measured by Ankylosing Spondylitis Quality of Life (ASQoL) and ASAS Health Index, respectively, were achieved compared to placebo. Greater improvements from baseline in fatigue as measured by FACIT-F were also observed compared to placebo.

Improvement in enthesitis as measured by change from baseline in MASES in patients with pre-existing enthesitis was also observed.

Significant improvements of inflammatory signs as assessed by MRI in the sacroiliac joints were achieved compared to placebo.

Improvements of inflammatory signs as measured by MRI in the spine and hsCRP were also observed.

Time to onset of efficacy was rapid across measures with greater responses seen as early as Week 2 for ASAS40. The efficacy of upadacitinib 15 mg was demonstrated across subgroups including gender, baseline BMI, symptom duration of non-radiographic axial spondyloarthritis, baseline hsCRP, MRI sacroiliitis, and prior use of bDMARDs.

Ankylosing Spondylitis (*AS, radiographic axial spondyloarthritis)*

Upadacitinib was compared to placebo in SELECT-AXIS 1 (NSAID-IR, biologic DMARD-naive population) and SELECT-AXIS 2 (Study 1) (NSAID-IR, biologic DMARD-IR population).

In both studies, by Week 14, a significantly higher proportion of patients treated with upadacitinib 15 mg achieved ASAS40, ASAS Partial Remission, and BASDAI50; there was also a significant improvement from baseline in ASDAS-CRP compared to placebo.

In SELECT-AXIS 2 (Study 1) by Week 14, a significantly higher proportion of patients treated with upadacitinib 15 mg also achieved ASAS20, ASDAS Inactive Disease, ASDAS Low Disease Activity; similar responses were observed in SELECT-AXIS 1 (nominal p value ≤0.001) .

Improvements in individual ASAS components were observed in both studies, including patient global assessment of disease activity, total back pain assessment, and inflammation compared to placebo. Significant improvements in physical function as assessed by the BASFI were achieved compared to placebo in both studies.

Patients showed improvement in back pain as assessed by the Total Back Pain component of ASAS response and the overall level of neck, back, or hip pain using BASDAI Question 2. Improvements were also demonstrated for peripheral pain and swelling (assessed by BASDAI question 3) and nocturnal back pain. Improvements in total and nocturnal back pain were observed as early as Week 2 in SELECT-AXIS 1. Improvements were observed as early as Week 1 for total back pain and Week 2 for nocturnal back pain in SELECT-AXIS 2 (Study 1).

Significant improvement in enthesitis as measured by change from baseline in MASES (Maastrich Ankylosing Spondylitis Enthesitis Score) in patients with pre-existing enthesitis were achieved compared to placebo in SELECT AXIS 2 (Study 1).

Significant improvements in health-related quality of life and overall health, as measured by ASQoL and ASAS Health Index, respectively were also achieved compared to placebo in SELECT AXIS 2 (Study 1), as was greater improvement from baseline in fatigue as measured by FACIT-F compared to placebo. Similar responses for ASQoL and ASAS Health Index were observed in SELECT-AXIS 1 (nominal p value ≤0.05).

Significant improvement in spinal mobility as measured by change from baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI) was also achieved in SELECT AXIS 2 (Study 1) compared to placebo.

Significant improvement of inflammatory signs in the spine and improvement of inflammatory signs in sacroiliac joints assessed by MRI, expressed as change from baseline in the SPARCC score, was achieved compared to placebo in both studies.

Improvement of inflammatory signs as measured by hsCRP was also observed.

Time to onset of efficacy was rapid across measures with greater responses seen for ASAS40 as early as Week 2 in SELECT-AXIS 1 and Week 4 in SELECT-AXIS 2 (Study 1). Efficacy across measures was maintained through 2 years in SELECT-AXIS 1.

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

Giant Cell Arteritis

Upadacitinib was compared to placebo in SELECT-GCA in patients 50 years of age and older with new onset or relapsing giant cell arteritis. Patients received upadacitinib once daily doses of 15 mg, 7.5 mg, or placebo for 52 weeks. All patients received background corticosteroid (prednisone or prednisolone) therapy. The upadacitinib-treated groups followed a pre-specified corticosteroid taper regimen with the aim to reach 0 mg by 26 weeks; the placebo-treated group followed a pre-specified corticosteroid taper regimen with the aim to reach 0 mg by 52 weeks.

Upadacitinib 15 mg and a 26-week corticosteroid taper showed superiority in achieving corticosteroid-free sustained remission (defined as having achieved both the absence of GCA signs and symptoms from Week 12 through Week 52 and adherence to the protocol-defined corticosteroid taper regimen) at Week 52 compared to placebo and a 52-week corticosteroid taper.

A significantly greater proportion of patients treated with upadacitinib 15 mg and a 26-week corticosteroid taper compared to placebo and a 52-week corticosteroid taper through Week 52 experienced:

- Sustained complete remission at Week 52. Sustained complete remission is defined as having achieved absence of GCA signs and symptoms from Week 12 through Week 52, normalization of ESR (to ≤ 30 mm/hr; if ESR > 30 mm/hr and elevation is not attributable to GCA, this criterion can still be met) from Week 12 through Week 52, normalization of hsCRP to < 1 mg/dL without elevation to ≥ 1 mg/dL (on 2 consecutive visits) from Week 12 through Week 52, and adherence to the protocol-defined corticosteroid taper regimen.
- Complete remission at Weeks 24 and 52

  A significantly lower proportion of patients treated with upadacitinib 15 mg and a 26-week corticosteroid taper experienced at least one GCA flare compared to placebo and a 52-week corticosteroid taper through Week 52.

Patients treated with upadacitinib 15 mg, and a 26-week corticosteroid taper compared to placebo and a 52-week corticosteroid taper through Week 52 also experienced:

- a significantly lower risk of flare as measured by time to first flare
- significantly lower cumulative corticosteroid exposure at Week 52 (among patients who completed 52 weeks of follow-up)
- significantly greater improvement in fatigue as measured by FACIT-Fatigue score from baseline at Week 52
- significantly greater improvement in health-related quality of life as measured by the Physical Component Summary score of SF-36 from baseline at Week 52

Atopic Dermatitis

Upadacitinib was compared to placebo in MEASURE UP 1, MEASURE UP 2, and AD UP in patients 12 years of age and older. In all three studies, patients received upadacitinib once daily doses of 15 mg, 30 mg or matching placebo for 16 weeks. In the AD UP study, patients also received concomitant topical corticosteroids (TCS).

In all three studies, a significantly greater proportion of patients treated with upadacitinib 15 mg or 30 mg achieved:

- vIGA-AD 0 or 1 response compared to placebo at week 16
- EASI 75 response compared to placebo at week 2 and week 16
- EASI 90 and EASI 100 response compared to placebo at week 16
- ≥ 4-point improvement on the Worst Pruritus NRS compared to placebo at week 16
- Rapid improvements in itch (week 1) and skin clearance (week 2) compared to placebo

In the MEASURE UP studies, a significantly greater proportion of patients treated with upadacitinib 15 mg or 30 mg achieved:

- ≥ 4-point improvement in ADerm-SS Skin Pain
- ≥ 12-point improvement in ADerm-IS Sleep
- DLQI 0 or 1
- HADS Anxiety < 8 and HADS Depression < 8

Results at week 16 continued to be maintained through week 52 in patients treated with upadacitinib 15 mg or 30 mg.

Ulcerative Colitis

Upadacitinib was compared to placebo in two replicate induction studies, UC-1 (U-ACHIEVE Induction) and UC-2 (U-ACCOMPLISH), and a maintenance study UC-3 (U-ACHIEVE Maintenance). All enrolled patients demonstrated prior treatment failure including inadequate response, loss of response, or intolerance to prior conventional and/or biologic treatment.

In UC-1 and UC-2, patients were randomised to upadacitinib 45 mg once daily or placebo for 8 weeks. By Week 8 of both studies, a significantly greater proportion of patients treated with upadacitinib 45 mg once daily compared to placebo achieved:

- Clinical remission per aMS, defined as SFS≤ 1 and not greater than baseline, RBS = 0, ES ≤ 1 without friability
- Clinical response per aMS, defined as decrease ≥ 2 points and ≥ 30% from baseline and a decrease in RBS ≥ 1 from baseline or an absolute RBS ≤ 1.
- Mucosal healing, defined as ES ≤ 1 without friability
- Histologic-endoscopic mucosal healing, defined as ES ≤ 1 without friability and Geboes score ≤ 3.1 (indicating neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue.)
- Deep mucosal healing, defined as ES = 0, Geboes score < 2 (indicating no neutrophil in crypts or lamina propria and no increase in eosinophil, no crypt destruction, and no erosions, ulcerations, or granulation tissue)
- Endoscopic remission (normalisation of the endoscopic appearance of the mucosa), defined as ES of 0

In both UC-1 and UC-2, patients treated with upadacitinib 45 mg once daily achieved statistically significant improvement in symptomatic response per paMS (defined as a decrease of ≥1 point and ≥30% from baseline and a decrease in RBS ≥ 1 or an absolute RBS ≤1) compared to placebo as early as Week 2.

Patients who did not achieve clinical response after 8 weeks of treatment with upadacitinib 45 mg once daily entered an 8-week open-label extended induction period. After the treatment of an additional 8 weeks (16 weeks total) of upadacitinib 45 mg once daily, a portion of those patients achieved clinical response per aMS.

In UC-3, patients who achieved clinical response per aMS at Week 8 from UC-1 and UC-2 were randomised to receive upadacitinib 15 mg, 30 mg or placebo once daily for up to 52 weeks. At Week 52 of UC-3, a significantly greater proportion of patients treated with upadacitinib 15 mg and 30 mg once daily compared to placebo achieved:

- Clinical remission per aMS, defined as SFS≤ 1 and not greater than baseline, RBS = 0, ES ≤ 1 without friability
- Maintenance of clinical remission per aMS among patients who achieved clinical remission at the end of induction treatment.
- Corticosteroid-free clinical remission, defined as clinical remission per aMS at Week 52 and corticosteroid-free for ≥90 days immediately preceding Week 52 among patients who achieved clinical remission at the end of the induction treatment.
- Mucosal healing defined as ES ≤ 1 without friability
- Histologic-endoscopic mucosal healing, defined as ES ≤ 1 without friability and Geboes score ≤ 3.1 (indicating neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue.)
- Deep mucosal healing, defined as ES = 0, Geboes score < 2 (indicating no neutrophil in crypts or lamina propria and no increase in eosinophil, no crypt destruction, and no erosions, ulcerations, or granulation tissue)

- Endoscopic remission (normalization of the endoscopic appearance of the mucosa), defined as ES of 0
- Maintenance of mucosal healing at Week 52 (ES ≤1 without friability) among patients who achieved mucosal healing at the end of induction

Among patients who responded to the induction treatment of 16-week upadacitinib 45 mg once daily, a portion of those patients maintained clinical response and achieved clinical remission per aMS at Week 52 with maintenance treatment of upadacitinib 15 mg and 30 mg once daily, respectively.

In all three studies, patients treated with upadacitinib demonstrated significantly greater and clinically meaningful improvement in health-related quality of life measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) total score compared to placebo. Improvements were seen in all 4 domain scores: systemic symptoms (including fatigue), social function, emotional function and bowel symptoms (including abdominal pain and bowel urgency).

Crohn's Disease

Upadacitinib 45 mg once daily as 12-week induction and 30 mg or 15 mg once daily as 52-week maintenance therapy was assessed in patients with inadequate response, loss of response, or intolerance to prior conventional and/or biologic(s), in U-EXCEED, U-EXCEL and U-ENDURE, representing a total of at least 64 weeks of therapy.

Upadacitinib 45 mg as induction treatment and 30 mg and 15 mg as maintenance treatment compared to placebo met the co-primary and most secondary endpoints at week 12 (induction) and

week 52 (maintenance), demonstrating statistically significant and clinically meaningful efficacy, with achievement of:

- clinical remission per stool frequency (SF) and abdominal pain score (APS), or as a Crohn`s Disease Activity Index (CDAI);
- clinical response per CDAI;
- endoscopic response, endoscopic remission, and mucosal healing. Greater proportion of patients treated with upadacitinib compared to placebo achieved SES-CD 0-2;
- corticosteroid-free clinical remission at week 12 among patients on corticosteroids at baseline, and corticosteroid-free for 90 days prior to week 52 and in clinical remission among patients on corticosteroids at baseline or among all patients; corticosteroid-free for 90 days prior to week 52 and in endoscopic remission at week 52;
- maintenance of clinical remission per SF/APS or CDAI at week 52;
- deep remission (clinical remission per SF/APS or CDAI and endoscopic remission) at week 52
- improvement in health-related quality of life measures, as measured by FACIT-F (with 45 mg induction at Week 12 and 45/30 mg at Week 52 only) and IBDQ
- resolution of extra-intestinal manifestations (with 45/30 mg at Week 52 only).

Onset of efficacy was rapid, with a significantly greater proportion of patients treated with upadacitinib 45 mg compared to placebo achieving: clinical response as early as Week 2 and clinical remission at Week 4.

Among patients who did not achieve clinical response (defined as ≥ 30% decrease in average daily very soft or liquid SF and/or ≥ 30% decrease in average daily AP score and neither greater than baseline) after 12 weeks of treatment with upadacitinib 45 mg once daily and received additional 12 weeks of upadacitinib 30 mg once daily, approximately half of the patients achieved clinical response at Week 24.

In the maintenance study, patients who demonstrated inadequate response or lost response were eligible to receive rescue treatment with upadacitinib 30 mg. Of the patients who were randomised to upadacitinib 15 mg group and received rescue treatment of upadacitinib 30 mg for at least 12 weeks, 84% (76/90) achieved clinical response per SF/APS and 48% (43/90) achieved clinical remission 12 weeks after initiating rescue.

Paediatric population

A total of 542 adolescents aged 12 to 17 years with moderate to severe atopic dermatitis were randomised across the three global Phase 3 studies, of which 344 were evaluated for the primary analysis. Adolescents in the primary analysis were randomised to receive either 15 mg (N=114) or 30 mg (N=114) upadacitinib or matching placebo (N=116), in monotherapy or combination with topical corticosteroids. Efficacy was consistent between adolescents and adults. The safety profile in adolescents was generally similar to that in adults, with dose dependent increases in the rate of some adverse events, including neutropenia and herpes zoster. At both doses, the rate of neutropenia was slightly increased in adolescents compared to adults. At both doses, the rate of herpes zoster was higher in adults compared to that in adolescents.

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 % to 60 %). 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.

Special populations

Renal impairment

Mild to moderate renal impairment has no clinically relevant effect on upadacitinib exposure (see Section 4.2). 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. Mild or moderate renal impairment has no clinically relevant effect on upadacitinib exposure (see section 4.2).

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 paediatric patients with rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, ulcerative colitis, and Crohn’s disease (see section 4.2).

Upadacitinib pharmacokinetics and steady-state concentrations are similar for adults and adolescents 12 to 17 years of age with atopic dermatitis. The posology in adolescent patients 30 kg to < 40 kg was determined using population pharmacokinetic modelling and simulation. No clinical exposure data are available in adolescents < 40 kg.

The pharmacokinetics of upadacitinib in paediatric patients (< 12 years of age) with atopic dermatitis have not been established.

Intrinsic factors

Age, sex, body weight, race, and ethnicity did not have a clinically meaningful effect on upadacitinib exposure. Upadacitinib pharmacokinetics are consistent between rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, giant cell arteritis, atopic dermatitis, ulcerative colitis and Crohn's disease patients.

5.3 Preclinical safety data

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

Upadacitinib, at exposures (based on AUC) approximately 4 and 10 times the clinical dose of 15 mg, 2 and 5 times the clinical dose of 30 mg, and 1.6 and 4 times the clinical dose of 45 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) (15 mg strength only)

Iron oxide red (E172)

Iron oxide yellow (E172) (45 mg strength only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

RINVOQ 15 mg prolonged release tablets

Prolonged release tablets in blisters: 2 years

Prolonged release tablets in bottles: 3 years

RINVOQ 30 mg prolonged-release tablets

Prolonged-release tablets in blisters: 2 years

Prolonged-release tablets in bottles: 3 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

RINVOQ 15 mg prolonged-release tablets:

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

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

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

Not all pack sizes may be marketed.

RINVOQ 30 mg prolonged-release tablets:

Polyvinylchloride/polyethylene/polychlorotrifluoroethylene - aluminium calendar blisters in cartons of 28, or 98 prolonged-release tablets.

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

Pack sizes: 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

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8 REGISTRATION NUMBER(S)

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RINVOQ 30 mg: 57/3.1/0624

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

RINVOQ 15 MG :06 April 2022

RINVOQ 30 mg:28 May 2024

10 DATE OF REVISION OF THE TEXT

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