ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

RINVOQ 15 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

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

Psoriatic arthritis

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

Ankylosing spondylitis

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

4.2 Posology and method of administration

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

Posology

The recommended dose of upadacitinib is 15 mg once daily.

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

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

Dose interruption

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

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

Table 1. Laboratory measures and monitoring guidance

Laboratory measure	Action	Monitoring guidance
Absolute Neutrophil Count (ANC)	Treatment should be interrupted if ANC is < 1,000 cells/mm^3 and may be restarted once ANC returns above this value	Evaluate at baseline and thereafter according to routine patient management
Absolute Lymphocyte Count (ALC)	Treatment should be interrupted if ALC is < 500 cells/mm^3 and may be restarted once ALC returns above this value	
Haemoglobin (Hb)	Treatment should be interrupted if Hb is < 8 g/dL and may be restarted once Hb returns above this value	
Hepatic transaminases	Treatment should be temporarily interrupted if drug-induced liver injury is suspected	
Lipids	Patients should be managed according to international clinical guidelines for hyperlipidaemia	12 weeks after initiation of treatment and thereafter according to international clinical guidelines for hyperlipidaemia

Special populations

Elderly

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

Renal impairment

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

Hepatic impairment

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

Paediatric population

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

Method of administration

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Immunosuppressive medicinal products

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

Serious infections

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

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

Consider the risks and benefits of treatment prior to initiating upadacitinib in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- who have resided or travelled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with upadacitinib. Upadacitinib therapy should be interrupted if a patient develops a serious or opportunistic infection. A patient who develops a new infection during treatment with upadacitinib should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and upadacitinib therapy should be interrupted if the patient is not responding to antimicrobial therapy. Upadacitinib therapy may be resumed once the infection is controlled.

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

Tuberculosis

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

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

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

Viral reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), was reported in clinical studies (see section 4.8). The risk of herpes zoster appears to be higher in Japanese patients treated with upadacitinib. If a patient develops herpes zoster, interruption of upadacitinib therapy should be considered until the episode resolves.

Screening for viral hepatitis and monitoring for reactivation should be performed before starting and during therapy with upadacitinib. Patients who were positive for hepatitis C antibody and hepatitis C virus RNA were excluded from clinical studies. Patients who were positive for hepatitis B surface antigen or hepatitis B virus DNA were excluded from clinical studies. If hepatitis B virus DNA is detected while receiving upadacitinib, a liver specialist should be consulted.

Vaccination

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

Malignancy

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

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

Non-melanoma skin cancer

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

Haematological abnormalities

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

Cardiovascular risk

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

Lipids

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

Hepatic transaminase elevations

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

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

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

Venous thromboembolism

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

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to affect the pharmacokinetics of upadacitinib

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

Coadministration with CYP3A4 inhibitors

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

Coadministration with CYP3A4 inducers

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

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

Potential for upadacitinib to affect the pharmacokinetics of other medicinal products

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

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

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

Upadacitinib is contraindicated during pregnancy (see section 4.3).

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

Breast-feeding

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

A risk to newborns/infants cannot be excluded.

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

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

Table 2. Adverse reactions

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

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

Rheumatoid arthritis

Description of selected adverse reactions

Infections

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

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

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

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

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

Opportunistic infections (excluding tuberculosis)

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

Hepatic transaminase elevations

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

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

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

Lipid elevations

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

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

Creatine phosphokinase

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

Neutropaenia

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

Psoriatic arthritis

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

Ankylosing spondylitis

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

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants ATC code: L04AA44

Mechanism of action

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

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

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

Pharmacodynamic effects

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

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

Lymphocytes

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

hsCRP

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

Clinical efficacy and safety

Rheumatoid arthritis

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

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

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

Table 3: Clinical trials summary

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

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

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

[a.] Patients were naïve to MTX or received no more than 3 weekly MTX doses

[b] Patients had inadequate response to MTX

[c] Patients who had an inadequate response to csDMARDs; patients with prior exposure to at most one bDMARD were eligible (up to 20% of total number of patients) if they had either limited exposure (<3 months) or had to discontinue the bDMARD due to intolerability

[d] Patients who had an inadequate response to MTX; patients with prior exposure to at most one bDMARD (except adalimumab) were eligible (up to 20% of total study number of patients) if they had either limited exposure (<3 months) or had to discontinue the bDMARD due to intolerability

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

Clinical response

Remission and low disease activity

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

ACR response

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

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

Table 4: Response and remission

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

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

Abbreviations: ACR20 (or 50 or 70) = American College of Rheumatology ≥20% (or ≥50% or ≥70%) improvement; ADA = adalimumab; CDAI = Clinical Disease Activity Index; CR = Clinical Remission; CRP = C-Reactive Protein, DAS28 = Disease Activity Score 28 joints; IR = inadequate responder; LDA = Low Disease Activity; MTX = methotrexate; PBO = placebo; UPA= upadacitinib

[a] SELECT-NEXT, SELECT-EARLY, SELECT-COMPARE, SELECT-BEYOND

[b] SELECT-MONOTHERAPY

[c] SELECT-EARLY

[d] SELECT-COMPARE

[e] multiplicity-controlled p≤0.001upadacitinib vs placebo or MTX comparison

[f] multiplicity-controlled p≤0.01 upadacitinib vs placebo or MTX comparison

[g] nominal p≤0.001 upadacitinib vs placebo or MTX comparison

[h] nominal p≤0.001upadacitinib vs adalimumab comparison

[i] nominal p≤0.01 upadacitinib vs adalimumab comparison

[j] nominal p<0.05 upadacitinib vs adalimumab comparison

[k] nominal p≤0.01 upadacitinib vs placebo or MTX comparison

[l] nominal p<0.05 upadacitinib vs MTX comparison

Note: Week 48-data derived from analysis on Full Analysis set (FAS) by randomised group using Non-Responder Imputation

Radiographic response

Inhibition of progression of structural joint damage was assessed using the modified Total Sharp Score (mTSS) and its components, the erosion score and joint space narrowing score, at weeks 24/26 and week 48 in SELECT-EARLY and SELECT-COMPARE.

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

Table 5: Radiographic changes

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

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

Physical function response and health-related outcomes

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

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

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

Abbreviations: ADA = adalimumab; HAQ-DI = Health Assessment Questionnaire-Disability Index; IR = inadequate responder; MTX = methotrexate; PBO = placebo; UPA = upadacitinib
[a] Data shown are mean
[b] Health Assessment Questionnaire-Disability Index: 0=best, 3=worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
[c] SELECT-EARLY, SELECT-NEXT, SELECT-COMPARE, SELECT-BEYOND
[d] SELECT-MONOTHERAPY
[e] SELECT-EARLY
[f] SELECT-COMPARE
[g] multiplicity-controlled p≤0.001 upadacitinib vs placebo or MTX comparison
[h] nominal p≤0.001 upadacitinib vs placebo or MTX comparison

[i] nominal p≤0.01 upadacitinib vs adalimumab comparison

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

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

Psoriatic arthritis

The efficacy and safety of upadacitinib 15 mg once daily were assessed in two Phase 3 randomised, double-blind, multicenter, placebo-controlled studies in patients 18 years of age or older with moderately to severely active psoriatic arthritis. All patients had active psoriatic arthritis for at least 6 months based upon the Classification Criteria for Psoriatic Arthritis (CASPAR), at least 3 tender joints and at least 3 swollen joints, and active plaque psoriasis or history of plaque psoriasis. For both studies, the primary endpoint was the proportion of patients who achieved an ACR20 response at week 12.

SELECT-PsA 1 was a 24-week trial in 1705 patients who had an inadequate response or intolerance to at least one non-biologic DMARD. At baseline, 1393 (82%) of patients were on at least one concomitant non-biologic DMARD; 1084 (64%) of patients received concomitant MTX only; and 311 (18%) of patients were on monotherapy. Patients received upadacitinib 15 mg or 30 mg once daily, adalimumab, or placebo. At week 24, all patients randomised to placebo were switched to upadacitinib 15 mg or 30 mg once daily in a blinded manner. SELECT-PsA 1 included a long-term extension for up to 5 years.

SELECT-PsA 2 was a 24-week trial in 642 patients who had an inadequate response or intolerance to at least one biologic DMARD. At baseline, 296 (46%) of patients were on at least one concomitant non-biologic DMARD; 222 (35%) of patients received concomitant MTX only; and 345 (54%) of patients were on monotherapy. Patients received upadacitinib 15 mg or 30 mg once daily or placebo. At week 24, all patients randomised to placebo were switched to upadacitinib 15 mg or 30 mg once daily in a blinded manner. SELECT-PsA 2 included a long-term extension for up to 3 years.

Clinical response

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

Treatment with upadacitinib 15 mg resulted in improvements in individual ACR components, including tender/painful and swollen joint counts, patient and physician global assessments, HAQ-DI, pain assessment, and hsCRP compared to placebo.

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

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

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

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

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

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

Patients who discontinued randomised treatment or were missing data at week of evaluation were imputed as non-responders in the analyses. For MDA, resolution of enthesitis, and resolution of dactylitis at week 24/56, the subjects rescued at week 16 were imputed as non-responders in the analyses.

[a] In patients with enthesitis at baseline (n=241, 270, and 265, respectively, for SELECT-PsA 1 and n=144 and 133, respectively, for SELECT-PsA 2)

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

Radiographic response

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

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

Table 8: Radiographic changes in SELECT-PsA 1

Treatment Group	PBO	UPA 15 mg	ADA 40 mg
Modified Total Sharp Score, mean change from baseline (95% CI)			
Week 24	0.25 (0.13, 0.36)	-0.04 (-0.16, 0.07)[c]	0.01 (-0.11, 0.13)
Week 56[a]	0.44 (0.29, 0.59)	-0.05 (-0.20, 0.09)	-0.06 (-0.20, 0.09)
Proportion of patients with no radiographic progression[b], % (95% CI)			
Week 24	92 (89, 95)	96 (94, 98)	95 (93, 97)
Week 56[a]	89 (86, 92)	97 (96, 99)	94 (92, 97)
Abbreviations: ADA = adalimumab; PBO = placebo; UPA= upadacitinib [a] All placebo data at week 56 derived using linear extrapolation [b] No progression defined as mTSS change ≤0.5 [c] multiplicity-controlled p≤0.001 upadacitinib vs placebo comparison			

Physical function response and health-related outcomes

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

Health-related quality of life was assessed by SF-36v2. In both studies, patients receiving upadacitinib 15 mg experienced statistically significant greater improvement from baseline in the Physical Component Summary score compared to placebo at week 12. Improvements from baseline were maintained through week 56 in both studies.

Patients receiving upadacitinib 15 mg experienced statistically significant improvement from baseline in fatigue, as measured by FACIT-F score, at week 12 compared to placebo in both studies. Improvements from baseline were maintained through week 56 in both studies.

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

Ankylosing spondylitis

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

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

Clinical response

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

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

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

Table 9: Clinical response in SELECT-AXIS 1

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

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

Abbreviations: ASAS20 (or ASAS40) = Assessment of SpondyloArthritis international Society ≥20% (or ≥40%) improvement; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score C-Reactive Protein; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; PBO = placebo; UPA= upadacitinib

[a] An ASAS20 (ASAS40) response is defined as a ≥20% (≥40%) improvement and an absolute improvement from baseline of ≥1 (≥2) unit(s) (range 0 to 10) in ≥3 of 4 domains (Patient Global, Total Back Pain, Function, and Inflammation), and no worsening in the potential remaining domain (defined as worsening ≥20% and ≥1 unit for ASAS20 or defined as worsening of > 0 units for ASAS40).

[b] primary endpoint

[c] multiplicity-controlled p≤0.001 upadacitinib vs placebo comparison

[d] multiplicity-controlled p≤0.01 upadacitinib vs placebo comparison

[e] comparison not multiplicity-controlled

[f] post-hoc analysis, not multiplicity-controlled

For binary endpoints, week 14 results are based on non-responder imputation analysis. For continuous endpoints, week 14 results are based on the least squares mean change from baseline using mixed models for repeated measures analysis.

Physical function response

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

Objective measure of inflammation

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

Paediatric population

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

5.2 Pharmacokinetic properties

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

Absorption

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

Distribution

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

Metabolism

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

Elimination

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

Renal impairment

Renal impairment has no clinically relevant effect on upadacitinib exposure. Upadacitinib AUC was 18%, 33%, and 44% higher in subjects with mild (estimated glomerular filtration rate 60 to 89 mL/min/1.73 m^2), moderate (estimated glomerular filtration rate 30 to 59 mL/min/1.73 m^2), and severe (estimated glomerular filtration rate 15 to 29 mL/min/1.73 m^2) renal impairment, respectively, compared to subjects with normal renal function. Upadacitinib C_{max} was similar in subjects with normal and impaired renal function.

Hepatic impairment

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

Paediatric population

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

Intrinsic factors

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

5.3 Preclinical safety data

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

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet contents:

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

Film coating:

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

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

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

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

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 December 2019

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

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

And

AbbVie Logistics B.V
Zuiderzeelaan 53
8017 JV Zwolle
NETHERLANDS

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

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

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

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

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

The physician educational material should contain:

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

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

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

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

The patient information pack should contain:

- Patient information leaflet
- A patient alert card

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Blister Carton (Individual carton)

1. NAME OF THE MEDICINAL PRODUCT

RINVOQ 15 mg prolonged-release tablets
upadacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

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

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1404/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rinvoq

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for 84 tablet multipack (with Blue Box)

1. NAME OF THE MEDICINAL PRODUCT

RINVOQ 15 mg prolonged-release tablets
upadacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

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

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1404/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rinvoq

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Intermediate carton of 84 tablet multipack (without Blue Box)

1. NAME OF THE MEDICINAL PRODUCT

RINVOQ 15 mg prolonged-release tablets
upadacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

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

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1404/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rinvoq

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton of 98 tablets

1. NAME OF THE MEDICINAL PRODUCT

RINVOQ 15 mg prolonged-release tablets
upadacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

98 prolonged-release tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

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

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1404/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rinvoq

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Inner carton of 49 tablets (for the 98 pack)

1. NAME OF THE MEDICINAL PRODUCT

RINVOQ 15 mg prolonged-release tablets
upadacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

49 prolonged-release tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

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

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1404/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rinvoq

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

RINVOQ 15 mg prolonged-release tablets
upadacitinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AbbVie (as logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

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

PC

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Bottle Carton (30 and 90 pack)

1. NAME OF THE MEDICINAL PRODUCT

RINVOQ 15 mg prolonged-release tablets
upadacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 prolonged-release tablets
90 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

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

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rinvoq

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

Bottle Label

1. NAME OF THE MEDICINAL PRODUCT

RINVOQ 15 mg prolonged-release tablets
upadacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

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

Important to open

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie (as logo)

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

RINVOQ 15 mg prolonged-release tablets
upadacitinib

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

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

What is in this leaflet

1. What RINVOQ is and what it is used for

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

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

- Rheumatoid Arthritis
- Psoriatic Arthritis
- Ankylosing Spondylitis

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

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

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

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

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

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

2. What you need to know before you take RINVOQ

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

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

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

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

Other medicines and RINVOQ
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because some medicines may reduce how well RINVOQ works or may increase the risk of getting side effects. It is very important to talk to your doctor or pharmacist if you are taking any of the following:
- medicines to treat fungal infections (such as itraconazole, posaconazole or voriconazole)
- medicines to treat bacterial infections (such as clarithromycin)
- medicines to treat Cushing's syndrome (such as ketoconazole)
- medicines to treat tuberculosis (such as rifampicin)
- medicines to treat seizures or fits (such as phenytoin)
- medicines that affect your immune system (such as azathioprine, ciclosporin and tacrolimus)

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

Pregnancy, breast-feeding and contraception

Pregnancy
RINVOQ must not be used during pregnancy.

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

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

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

3. How to take RINVOQ

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

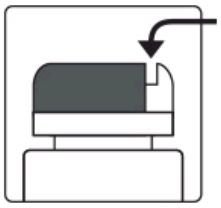
The recommended dose is one 15 mg tablet once a day.
- Swallow the tablet whole with water. Do not split, crush, chew or break the tablet before swallowing as it may change how much medicine gets into your body.
- To help you remember to take RINVOQ, take it at the same time every day.
- The tablets can be taken with or without food.
- Do not swallow the desiccant.

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

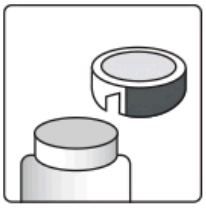
If you forget to take RINVOQ
- If you miss a dose, take it as soon as you remember.
- If you forget your dose for an entire day, just skip the missed dose and take only a single dose as usual the following day.
- Do not take a double dose to make up for a forgotten tablet.

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

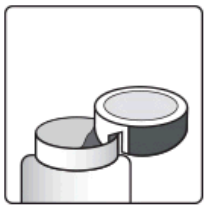
How to open the bottle



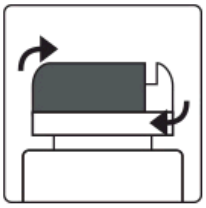
Foil Cutting Tool - on the cap of the bottle



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



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



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

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

4. Possible side effects

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

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

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

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

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

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

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

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

5. How to store RINVOQ

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

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

This medicine does not require any special temperature storage conditions.

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

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

6. Contents of the pack and other information

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

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

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

The tablets are provided in blisters or bottles.

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

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

Not all pack sizes may be marketed.

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This leaflet was last revised in

Other sources of information

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

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

QR code to be included

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

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for upadacitinib, the scientific conclusions of CHMP are as follows:

In view of available data on herpes zoster from clinical trials and in view of a plausible mechanism of action the PRAC recommended the update of section 4.4 of the SmPC to add a warning on higher risk of herpes zoster in Japanese patients treated with upadacitinib. The PRAC concluded that the product information of products containing upadacitinib should be amended accordingly.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for upadacitinib the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing upadacitinib is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.