Date: 20 March 2020
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Rinvoq

International non-proprietary name: upadacitinib, upadacitinib hemihydrate
Pharmaceutical form: prolonged-release tablet
Dosage strength: 15 mg
Route(s) of administration: oral
Marketing Authorisation Holder: AbbVie AG
Marketing Authorisation No.: 67257
Decision and Decision date: approved on 20 January 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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Table of contents

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1 Terms, Definitions, Abbreviations

ACR	American College of Rheumatology
ADA	Adalimumab
ADME	Absorption, Distribution, Metabolism, Elimination
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BCRP	Breast Cancer Resistance Protein
bDMARD	biologic Disease-Modifying Anti-Rheumatic Drug
BID	twice daily
Cmax	Maximum observed plasma/serum concentration of drug
CPK	Creatine Phosphokinase
CRP	C-Reactive Protein
csDMARD	conventional synthetic Disease- Modifying Anti-Rheumatic Drug
CYP	Cytochrome P450
DAS	Disease Activity Score
DDI	Drug Drug Interaction
DILI	Drug Induced Liver Injury
DMARD	Disease-Modifying Anti-Rheumatic Drug
EC_{50}	Half Maximal Effective Concentration
ED	Effective Dose
ESRD	Endstage Renal Disease
ER	Extended Release
ERA	Environmental Risk Assessment
EULAR	European League Against Rheumatism
GLP	Good Laboratory Practice
HAQ-DI	Health Assessment Questionnaire – Disability Index
HPLC	High Pressure Liquid Chromatography
HPMC	Hydroxypropyl Methylcellulose
IC_{50}	Half Maximal Inhibitory Concentration
ICH	International Council for Harmonisation
IFNγ	Interferon Gamma
Ig	Immunoglobulin
IL	Interleukin
INN	International Nonproprietary Name
IR	Immediate Release
JAK	Janus Kinase
LDA	Low Disease Activity
LoQ	List of Questions
Max	Maximum
MAH	Marketing Authorisation Holder
MATE	Multidrug and Toxin Extrusion
Min	Minimum
MTX	Methotrexate
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
OATP	Organic Anion Transporting Polypeptide
PD	Pharmacodynamics

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PSP	Pediatric Study Plan (US-FDA)
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
QD	once daily
RA	Rheumatoid Arthritis
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
STAT	Signal Transduction Activators of Transcript
TNF	Tumour Necrosis Factor
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
Tyk2	Tyrosine kinase 2
UPA	Upadacitinib
UV	Ultra Violet Spectrometry
VTE	Venous Thromboembolic Event

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance (INN) of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

RINVOQ is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis.
RINVOQ may be used in combination with methotrexate or other csDMARDs or as monotherapy in adult patients.

2.2.2 Approved Indication

RINVOQ is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis, who had an inadequate response or are intolerant to a treatment with one or more conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD).
RINVOQ may be used in combination with methotrexate or other csDMARDs or as monotherapy in adult patients.

2.2.3 Requested Dosage

Treatment with RINVOQ should be initiated by physicians experienced in the diagnosis and treatment of rheumatoid arthritis. The recommended oral dose of RINVOQ is 15 mg once daily with or without food. RINVOQ tablets should be swallowed whole. RINVOQ should not be split, crushed or chewed.
It is recommended that RINVOQ is not used in patients with an absolute lymphocyte count (ALC) less than 500 cells/mm3, an absolute neutrophil count (ANC) less than 1000 cells/mm3 or who have hemoglobin levels less than 8 g/dL.
If a patient develops a serious infection, RINVOQ treatment should be interrupted until the infection is controlled.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	11 January.2019
Formal control completed	14 January 2019
List of Questions (LoQ)	24 April 2019
Answers to LoQ	22 July 2019
Predecision	17 October 2019
Answers to Predecision	22 November 2019
Final Decision	20 January 2020
Decision	approval

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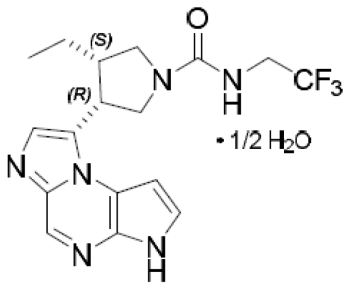
2.4 Medical Context

The aetiology of rheumatoid arthritis (RA) has not yet been fully explained. It is assumed to be an autoimmune condition that results in a predominance of pro-inflammatory cytokines.
Non-steroidal anti-inflammatory drugs (NSAIDs), selective cyclooxygenase-2 (COX-2) inhibitors, phosphodiesterase 4 inhibitors, glucocorticoids, and disease-modifying anti-rheumatic drugs (DMARDs) are used in therapy. In addition to the 'classics' (csDMARDs) such as methotrexate (MTX), hydroxychloroquine, sulfasalazine and leflunomide, these also include various biologics (bDMARDs). They are used as 'second-line treatment' in accordance with the relevant guidelines, usually in combination with MTX, when the response to csDMARDs is inadequate.
The bDMARDs currently approved in Switzerland are antagonists of tumour necrosis factor alpha (TNF-α), interleukins IL-1 and IL-6, CTLA (cytotoxic T-lymphocyte-associated Protein), CD20 (B cells) and Janus kinase (JAK) inhibitors.
JAK play an important role in the intracellular signalling of cytokine receptors (especially IFN) and growth factors. The JAK family comprises JAK 1, 2 and 3 as well as tyrosine kinase 2. JAK1 is relevant mainly to inflammatory cytokines, JAK2 to erythrocyte maturation, and JAK3 to lymphocyte function.
In Switzerland, two JAK inhibitors are currently approved for the treatment of RA: tofacitinib (Xeljanz®, 2013) and baricitinib (Olumiant®, 2017). They are both orally administered low-molecular synthetic agents.

3 Quality Aspects

3.1 Drug Substance

INN: Upadacitinib
Chemical name: (3S,4R)-3-Ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrate (2:1)
Molecular formula: $C_{17}H_{19}F_3N_6O \cdot ½\ H_2O$ (hemihydrate)
Molecular mass: 389.38 g/mol (hemihydrate); 380.38 g/mol (anhydrate)
Molecular structure:



Physico-chemical properties: Upadacitinib is a crystalline white to light brown powder. Upadacitinib contains two stereogenic centres and is manufactured as a single stereoisomer. The compound is considered highly soluble in the biopharmaceutical classification system.

Synthesis: The drug substance is manufactured by a multiple step chemical synthesis with final crystallisation resulting in the hemihydrate form. The synthesis of the drug substance and the necessary in-process controls are described in detail.

Structure elucidation: The structure of upadacitinib has been fully elucidated using several spectroscopic techniques such as mass spectrometry, infrared spectroscopy, nuclear magnetic resonance spectroscopy and X-ray crystallography.

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Specifications: In order to ensure a consistent quality of upadacitinib, the specifications include all relevant test parameters as recommended by the relevant ICH Guidelines.

Stability: The bulk drug substance is packaged in low-density polyethylene (LDPE) bags. A stability study was carried out according to the current guideline recommendations, and a satisfactory retest period was established based on the results of this study.

3.2 Drug Product

Description and composition: Upadacitinib tablets are presented as prolonged-release, film-coated tablets containing 15.4 mg of upadacitinib hemihydrate, which is equivalent to 15 mg of upadacitinib. The tablets are oblong, biconvex and purple coloured. One side is debossed with “a15”, the other side is plain. The excipients of the tablet cores are microcrystalline cellulose, hypromellose, mannitol (E421), tartaric acid, silica (colloidal anhydrous) and magnesium stearate. The purple film-coating of the tablet is composed of polyvinyl alcohol, macrogol, talc, titanium dioxide (E171), red and black iron oxide (E172).

Pharmaceutical development: Upadacitinib tablets were developed as prolonged-release tablets to be administered orally once daily in order to achieve the appropriate pharmacokinetic profile. Hydroxypropyl methylcellulose (HPMC) is used as a release control polymer.

Manufacture: The manufacturing process is described with a sufficient level of detail. Appropriate in-process controls are applied in order to achieve a consistent quality of the tablets.

Specification: Adequate tests and criteria for release and shelf-life are established for the control of the finished product. The specifications include the parameters of description (visual examination), identification (HPLC, UV), assay (HPLC), uniformity of dosage units (HPLC), degradation products (HPLC), water content (loss on drying) and dissolution testing. The test methods are adequately validated according to the recommendations of the current scientific guidelines.

Container-Closure System: Upadacitinib prolonged-release tablets are packaged in clear PVC/PE/PCTFE blisters with push-through aluminium foil lidding.

Stability: Appropriate stability data are presented for three primary stability batches and three commercial site-specific stability batches. Based on these data, a shelf-life was established for the prolonged-release tablets. The storage recommendation is “Do not store above 25°C”.

3.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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4 Nonclinical Aspects

Pharmacology

Upadacitinib is a reversible ATP competitive inhibitor of the JAK family of kinases. It has a high affinity for JAK1 (IC_{50}= 0.043 µM), but also inhibits JAK2, JAK3 and Tyk2 to a lesser extent (IC_{50} values of 0.120 µM, 2.3 µM and 4.7 µM, respectively).
Upadacitinib binding kinetics was characterised by rapid association and dissociation. It showed low affinity binding over a panel of 60 kinases.
In cellular assays, upadacitinib inhibited IL-2 and IL-6 induced STAT5/3 phosphorylation (EC_{50} values of 13 nM and 9 nM respectively) and, to a lesser extent, erythropoietin-induced STAT5 phosphorylation (EC_{50}~628 nM).
The potency of upadacitinib was further confirmed *in vivo* in acute concanavalin A-induced IFNγ arthritis and in chronic adjuvant-induced arthritis rat models. In the acute model, upadacitinib induced dose-dependent inhibition of IFN-γ release, with ED_{50} and ED_{80} values of 0.4 mg/kg and 5.8 mg/kg, respectively. In the chronic model, an inhibition of paw swelling was observed at an exposure of 0.034°µg•hr/mL ($AUC_{0\text{-}12h}$), which was about 11-fold lower than the human exposure. Histological and micro-computed tomography of the ankle showed inhibition of bone erosion, cartilage damage, and inflammation at doses higher than 3 mg/kg/day.
Safety pharmacology studies were conducted to investigate effects on cardiovascular, respiratory, and central nervous systems. The IC_{50} value for inhibition of the hERG channel was 39.5 µg/mL, which is >2000-fold the level of unbound drug in plasma at an oral clinical dose of 15 mg/day (0.019°µg/mL). In dogs, a dose-dependent decrease of mean arterial blood pressure was observed at single doses of ≥ 1.5 mg/kg at plasma levels (Cmax 5-fold the human Cmax). Upadacitinib increased heart rate by ~30% at 5 mg/kg (Cmax = 0.653 µg/mL or 16-fold the human Cmax). In the 4-week (doses up to 5 mg/kg/day) and 39-week (doses up to 1.5 mg/kg/day) toxicity studies in dogs, no effects on heart rate variability were observed. Decreased motor activity was observed in rats after a single oral dose of 100 mg/kg (Cmax = 13.5 µg/mL or 329-fold the human Cmax). No effects were observed on the heart rate, blood pressure or the nervous system in the clinical studies.
No effects on the respiratory system were observed in rats after single oral doses of up to 100 mg/kg.

Pharmacokinetics

The pharmacokinetics of upadacitinib was investigated after single and repeated oral administration in CByB6F1-Tg(HRAS)2Jic wild-type mice, single intravenous and oral administration in Sprague Dawley rats and Beagle dogs, and repeated oral dosing in mice, rabbits, rats, and dogs (toxicokinetics).
The pharmacokinetic profile of upadacitinib was generally characterised by moderate to high plasma clearance, high volumes of distribution and half-lives ranging from 1.3 to 3.1 hours in rats and dogs. Upadacitinib was absorbed from solution formulations with peak concentrations 1 to 2.5 hours after oral dosing, similar to the absorption in humans. In mice, upadacitinib was absorbed and eliminated more rapidly than in other species. Bioavailability was moderate in rats (30.5%) and higher in dogs (76.8%), similar to the bioavailability in humans (76%).
Upadacitinib exposure after repeated oral dose administration in mice, rats, rabbits and dogs was similar to the exposure after single administration. There were no significant sex differences in upadacitinib exposures in mice and dogs. In rats, AUC values in females were consistently higher than in males (about 2-fold). In all species, Cmax and AUC values increased more than dose proportionally after oral administration.
In a tissue distribution study following an oral administration of 5 mg/kg [^{14}C]upadacitinib to male pigmented rats, extensive distribution of drug-derived radioactivity was observed, with the exception of the CNS and eye lens. The uveal tract had measurable levels of radioactivity for up to 192 h, which suggested an affinity for melanin-containing tissues. Upadacitinib was shown to cross the placenta and passed into the milk of lactating rats.
Upadacitinib showed different plasma protein binding at 1 µM across the different species (mouse 72%, rat 59%, dog 31%, and human 52%). Mean blood-to-plasma ratios were 0.99, 1.28, 1.18, and

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1.00 in mice, rats, dogs, and humans, respectively, indicating no preferential partitioning to the cellular compartments.
In vitro studies showed that the metabolism of upadacitinib is mainly attributed to CYP3A4 and, in a minor way, to CYP2D6.
In all species, unchanged upadacitinib was the primary circulating component in plasma. Mice, rats, and dogs exhibited similar metabolic pathways as in humans. The human metabolites M4 (major) and M11 (minor) were observed in adequate concentrations in rats and dogs.
Upadacitinib and metabolites were mainly eliminated through the biliary route in rats. In dogs and humans, elimination through the faecal and urinary routes was of equal importance.
In *in-vitro* studies, upadacitinib was a weak inducer of CYP3A4 and did not inhibit CYP isoforms 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4. Upadacitinib was not a substrate for organic anion transporting polypeptide (OATP) 1B1, 1B3 or organic cation transporter (OCT1), but it was a substrate for the efflux transporters, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Upadacitinib was not a substrate for renal transporters OCT2, OAT1, OAT3, MATE1, and MATE2K. Upadacitinib was shown to be a substrate for P-gp and BCRP.

Toxicology

The toxicological evaluation was conducted in rats and dogs, as the metabolic profile in humans was adequately represented by these species. Mice and rabbits were used as a second species for carcinogenicity and reproduction toxicology assessments.
The route of administration and the dosing schedule were the same as those intended for clinical use. The duration of the studies in rodents and non-rodents support the clinical indication.
The toxicity profile of upadacitinib was evaluated in toxicity studies with daily dosing for up to 26°weeks in rats (doses of 5, 20, or 50 mg/kg/day) and 39 weeks in dogs (doses of 0.1, 0.5 or 1.5°mg/kg/day).
In both species, upadacitinib-related effects included decreases in circulating lymphocytes and decreased cellularity of lymphoid tissues as well as suppression of erythropoiesis with resultant decreases in red blood cell (RBC) mass and/or reticulocytes. Decreases in lymphocytes reflect JAK1 and/or JAK3 inhibition, while decreases in RBC mass reflect inhibition of JAK2. Although upadacitinib is mainly a JAK1 selective inhibitor, effects on JAK2 activity occur at higher exposures. Demodicosis as well as inflammation of the paws and interdigital cysts were observed in dogs, which can be attributed to immunosuppression.
Observed dose-dependent decreases in thymus and spleen weights correlated with decreased numbers of lymphocytes in the thymus and spleen and bone marrow hypocellularity. These findings are consistent with the expected effects of inhibition of JAK enzyme activity and the known roles of JAK-dependent cytokines on the immune system.
In rats, nephrotoxicity (renal tubular degeneration/regeneration) was observed at exposures 30-fold above the clinical exposure in RA patients administered 15 mg/day. Renal dysfunction incidence in clinic was low and is not considered a risk. Adverse liver findings, consisting of moderate to marked multifocal, mid-zonal, or diffuse liver necrosis, were only observed in animals, with early mortality in the 4-week toxicity study at an exposure about 100-fold the clinical exposure. According to the RMP, few cases of hepatic disorder were reported as serious. DILI was added as an important potential risk in the RMP.
In a juvenile toxicity study in rats administered upadacitinib orally at 5 or 20 mg/kg/day from postnatal days 15 through 63, a decreased lymphocyte count was associated with dose-dependent decreases in spleen and thymus weight and a decrease in lymphoid cellularity. No effects were observed in the kidney, in contrast to the adult animals in the repeated dose toxicity studies.
Upadacitinib tested negative for phototoxicity in the *in vitro* 3T3 neutral red uptake assay.
Upadacitinib tested negative for genotoxicity in the bacterial reverse mutation test, chromosomal aberration assay in human lymphocytes, and in the *in vivo* rat micronucleus assay.
In carcinogenicity studies conducted in CByB6F1-Tg(HRAS)2Jic transgenic mice and in Sprague Dawley rats, there were no test item-related pre-neoplastic or neoplastic findings in mice and rats at exposures 2.9-, and 4.2- fold the clinical exposure in RA patients administered 15 mg/day.

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In a fertility and early embryonic development study in rats with oral administration of upadacitinib up to 50 and 75 mg/kg/day in male and female animals, respectively, no adverse effects were observed on fertility or reproductive capacity. Dose-related increases in foetal resorptions associated with post-implantation losses were observed at ≥25 mg/kg/day.
Upadacitinib was teratogenic in both rats and rabbits. In an embryo-foetal development study in female rats administered upadacitinib orally at doses of 5 mg/kg/day up to 75 mg/kg/day, skeletal malformations were observed at all doses. The malformations observed were misshapen humerus and bent scapula, bent, misshapen, or shortened long bones, and rib/vertebral defects. Skeletal variations were observed at 25 and 75 mg/kg/day. As the NOAEL for developmental toxicity could not be established in this study, a second study in female rats was conducted with upadacitinib at 1.5 and 4 mg/kg/day with the same design as for the first study. At 4 mg/kg/day, similar malformations as described above were observed in one foetus. The exposure at the NOAEL for developmental toxicity (1.5 mg/kg/day) was 0.29-fold the clinical exposure in RA patients administered 15 mg/day.
In rabbits, an increased incidence of cardiac malformations was observed at 25 mg/kg/day, corresponding to an exposure 14-fold the clinical exposure in patients administered 15 mg/day.
Adequate contraception recommendation is described in the information for healthcare professionals.
The recommendation for pregnancy and lactation is adequate.
In a pre-/postnatal development study in rats administered upadacitinib orally at doses up to 10°mg/kg/day, no maternal toxicity and no effects were observed in any of the endpoints measured in the offspring at an exposure 2.8-fold the clinical exposure in RA patients at 15 mg once daily (QD).
Immunotoxicity was investigated in a dedicated study in adult rats administered 60 mg/kg/day upadacitinib orally for eight weeks and in the juvenile toxicity study in rats. In both studies, a decrease in total T cells, T helper cells, T cytotoxic cells, B cells, NK (natural killer) cells and NKT cells was observed at all doses. Upadacitinib suppressed T-cell dependent antibody responses in adult and juvenile animals.
The safety margins related to human exposure are low or non-existent. However, all toxicity concerns are adequately monitored clinically or adequate measures are taken (contraception measures).
The RMP adequately describes the results of the nonclinical studies and their relevance for human use.
Based on the ERA, upadacitinib has no potential for bioaccumulation and does not represent a risk for the environment.
No safety concerns are expected with impurities or excipients.

Nonclinical conclusions

In conclusion, the pharmaco-toxicological profile of upadacitinib is considered to be sufficiently well characterised. The submitted nonclinical data support the approval of upadacitinib in the proposed indication. The relevant information has been included in the information for healthcare professionals.
From the preclinical viewpoint, the application can be approved.

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5 Clinical and Clinical Pharmacology Aspects

5.1 Clinical Pharmacology

Absorption
Upadacitinib was rapidly absorbed, with a median T_{max} of ~1 h following intake of immediate-release (IR) capsules and ~2h following intake of extended-release (ER) tablets. The absolute bioavailability of upadacitinib has not been determined but is estimated to be at least 60%, based on mass balance data.

Biopharmaceutical development
The biopharmaceutical bridging between the various upadacitinib formulations used during clinical development and the market-image extended release formulation was acceptable.

Distribution
Upadacitinib plasma protein binding is ~ 52%. The absolute volume of distribution is estimated to be ~294 L (PopPK).

Metabolism
Upadacitinib is metabolised by CYP3A4 and, to a lesser extent, by CYP2D6, based on *in vitro* data. Since the CYP2D6 metabolic phenotype (based on genotype analysis) does not correlate with upadacitinib oral clearance, the contribution of CYP2D6 to upadacitinib metabolism is considered to be low.

In a mass balance study, unchanged upadacitinib accounted for 79.4% of the total radioactivity in plasma. Two metabolites, M4 and M11, accounted for 13.4% and 7.1% of the total plasma radioactivity.

Excretion
In a mass balance study with radioactively labelled upadacitinib, 42.6% of the dosed radioactivity was recovered in urine and 53.4% was recovered in faeces up to 216 hours post-dose.
In urine, 23.6% of the radioactive dose was recovered as unchanged parent drug, while M4 was the most abundant metabolite in urine (9.6% of the dose), followed by M10 (3.6% of the dose). Ten minor metabolites were found in urine (M2, M3, M6/M8, M10, M11, M22, and three unknown urinary metabolites), each of which accounted for < 4% of the total radioactivity.
In faeces, 37.8% of the administered radioactive dose was recovered as unchanged parent drug. It is not clear whether this part of the dose was actually absorbed and excreted again, or whether it was never absorbed at all. M11 was the most abundant metabolite in faeces (6.3% of the dose). In addition, 10 minor metabolites were found in faeces (M1, M2, M8, M11, M22, M23, and four unknown metabolites), each of which accounted for ≤ 3% of the total radioactive dose.

In total ~ 61% of the administered radioactive dose was excreted as unchanged parent drug in urine and faeces.
The rest of the administered radioactive dose was excreted as M4 (9.6%) and M11 (6.4%), while the other metabolites (M1, M2, M3, M6/M8, M8, M10, M22, M23, and unidentified radioactive species) each accounted for < 4% of the total administered dose.

Upadacitinib mean terminal $t_{1/2}$ ranged from 6 to 16 h for the IR capsules and 9 to 14 h for the ER tablets.

Special Populations / Intrinsic Factors
The PK of upadacitinib in subjects with mild and moderate hepatic impairment was studied in a dedicated PK study. There are no PK data in subjects with severe hepatic impairment.

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In subjects with mild hepatic impairment, upadacitinib C_{max}, AUC_t, and AUC_{inf} were elevated to 1.04-fold, 1.27-fold, and 1.28-fold, respectively.
In subjects with moderate hepatic impairment, upadacitinib C_{max}, AUC_t, and AUC_{inf} were elevated to 1.43-fold, 1.25-fold, 1.24-fold, respectively, compared to subjects with normal hepatic function.
The applicant recommends no dose adjustment in case of mild and moderate hepatic impairment. Administration in patients with severe hepatic impairment is not recommended. The applicant`s dosing recommendations are approved.

The PK of upadacitinib in subjects with mild, moderate and severe renal impairment was studied in a dedicated PK study. There are no PK data in subjects with end stage renal disease (ESRD) under dialysis.
The applicant applied various statistical approaches to analyse the effect of renal impairment. In summary, upadacitinib AUC_{inf} was 18 to 25%, 33 to 36% and 32 to 48% higher in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function. Upadacitinib C_{max} values were similar in subjects with mild and moderate renal impairment and only slightly increased, by 13 to 22%, in subjects with severe renal impairment and compared to subjects with normal renal function.
In the information for healthcare professionals, the applicant recommends no dose adjustment in subjects with mild, moderate and severe renal impairment. The applicant`s dosing recommendations are approved.

In a PopPK analysis, no significant covariate effects were found for gender and race. Body weight was a significant covariate on volume of distribution, but the effect on exposure was small and is considered not clinically relevant. Patients with RA were estimated to have a 33% higher AUC compared to healthy subjects.

Interactions
Effects of other substances on upadacitinib
Upadacitinib is metabolised by CYP3A4 and, to a lesser extent, by CYP2D6. Concomitant administration of upadacitinib with the strong CYP3A4/5 inhibitor ketoconazole caused increases in the mean upadacitinib C_{max} and AUC_{inf} values to 1.7-fold and 1.75-fold, respectively, compared to the intake of upadacitinib alone.
The applicant recommends caution during the long-term concomitant administration of upadacitinib and strong CYP3A4 inhibitors. The applicant`s dosing recommendation is approved.

Concomitant intake of upadacitinib with the multiple enzyme and transporter inducer rifampicin caused decreases in upadacitinib C_{max} and AUC to 0.5-fold and 0.4-fold, respectively. This could lead to reduced efficacy. Concomitant use with strong inducers is not recommended.

Concomitant intake of upadacitinib with a single dose of rifampicin caused only a mild increase in upadacitinib exposure, indicating that OATPs do not play a relevant role in upadacitinib disposition.

Effects of upadacitinib on other substances
The DDI potential of upadacitinib on other drugs was evaluated after multiple once-daily doses of 30 mg ER tablets in several clinical DDI studies.
Upadacitinib caused slight reductions in the exposure of the CYP 3A4 substrate midazolam (to 0.74–fold for both AUC and C_{max}), the CYP3A4 substrate atorvastatin (to 0.88-fold for Cmax and to 0.77-fold for AUC) and rosuvastatin (substrate of OATPs, BCRP and, to a lesser extent, CYP2C9, reduction to 0.77-fold for C_{max}, and to 0.71-fold for AUC_t). Single doses of rosuvastatin and atorvastatin had no effect on the upadacitinib steady-state exposure (AUC_{0-24}).
Overall, these effects indicate a weak inducing effect of upadacitinib. However, a general recommendation for a dose adjustment is not required,

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Other interaction studies did not indicate further clinically relevant interaction effects (see information for healthcare professionals).

Pharmacodynamics
Mechanism of Action and primary Pharmacology
It is postulated, on the basis of *in vitro* studies, that upadacitinib is a stronger inhibitor of JAK1 than of JAK2 or JAK3. This applies primarily to IL-6-induced STAT3 phosphorylation and IL-7-induced STAT5 phosphorylation.

Secondary Pharmacology (Safety)
The potential of upadacitinib to affect the QT interval was not investigated in a tQT/QTc study, but was based on an exposure-response analysis. This analysis indicated that upadacitinib did not cause a prolongation of the QT interval.

5.2 Dose Finding and Dose Recommendation

In two double-blind, controlled phase 2 studies, the efficacy of 12 weeks of treatment with IR capsules was investigated in parallel groups, each containing approximately 50 patients with moderate to severe RA, using the following doses:

- 2x3 mg
- 2x6 mg
- 2x12 mg
- 2x18 mg
- Placebo
- 1x24 mg (in study 13-537 only)

One study (M13-537) examined patients who previously responded inadequately to MTX. The other study (M13-550) examined patients with active RA despite treatment with at least one TNF inhibitor. Both studies demonstrated that the disease progressed more favourably, with respect to the primary endpoint (ACR20) and also the other secondary endpoints (including ACR50/70), in patients taking any of the investigated upadacitinib (UPA) doses than in the placebo group. Numerically, the 2x12 mg dose proved to be the best in both studies. It can be presumed from both studies that, at lower doses, the effect is dose-dependent, a trend that was more evident in study M13-550 (in patients not responding to TNF inhibitors).

Adverse events (AE) were more frequent under UPA treatment than placebo; overall, the safety data indicate dose dependency in this respect. In the subsequent clinical programme, 15 mg and 30 mg UPA ER tablets were developed. The results from the relevant M14-680 study suggest that the 15 mg and 30°mg UPA ER tablets, whether taken under fasting conditions or after eating, result in exposures comparable to those obtained with 2x6 mg and 2x12 mg capsules, respectively.
In the pivotal studies, the efficacy and safety of both the 15 mg and the 30 mg dose were, and are being, investigated in some cases. Somewhat better efficacy tends to be seen, on the one hand, with the higher dose, but on the other hand there are more safety issues.

5.3 Efficacy

Five pivotal studies with a complex design have been presented. All studies involved double-blind, controlled, parallel-group comparisons in patients over 18 years with moderate to severe RA (ACR, EULAR).
Two studies investigated the efficacy of upadacitinib as a single agent following different previous treatments. Three placebo-controlled studies examined upadacitinib as an adjunct to csDMARDs (~90% MTX), and one study also entailed an active comparison with adalimumab (ADA, adalimumab administration/dosage as approved in Switzerland). Further details regarding size, treatments and

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endpoints are summarised in the information for healthcare professionals in Table 4, “Clinical efficacy” section.
In all comparisons, a numerically distinct and highly significant advantage is described for both doses of upadacitinib versus MTX or placebo & MTX, in relation to the standard clinical and radiological endpoints. Compared with ADA, superiority (ACR50 week 12; HAQ-DI, pain score week°12) or non-inferiority (LDA share due to DAS28/CRP≤3.2) was demonstrated in predefined and hierarchically controlled endpoints. Further results are given in the information for healthcare professionals in Tables 5-7, “Clinical efficacy” section.
All five pivotal studies have their own ongoing long term extension studies. In three of these long-term studies, the proposed 15 mg dose is being compared against 30 mg. One study entails a comparison of the two doses against MTX, and one study is comparing upadacitinib 15 mg with ADA. The final results of these long-term studies are not yet available.

5.4 Safety

In the phase 2 and 3 studies taken into consideration, the (undated) clinical safety summary reports that a total of 4.443 subjects were exposed to at least one dose of upadacitinib, including 2.972 patients who were exposed for longer than 48 weeks. The total exposure so far amounts to 5263 patient years.
The presented development programme allows for the following controlled comparisons:

- UPA mono 15 mg and 30 mg versus MTX mono
  - Treatment duration 3 months: in each case approx. 500 patients
  - Treatment duration 24 weeks: in each case approx. 250 patients
  - Treatment duration 2 years: ongoing
- UPA & DMARD versus placebo & DMARD
  - UPA 15 mg versus placebo; treatment duration 3 months: in each case approx. 1000 patients
  - UPA 15 mg and UPA 30 mg versus placebo; treatment duration 3 months: in each case approx. 300 patients
- UPA & DMARD versus ADA & DMARD versus placebo & DMARD
- UPA versus ADA versus placebo 3 months: approximately 320 patients on ADA, in each case approx. 650 patients on UPA/PL
- UPA versus ADA (no placebo) 26 weeks. Populations partly mixed following rescue therapies.

Comparison of monotherapies: Similar rates of AEs were found under UPA 15 mg and under MTX. Under UPA 30 mg, the frequency was slightly higher than under MTX and UPA 15 mg.
Severe infections (serious infections, opportunistic infections and herpes zoster), anaemia, neutropenia, gastrointestinal perforations and creatine phosphokinase (CPK) elevations occurred more frequently under UPA.
Comparison UPA & DMARD versus placebo & DMARD: The number of dose-dependent AEs and serious adverse events (SAEs) under UPA & DMARD was slightly higher than under placebo & DMARD.
Comparison UPA & DMARD versus ADA & DMARD: Under UPA & DMARD, however, SAEs were numerically somewhat less frequent than under ADA & DMARD.
Severe infections (serious infections and herpes zoster) were more frequent under UPA than under ADA or placebo. Hepatic disorders, neutropenia, gastrointestinal perforations and CPK elevations occurred more frequently under UPA.
Incorporation of the hitherto included long-term data (up to one year): The differences are still similar; in particular, no conclusive evidence of an increase in the rate of malignancies, or cardiovascular or VTE events has been reported to date.

The number of deaths per 100 patient years occurring in the pivotal studies during the controlled phase was lowest under UPA 15 mg and highest under UPA 30 mg.

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5.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

The presented study documentation consistently describes an advantage over MTX in terms of standard clinical and radiological endpoints when treating patients with at least moderate RA and various pretreatments with UPA, either in combination with MTX or as a single agent. The effects are within a range that can be expected from a modern DMARD. In combination with MTX, advantages are also described for various clinical endpoints in comparison with ADA; with respect to radiological endpoints, the course under UPA was slightly less advantageous, numerically, than with ADA. Safety issues were more frequently noted in the presented studies compared with the mentioned comparative treatments. These consisted mainly of infections (serious infections, reactivation of Tuberculosis, hepatitis, herpes zoster), rare cases of gastrointestinal perforation, and the following changes in laboratory values: neutropenia, CPK elevations and hyperlipidaemia.
With respect to efficacy the higher dose of 30 mg, which has been, and is being, closely investigated in pivotal studies, the frequencies of reported safety signals and deaths are both consistently higher than in the 15 mg dose.
Based on the postulated mechanism of action and theoretical considerations in the context of what generally amounts to only limited experience with JAK inhibitors, the available data leave open the possibility of significant long-term risks, especially due to immunosuppression. Upadacitinib has been associated with increased rates of viral reactivation, which may indicate suppression of the response to booster antigens. The effect of upadacitinib on the specific humoral immune response has not been studied for neo- or booster antigens and results of vaccination studies are currently missing. The documentation does not answer the question of whether the treatment could block the immune response to neo- and / or booster antigens for a long period. This should be considered in an individual risk-benefit analysis before beginning treatment with upadacitinib.

5.6 Approved Indication and Dosage

See Information for healthcare professionals in the Appendix.

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6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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7 Appendix

7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the Information for healthcare professionals relating to Rinvoq, prolonged-release tablet was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference documents, which are valid and relevant for the effective and safe use of medicinal products in Switzerland, are the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the Information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

RINVOQ®

Composition

Active substances

Upadacitinib as upadacitinib hemihydrate

Excipients

Microcrystalline cellulose, hypromellose, mannitol (E421), tartaric acid, silica (colloidal anhydrous), magnesium stearate, polyvinyl alcohol, macrogol, talc, titanium dioxide (E171), black iron oxide (E172), iron oxide red (E172).

Pharmaceutical form and active substance quantity per unit

RINVOQ 15 mg prolonged-release tablets.
Purple or mottled purple oblong biconvex prolonged-release tablets imprinted on one side with ‘a15’.
Each prolonged-release tablet contains upadacitinib hemihydrate, equivalent to 15 mg of upadacitinib.

Indications/Uses

RINVOQ is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis, who had an inadequate response or are intolerant to a treatment with one or more conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD).
RINVOQ may be used in combination with methotrexate or other csDMARDs or as monotherapy in adult patients.

Dosage/Administration

Treatment with RINVOQ should be initiated by physicians experienced in the diagnosis and treatment of rheumatoid arthritis.
The recommended oral dose of RINVOQ is 15 mg once daily with or without food. RINVOQ tablets should be swallowed whole. RINVOQ should not be split, crushed or chewed.

It is recommended that RINVOQ is not used in patients with an absolute lymphocyte count (ALC) less than 500 cells/mm^3, an absolute neutrophil count (ANC) less than 1000 cells/mm^3 or who have hemoglobin levels less than 8 g/dL.
If a patient develops a serious infection, RINVOQ treatment should be interrupted until the infection is controlled (see «Warnings and Precautions»).

Table 1: Recommended Dose Interruption for Laboratory Abnormalities

Laboratory measure	Action
Absolute Neutrophil Count (ANC)	Treatment should be interrupted if ANC is < 1000 cells/mm^3 and may be restarted once ANC return above this value
Absolute Lymphocyte Count (ALC)	Treatment should be interrupted if ALC is < 500 cells/mm^3 and may be restarted once ALC return above this value
Hemoglobin (Hb)	Treatment should be interrupted if Hb is < 8 g/dL and may be restarted once Hb return above this value
Hepatic transaminases	Treatment should be temporarily interrupted if drug-induced liver injury is suspected

Immunosuppressive medicinal products

Combination with other potent immunosuppressants such as azathioprine, cyclosporine, tacrolimus, and biologic DMARDs or other Janus kinase (JAK) inhibitors has not been evaluated in clinical studies and is not recommended.

Special dosage instructions

Patients with impaired hepatic function

No dose adjustment is required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. RINVOQ is not recommended for use in patients with severe hepatic impairment (Child Pugh C) (see «Pharmacokinetics»).

Patients with impaired renal function

No dose adjustment is required in patients with mild, moderate or severe renal impairment. The use of RINVOQ has not been studied in subjects with end stage renal disease (estimated glomerular filtration rate <15 ml/min/1.73 m^2).

Elderly patients

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

Children and adolescents

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

Missed dose

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

Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section «Composition»).

Warnings and precautions

Serious infections
Serious and sometimes fatal infections have been reported in patients receiving Rinvoq. The most frequent serious infections reported with RINVOQ included pneumonia and cellulitis (see «Undesirable effects»). Among opportunistic infections, tuberculosis, multidermatomal herpes zoster, oral/esophageal candidiasis and cryptococcosis were reported with RINVOQ.
Avoid use of RINVOQ in patients with an active, serious infection, including localized infections.
Consider the risks and benefits of treatment prior to initiating RINVOQ in patients:

- with chronic or recurrent infections
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses

  or

- with underlying conditions that may predispose them to infection.

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

Tuberculosis
Patients should be screened for tuberculosis (TB) before starting RINVOQ therapy. RINVOQ should not be given to patients with active TB. TB prophylaxis must be initiated prior to initiation of RINVOQ in patients with previously untreated latent TB. Consultation with a physician with expertise in the treatment of TB is recommended if it has to be decided whether an anti-TB therapy is appropriate for

an individual patient. Monitor patients for the development of signs and symptoms of TB, including patients who were tested negative for latent TB infection prior to initiating therapy.

Viral reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster) and hepatitis B, were reported in clinical studies (see «Undesirable effects»). If a patient develops herpes zoster, consider temporarily interrupting RINVOQ until the episode resolves.

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

Vaccination

No data are available on the response to vaccination with live or inactivated vaccines in patients receiving RINVOQ. Based on the current data, it cannot be assessed to which extent RINVOQ inhibits the immune response to neo and/or booster antigens. Use of live, attenuated vaccines during, or immediately prior to, RINVOQ therapy is not recommended. Prior to initiating RINVOQ, it is recommended that patients be brought up to date with all immunizations, including prophylactic zoster vaccinations, in agreement with current immunization guidelines.

Malignancy

Immunomodulatory medications may increase the risk of malignancies including lymphoma. The effect of RINVOQ treatment on malignancies is not known.

Malignancies were observed in clinical studies of RINVOQ (see «Undesirable effects»). Consider the risks and benefits of RINVOQ treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing RINVOQ in patients who develop a malignancy.

Non-Melanoma Skin Cancer (NMSC)

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

Thromboembolic events

Thromboembolic events (deep vein thrombosis, lung embolism and arterial thrombosis) with sometimes fatal outcome were observed under the treatment with JAK inhibitors including RINVOQ.

Gastrointestinal perforations
Gastrointestinal perforations were rarely observed under the treatment with RINVOQ.

Hematological abnormalities
Neutropenia – Treatment with RINVOQ was associated with an increased incidence of neutropenia (ANC < 1000 cells/mm^3). There was no clear association between low neutrophil counts and the occurrence of serious infections.
Lymphopenia - ALCs < 500 cells/mm^3 were reported in RINVOQ clinical studies. There was no clear association between low lymphocyte counts and the occurrence of serious infections.
Anemia – Decreases in hemoglobin levels to < 8 g/dL were reported in RINVOQ clinical studies.
The majority of the above hematologic laboratory changes were transient and resolved with temporary treatment interruption.
Evaluate at baseline and thereafter according to routine patient management. Treatment should not be initiated or should be temporarily interrupted in patients who meet the criteria described in Table 1 (see «Dosage/Administration»).

Lipids
Treatment with RINVOQ was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol (see Undesirable effects). Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.
Patients should be monitored 12 weeks after initiation of treatment and thereafter according to the international clinical guidelines for hyperlipidemia.

Hepatic Transaminase Elevations
Treatment with RINVOQ was associated with increased incidence of liver enzyme elevation compared to placebo.
Evaluate at baseline and thereafter according to routine patient management. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury.
If increases in ALT or AST are observed during routine patient management and drug-induced liver injury is suspected, RINVOQ should be interrupted until this diagnosis is excluded.

Interactions

Potential for other medicinal products to affect the pharmacokinetics of upadacitinib
Upadacitinib is metabolized in vitro by CYP3A with a minor contribution from CYP2D6.

Strong CYP3A4 inhibitors

Upadacitinib exposure is increased when co-administered with strong CYP3A inhibitors (such as ketoconazole). RINVOQ should be used with caution in patients receiving chronic treatment with strong CYP3A inhibitors. Consider alternatives to strong CYP3A inhibitor medications when used in the long-term.

Strong CYP3A4 inducers

Upadacitinib exposure is decreased when co-administered with strong CYP3A inducers (such as rifampin), which may lead to reduced therapeutic effect of RINVOQ (see «Pharmacokinetics»).
The concomitant use of RINVOQ with strong CYP3A4 inducers is not recommended.

Other interactions

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

The effect of co-administered medicinal products on upadacitinib plasma exposures is provided in Table 2.

Table 2. Drug Interactions: Change in Pharmacokinetics of Upadacitinib in the presence of Co-administered Drugs

				Ratio (90% CI)[a]		
Co-administered Drug	**Regimen of Co-administered Drug**	**Regimen of Upadacitinib**	**N**	**C_{max}**	**AUC**	**Clinical Impact**
Ketoconazole	400 mg daily x 6 days	3 mg single dose [b]	11	1.70 (1.55-1.89)	1.75 (1.62-1.88)	Use with caution if used chronically.
Rifampicin	600 mg once daily x 9 days	12 mg single dose [b]	12	0.49 (0.44-0.55)	0.39 (0.37-0.42)	May decrease efficacy Concomitant intake not recommended

CI: Confidence interval

[a] Ratios for C_{max} and AUC compare co-administration of the medication with upadacitinib vs. administration of upadacitinib alone.

[b] Upadacitinib was administered as an immediate-release formulation.

Potential for Upadacitinib to Affect the Pharmacokinetics of Other Drugs
The effect of upadacitinib on plasma exposures of other drugs is provided in Table 3.

Table 3. Drug Interactions: Change in Pharmacokinetics of Co-administered Drugs in the Presence of Upadacitinib.

				Ratio (90% CI)[a]		
Co-administered Drug	**Regimen of Co-administered Drug**	**Regimen of Upadacitinib**	**N**	**C_{max}**	**AUC**	**Clinical Impact**
Midazolam	5 mg single dose	30 mg once daily x 10 days	20	0.74 (0.68-0.80)	0.74 (0.68-0.80)	No dose adjustment
Rosuvastatin	5 mg single dose	30 mg once daily x 10 days	12	0.77 (0.63-0.94)	0.67 (0.56-0.82)	No dose adjustment
Atorvastatin	10 mg single dose	30 mg once daily x 10 days	24	0.88 (0.79-0.97)	0.77 (0.70-0.85)	No dose adjustment

CI: Confidence interval
[a] Ratios for C_{max} and AUC compare co-administration of the medication with upadacitinib vs. administration of medication alone.

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

Pregnancy, lactation

Pregnancy

There are limited data on the use of upadacitinib in pregnant women. Studies in animals have shown reproductive toxicity (see «Preclinical Data»). 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*.
RINVOQ must not be used during pregnancy unless clearly necessary. Females of reproductive potential should be advised that effective contraception should be used during treatment and for 4 weeks following the final dose of RINVOQ.

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

Lactation

It is unknown whether upadacitinib/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of upadacitinib in milk.
A risk to newborns/infants is possible. RINVOQ should not be used during breast-feeding. A decision must be made whether to discontinue breast-feeding or to discontinue RINVOQ 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 «Preclinical Data»).

Effects on ability to drive and use machines

The effect of RINVOQ on the ability to drive or use machines has not been specifically investigated.

Undesirable effects

Summary of the safety profile

The most commonly reported adverse drug reactions (ADRs) occurring in ≥ 2% of patients treated with RINVOQ either as monotherapy or in combination with conventional synthetic DMARDs were upper respiratory tract infections, nausea, cough and blood creatine phosphokinase (CPK) increased.
A total of 4443 patients with rheumatoid arthritis were treated with upadacitinib in clinical studies representing 5263 patient-years of exposure, of whom 2972 were exposed to RINVOQ for at least one year. In the Phase 3 studies, 2630 patients received at least 1 dose of RINVOQ 15 mg, of whom 1607 were exposed for at least one year.
Three placebo-controlled studies were integrated (1035 patients on RINVOQ 15 mg once daily and 1042 patients on placebo) to evaluate the safety of RINVOQ 15 mg in comparison to placebo for up to 12-14 weeks after treatment initiation.

Summary of adverse reactions

The adverse reactions are listed below by body system organ class and frequency. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) or very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Infections and infestations
Very Common: Upper respiratory tract infections (URTI)* (13.5 %)
Uncommon: Pneumonia, Herpes zoster, Herpes simplex**, Oral candidiasis

Blood and lymphatic system disorders
Common: Neutropenia

Metabolism and nutrition disorders
Common: Hypercholesterolemia

Respiratory, thoracic and mediastinal disorders
Common: Cough

Gastrointestinal disorders
Common: Nausea

General disorders
Common: Pyrexia

Investigations
Common: Blood creatine phosphokinase (CPK) increased

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

Specific Adverse Reactions
Infections
In placebo-controlled clinical studies with background DMARDs, the frequency of infection over 12/14 weeks in the RINVOQ 15 mg group was 27.4% compared to 20.9% in the placebo group. In MTX-controlled studies, the frequency of infection over 12/14 weeks in the RINVOQ 15 mg monotherapy group was 19.5% compared to 24.0% in the MTX group The overall long-term rate of infections for the RINVOQ 15 mg group across all five Phase 3 clinical studies (2630 patients) was 93.7 events per 100 patient-years.
In placebo-controlled clinical studies with background DMARDs, the frequency of serious infection over 12/14 weeks in the RINVOQ 15 mg group was 1.2% compared to 0.6% in the placebo group. In MTX-controlled studies, the frequency of serious infection over 12/14 weeks in the RINVOQ 15 mg monotherapy group was 0.6% compared to 0.4% in the MTX group. The overall long-term rate of serious infections for the RINVOQ 15 mg group across all five Phase 3 clinical studies was 3.8 events per 100 patient-years. The most frequently reported serious infections were pneumonia and cellulitis. The rate of serious infections remained stable with long term exposure.

Tuberculosis

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

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

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

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

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

Hepatic transaminase elevations
In placebo-controlled studies with background DMARDs, for up to 12/14 weeks, alanine transaminase (ALT) and aspartate transaminase (AST) elevations ≥ 3 x upper limit of normal (ULN) in at least one measurement were observed in 2.1% and 1.5% of patients treated with RINVOQ 15 mg, compared to 1.5% and 0.7%, respectively, of patients treated with placebo. Most cases of hepatic transaminase elevations were asymptomatic and transient.
In MTX-controlled studies, for up to 12/14 weeks, ALT and AST elevations ≥ 3 x upper limit of normal (ULN) in at least one measurement were observed in 0.8% and 0.4% of patients treated with RINVOQ 15 mg, compared to 1.9% and 0.9% respectively of patients treated with MTX.
The pattern and incidence of elevation in ALT/AST remained stable over time including in long-term extension studies.

Lipid elevations

RINVOQ 15 mg treatment was associated with increases in lipid parameters including total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol. Elevations in LDL and HDL cholesterol peaked by week 8 and remained stable thereafter. In controlled studies, for up to 12/14 weeks, changes from baseline in lipid parameters in patients treated with RINVOQ 15 mg are summarized below:

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

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

Neutropenia
In placebo-controlled studies with background DMARDs, for up to 12/14 weeks, decreases in neutrophil counts, below 1000 cells/mm^3 in at least one measurement occurred in 1.1% and <0.1% of patients in the RINVOQ 15 mg and placebo groups, respectively. In clinical studies, treatment was

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

Lymphopenia
In placebo-controlled studies with background DMARDs, for up to 12/14 weeks, decreases in lymphocyte counts below 500 cells/mm^3 in at least one measurement occurred in 0.9% and 0.7% of patients in the RINVOQ 15 mg and placebo groups, respectively.

Anemia
In placebo-controlled studies with background DMARDs, for up to 12/14 weeks, hemoglobin decrease below 8 g/dL in at least one measurement occurred in <0.1 % of patients in both the RINVOQ 15 mg and placebo groups.

Reporting suspected adverse 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 new or serious adverse reaction via the online portal ElViS (Electronic Vigilance System). Please find more information under www.swissmedic.ch.

Overdose

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

Properties/Effects

ATC code

pending

Mechanism of action

Janus Kinases (JAKs) are important intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, 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 inhibitor of JAK1. Upadacitinib more potently inhibits JAK1 compared to JAK2 and JAK3. In cellular potency assays that correlated with the *in vivo* pharmacodynamic responses, upadacitinib demonstrated 50–70-fold greater selectivity for JAK1 over JAK2 and >100-fold for JAK1 over JAK3.

Pharmacodynamics

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

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

Immunoglobulins
In the controlled period, small decreases from baseline in mean IgG and IgM levels were observed with upadacitinib treatment; however, the mean values at baseline and at all visits were within the normal reference range.

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

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

Clinical efficacy

The efficacy and safety of RINVOQ 15 mg once daily was assessed in five Phase 3 randomized, double-blind, multicenter studies in patients with moderately to severely active rheumatoid arthritis and fulfilling the ACR/EULAR 2010 classification criteria (see Table 4). Patients over 18 years of age

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.

Table 4. Clinical Trial Summary

Study Name	Population (n)	Treatment Arms	Key Outcome Measures
SELECT-EARLY	MTX-naive[a] (947)	• Upadacitinib 15 mg • Upadacitinib 30 mg • MTX Monotherapy	Primary Endpoint: • ACR50 at Week 12 Key Secondary Endpoints: • Clinical Remission (DAS28-CRP <2.6) at Week 24 • Low Disease Activity (DAS28-CRP ≤3.2) at Week 12 • Δ Physical Function (HAQ-DI) at Week 12 • Radiographic progression (ΔmTSS) at Week 24
SELECT-MONOTHERAPY	MTX-IR[b] (648)	• Upadacitinib 15 mg • Upadacitinib 30 mg • MTX Monotherapy	Primary Endpoint: • ACR20 at Week 14 Key Secondary Endpoints: • Low Disease Activity (DAS28-CRP ≤3.2) at Week 14 • Clinical Remission (DAS 28-CRP <2.6) at Week 14 • Δ Physical Function (HAQ-DI) at Week 14
SELECT-NEXT	csDMARD-IR[c] (661)	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo On background csDMARDs	Primary Endpoint: • ACR20 at Week 12 Key Secondary Endpoints: • Low Disease Activity (DAS28-CRP ≤3.2) at Week 12 • Clinical Remission (DAS28-CRP <2.6) at Week 12 • Δ Physical Function (HAQ-DI) at Week 12

SELECT-COMPARE	MTX-IR[d] (1629)	• Upadacitinib 15 mg • Placebo • Adalimumab 40 mg On background MTX	Primary Endpoint: • ACR20 at Week 12 Key Secondary Endpoints: • Clinical Remission (DAS28-CRP <2.6) at Week 12 • Low Disease Activity (DAS28-CRP ≤3.2) at Week 12 • ACR50 vs adalimumab at Week 12 • Δ Physical Function (HAQ-DI) at Week 12 • Radiographic progression (ΔmTSS) at Week 26
SELECT-BEYOND	bDMARD-IR[e] (499)	• Upadacitinib 15 mg • Upadacitinib 30 mg • Placebo On background csDMARDs	Primary Endpoint: • ACR20 at Week 12 Key Secondary Endpoint: • Low Disease Activity (DAS28-CRP ≤3.2) at Week 12 • Δ Physical Function (HAQ-DI) at Week 12

Abbreviations: ACR20 (or 50) = American College of Rheumatology ≥20% (or ≥50%) improvement, bDMARD = biologic disease-modifying anti-rheumatic drug; CR = Clinical Response, 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, IR = inadequate responder, MTX = methotrexate

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

[b] Patients had inadequate response to MTX

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

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

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

Clinical Response

Remission and low disease activity

In all studies, a higher proportion of patients treated with RINVOQ 15 mg achieved both low disease activity (DAS28 CRP ≤3.2) and clinical remission (DAS28 CRP <2.6) compared to placebo, MTX, or adalimumab (Table 5). Compared to adalimumab, higher responses were achieved as early as Week 8 and maintained through Week 48. Higher responses were also observed for other disease activity outcomes including CDAI ≤2.8, SDAI ≤3.3, and Boolean remission. Overall, both low disease activity and clinical remission rates were consistent across patient populations, with or without MTX.

ACR Response

In all studies, more patients treated with RINVOQ 15 mg achieved ACR20, ACR50, and ACR70 responses at 12 weeks compared to placebo, MTX or adalimumab (Table 5). 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 RINVOQ 15 mg, alone or in combination with csDMARDs, resulted in greater improvements in individual ACR components, including tender and swollen joint counts, patient and physician global assessments, HAQ-DI, pain assessment, and hsCRP, compared to placebo, MTX monotherapy or adalimumab (Table 6).

In SELECT-COMPARE, a higher proportion of patients treated with RINVOQ 15 mg achieved ACR20/50/70 at Weeks 12 through 48 compared to adalimumab (Table 6).

Table 5. Response and Remission

Study	SELECT EARLY MTX-naive		SELECT MONO MTX-IR		SELECT NEXT csDMARD-IR		SELECT COMPARE MTX-IR			SELECT BEYOND bDMARD-IR	
	MTX	UPA 15 mg	MTX	UPA 15 mg	PBO	UPA 15 mg	PBO	UPA 15 mg	ADA 40 mg	PBO	UPA 15 mg
N	314	317	216	217	221	221	651	651	327	169	164
Week											
ACR20 (% of patients)											
12[a]/14[b]	54	76[g]	41	68[e]	36	64[e]	36	71[e,i]	63	28	65[e]
24[c]/26[d]	59	79[g]					36	67[g,i]	57		
48	57	74[g]						65[i]	54		
ACR50 (% of patients)											
12[a]/14[b]	28	52[e]	15	42[g]	15	38[g]	15	45[g,h]	29	12	34[g]
24[c]/26[d]	33	60[g]					21	54[g,i]	42		
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,i]	13	7	12
24[c]/26[d]	18	44[g]					10	35[g,i]	23		
48	29	51[g]						36[i]	23		

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

Abbreviations: ACR20 (or 50 or 70) = American College of Rheumatology ≥20% (or ≥50% or ≥70%) improvement; ADA = adalimumab; CDAI = Clinical Disease Activity Index; CR = Clinical Remission; CRP = c-reactive protein, DAS28 = Disease Activity Score 28 joints; LDA = Low Disease Activity; MTX = methotrexate; PBO = placebo; SDAI = Simple Disease Activity Index; UPA= upadacitinib

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

[b] SELECT-MONOTHERAPY

[c] SELECT-EARLY

[d] SELECT-COMPARE

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

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

[g] Upadacitinib vs placebo or MTX comparison (These comparisons are not controlled for multiplicity)

[h] p≤0.001upadacitinib vs adalimumab comparison

[i] Upadacitinib vs adalimumab comparison (These comparisons are not controlled for multiplicity)

Table 6: Components of ACR Response (mean change from baseline)[a]

Study	**SELECT EARLY MTX-Naive**		**SELECT MONO MTX-IR**		**SELECT NEXT csDMARD-IR**		**SELECT COMPARE MTX-IR**			**SELECT BEYOND bDMARD-IR**	
	MTX	UPA 15 mg	MTX	UPA 15 mg	PBO	UPA 15 mg	PBO	UPA 15 mg	ADA 40 mg	PBO	UPA 15 mg
N	314	317	216	217	221	221	651	651	327	169	164
Week											
Number of tender joints (0-68)											
12[b]/	-13	-17[h]	-11	-15[h]	-8	-14[h]	-10	-16[h,I]	-14	-8	-16[h]

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

Abbreviations: ACR = American College of Rheumatology; ADA = adalimumab; CRP = c-reactive protein; HAQ-DI = Health Assessment Questionnaire Disability Index; IR = inadequate responder; MTX = methotrexate; PBO = placebo; UPA = upadacitinib

[a] Data shown are mean

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

[c] SELECT-MONOTHERAPY

[d] SELECT-EARLY

[e] SELECT-COMPARE

[f] Visual analog scale: 0 = best, 100 = worst

[g] Health Assessment Questionnaire-Disability Index: 0=best, 3=worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

[h] Upadacitinib vs placebo or MTX comparison (These comparisons are not controlled for multiplicity)

[i] p≤0.001 upadacitinib vs placebo or MTX comparison

[j] p≤0.001 upadacitinib vs adalimumab comparison

[k] p≤0.01 upadacitinib vs adalimumab comparison

[l] Upadacitinib vs adalimumab comparison (These comparisons are not controlled for multiplicity)

Radiographic response

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

Treatment with RINVOQ 15 mg resulted in significantly greater inhibition of the progression of structural joint damage compared to placebo at week 26 and 48 in SELECT-COMPARE and as monotherapy compared to MTX at week 24 in SELECT-EARLY (Table 7). Statistically significant results were also achieved for both erosion and joint space narrowing scores. The proportion of patients with no radiographic progression (mTSS change ≤ 0) was significantly higher with RINVOQ 15 mg compared to placebo at week 26 and 48 (SELECT-COMPARE) and compared to MTX at week 24 (SELECT-EARLY).

Table 7: Radiographic Changes

Study	**SELECT EARLY MTX-Naive**		**SELECT COMPARE MTX-IR**		
Treatment Group	MTX	UPA 15 mg	PBO[a]	UPA 15 mg	ADA 40 mg

Modified Total Sharps Score, mean change from baseline					
Week 24[b]/26[c]	0.7	0.1[f]	0.9	0.2[e]	0.1
Week 48			1.7	0.3[e]	0.4
Erosion Score, mean change from baseline					
Week 24[b]/26[c]	0.3	0.1[e]	0.4	0[e]	0
Week 48			0.8	0.1[e]	0.2
Joint Space Narrowing Score, mean change from baseline					
Week 24[b]/26[c]	0.3	0.1[g]	0.6	0.2[e]	0.1
Week 48			0.8	0.2[e]	0.2
Proportion of patients with no radiographic progression[d]					
Week 24[b]/26[c]	77.7	87.5[f]	76.0	83.5[f]	86.8
Week 48			74.1	86.4[e]	87.9

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

[a] All placebo data at week 48 derived using linear extrapolation

[b] SELECT-EARLY

[c] SELECT-COMPARE

[d] No progression defined as mTSS change ≤0.

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

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

[g] p≤0.05 upadacitinib vs placebo or MTX comparison

Physical function response and health-related outcomes

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

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

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

Across all studies, greater improvement in physical component summary (PCS) score of the Short Form Health Survey (SF-36) compared to placebo or MTX was documented. In SELECT-EARLY, SELECT-MONOTHERAPY, and SELECT-COMPARE patients receiving RINVOQ 15 mg experienced

significantly greater improvement in mental component summary (MCS) scores and in all 8 domains of SF-36 compared to placebo or MTX.
Fatigue was assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F) in SELECT-EARLY, SELECT-NEXT and SELECT- COMPARE studies. Treatment with RINVOQ 15 mg resulted in improvement in fatigue compared to placebo, MTX, or adalimumab.
RA-associated work instability was assessed by the Rheumatoid Arthritis-Work Instability Scale (RA-WIS) in employed patients in SELECT-NEXT and SELECT-COMPARE. Treatment with RINVOQ 15 mg resulted in significantly greater reduction in work instability compared to placebo.

Pharmacokinetics

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 extended-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_{inf} 29% and C_{max} 39%). In clinical trials, RINVOQ was administered without regard to meals (see «Dosage and Administration»).

Distribution

Upadacitinib is 52% bound to plasma proteins. Upadacitinib has a blood to plasma ratio of 1.0 indicating that it partitions similarly between plasma and blood cellular components.

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, upadacitinib accounted for 79% of the total radioactivity in plasma while the two main metabolites detected (products of monooxidation followed by glucuronidation or monooxidation followed by ring opening) accounted for 13% and 7.1% of the total plasma radioactivity, respectively. 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 feces (38%). Approximately 34% of upadacitinib dose was excreted as metabolites. Upadacitinib mean terminal elimination half-life ranged from 9 to 14 hours.

Kinetics in specific patient groups

Hepatic impairment

Upadacitinib AUC was 28% and 24% higher in subjects with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment, respectively, compared to subjects with normal liver function. Upadacitinib C_{max} was unchanged in subjects with mild hepatic impairment and 43% higher in subjects with moderate hepatic impairment compared to subjects with normal liver function. Upadacitinib was not studied in patients with severe hepatic impairment (Child-Pugh C).

Renal impairment

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. Upadacitinib was not studied in subjects with end stage renal impairment (estimated glomerular filtration rate <15 ml/min/1.73 m^2) or in subjects undergoing renal dialysis.

Other Intrinsic Factors

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

Preclinical data

In nonclinical studies in animals, decreases in circulating lymphocytes and decreased cellularity of lymphoid tissues, as well as suppression of erythropoiesis, were observed in rats and dogs at clinically relevant doses. Secondary effects related to opportunistic infections, such as demodicosis (mange) in dogs, were observed at exposures approximately two times the expected exposures (AUC) at the clinical dose of 15 mg.

Mutagenicity

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

Carcinogenicity

Upadacitinib, at exposure levels approximately 4 and 10 times the clinical dose of 15 mg (on an AUC basis at oral doses in male and female rats at 15 and 20 mg/kg/day, respectively), was not carcinogenic based on 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.

Reproductive toxicity

Upadacitinib is teratogenic in both rats and rabbits when given at exposures of 1.6 or 15 times the clinical dose of 15 mg (on an AUC basis at maternal oral doses of 4 mg/kg/day or 25 mg/kg/day, respectively). Effects in rats included an increase in two particular skeletal malformations (i.e., misshapen humerus and bent scapula) and an increase in bent bones of the fore- and hind-limbs. Developmental effects in rabbits included an increase in post-implantation losses, increase in total and early resorptions, lower fetal body weights, and increased incidence of cardiac malformations. 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.

Upadacitinib had no effect on fertility in male or female rats at doses up to 50 mg/kg/day in males and 75 mg/kg/day in females in a fertility and early embryonic development study. Dose related increases in foetal resorptions associated with post-implantation losses at 25 and 75 mg/kg/day in this study were attributed to the developmental/teratogenic effects of upadacitinib in rats.
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.

Other information

Shelf life

The drug product can be used only up to the expiry date identified by «EXP».

Special precautions for storage

Do not store above 25 °C.
Store in the original blister to protect from moisture.
Keep out of reach of children.

Authorisation number

67257 (Swissmedic)

Packs

RINVOQ 15 mg: blister with 28 prolonged-release tablets (B)

Marketing authorisation holder

AbbVie AG, 6341 Baar

Date of revision of the text

January 2020