

Upacit XRTM 15 mg Tablet
(Upadacitinib)
Extended Release Tablets

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COMPOSITION:

Each film coated extended release tablet contains:
Upadacitinib Hemihydrate equivalent to
Upadacitinib 15 mg.

Product Specs.: Innovator

CLINICAL PARTICULARS:

Therapeutic Indications:

Upadacitinib is a Janus kinase (JAK) inhibitor indicated for the treatment of:

- Moderately to severely active rheumatoid arthritis (RA) in adults who have had an inadequate response or intolerance to one or more TNF blockers.
- Active psoriatic arthritis (PsA) in adults and paediatric patients ≥ 2 years of age who have had an inadequate response or intolerance to one or more TNF blockers.
- Refractory, moderate to severe atopic dermatitis (AD) in adults and paediatric patients ≥ 12 years of age whose disease is not adequately controlled with other systemic drugs, including biologics, or when those therapies are inadvisable.
- Moderately to severely active ulcerative colitis (UC) in adults who have had an inadequate response or intolerance to one or more TNF blockers (as maintenance therapy following induction; 15 mg is the standard maintenance dose).
- Moderately to severely active Crohn's disease (CD) in adults who have had an inadequate response or intolerance to one or more TNF blockers (as maintenance therapy following induction).
- Active ankylosing spondylitis (AS) in adults who have had an inadequate response or intolerance to one or more TNF blockers.
- Active non-radiographic axial spondylarthritis (nr-axSpA) with objective signs of inflammation in adults who have had an inadequate response or intolerance to TNF blocker therapy.
- Active polyarticular juvenile idiopathic arthritis (pJIA) in patients ≥ 2 years of age who have had an inadequate response or intolerance to one or more TNF blockers.
- Giant cell arteritis (GCA) in adults.

Limitations of use:

Upadacitinib is not recommended for use in combination with other JAK inhibitors, biologic DMARDs/immunomodulators, or with potent immunosuppressants such as azathioprine and cyclosporine.

POSLOGY AND METHOD OF ADMINISTRATION:

General administration:

- Take orally, with or without food, at approximately the same time each day.
- Swallow tablets whole; do not split, crush, or chew.

Rheumatoid Arthritis, Ankylosing Spondylitis, Non-radiographic Axial Spondylarthritis: 15 mg once daily.

Psoriatic Arthritis (adults): 15 mg once daily.

Atopic Dermatitis:

Adults < 65 years and paediatric patients ≥ 12 years (≥ 40 kg): initiate at 15 mg once daily; may increase to 30 mg once daily if response is inadequate.

Adults ≥ 65 years: 15 mg once daily.

Ulcerative Colitis / Crohn's Disease (maintenance):

Following induction with the 45 mg once-daily dose, the recommended maintenance dosage is 15 mg once daily. A 30 mg once-daily maintenance dose may be considered in patients with refractory, severe, or extensive disease; discontinue if an adequate response is not achieved at 30 mg. Use the lowest effective dose to maintain response.

Giant Cell Arteritis: 15 mg once daily in combination with a tapering course of corticosteroids; may be continued as monotherapy at 15 mg once daily after corticosteroid discontinuation.

Special populations:

- **Renal impairment:** No dose adjustment needed for mild-to-moderate impairment in most indications; dose reductions apply for severe renal impairment in UC/CD/AD (see full prescribing information). Not recommended in end-stage renal disease for UC/AD.
- **Hepatic impairment:** No adjustment needed for mild-to-moderate (Child-Pugh A/B) impairment. Not recommended in severe hepatic impairment (Child-Pugh C).
- **Elderly (≥ 65 years):** 15 mg once daily is the recommended dose; use with caution given increased risk of serious infection and malignancy.
- **Concomitant strong CYP3A4 inhibitors:** Dose modification may be required depending on indication.

Missed dose:

If a dose is missed, take it as soon as remembered on the same day; do not take two doses on the same day to make up for a missed dose.

CONTRAINDICATIONS:

- Known hypersensitivity to upadacitinib or to any of the excipients
- Active, serious infections, including active tuberculosis
- Severe hepatic impairment (Child-Pugh C)
- Pregnancy

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Boxed warning (class warning for JAK inhibitors) – Serious Infections, Mortality, Malignancy, Major Adverse Cardiovascular Events (MACE), and Thrombosis:

Patients treated with upadacitinib are at increased risk for serious infections that may lead to hospitalisation or death, including tuberculosis, invasive fungal infections, and other opportunistic infections. Higher rates of all-cause mortality (including sudden cardiovascular death), malignancy (including lymphoma), major adverse cardiovascular events, and thrombosis have been observed with JAK inhibitors compared with TNF blockers, particularly in patients ≥ 50 years of age with at least one cardiovascular risk factor. Consider the risks and benefits before initiating or continuing therapy, particularly in current or past smokers and patients with cardiovascular risk factors.

Serious infections:

Avoid initiation in patients with an active, serious infection. Evaluate for latent and active tuberculosis before and periodically during treatment; treat latent TB before starting Upadacitinib. Screen for viral hepatitis. Interrupt treatment if a serious or opportunistic infection develops.

Malignancy:

Consider risks and benefits, particularly in patients with a known malignancy, those who develop malignancy on treatment, and current or past smokers. Periodic skin examination is recommended; non-melanoma skin cancer has been reported.

Cardiovascular and thrombotic events:

Discontinue in patients who experience myocardial infarction or stroke. Avoid use in patients at increased risk of thrombosis; discontinue and evaluate promptly if symptoms of thrombosis occur.

Hypersensitivity:

Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported. Discontinue if a clinically significant hypersensitivity reaction occurs.

Gastrointestinal perforation:

Monitor patients at risk (e.g., history of diverticulitis, concomitant NSAIDs or corticosteroids); evaluate promptly for new-onset abdominal pain.

Hypoglycaemia in patients with diabetes:

Hypoglycaemia, including severe hypoglycaemia, has been reported. Consider increased blood glucose monitoring in patients with diabetes.

Laboratory abnormalities:

Neutropenia, lymphopenia, anaemia, elevated liver enzymes, and increases in lipid parameters (LDL-C, HDL-C, triglycerides) have been observed. Monitor blood counts, liver enzymes, and lipid parameters at baseline and periodically; interrupt treatment per laboratory thresholds (ANC < 1000 cells/mm³, ALC < 500 cells/mm³, Hb < 8 g/dL, or suspected drug-induced liver injury).

Vaccinations:

Avoid live vaccines during and immediately before treatment. Update immunisations, including herpes zoster vaccination, prior to initiation.

Medication residue in stool:

Reported mainly in patients with anatomic or functional GI conditions with shortened transit time (e.g., ostomy, intestinal resection). Advise patients to report this; consider alternative treatment if therapeutic response is inadequate.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:

- **Strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin):** may increase upadacitinib exposure; dose adjustment may be required depending on indication.
- **Strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, St John's Wort):** co-administration is not recommended, as this may reduce upadacitinib efficacy.

- **Live vaccines:** avoid concomitant use.
- **Other immunosuppressants/biologic DMARDs/other JAK inhibitors:** combination not recommended due to potential for additive immunosuppression.

FERTILITY, PREGNANCY AND LACTATION:

Pregnancy: Contraindicated in pregnancy. Animal studies showed increased fetal malformations. Verify pregnancy status before initiating treatment in females of reproductive potential. Effective contraception must be used during treatment and for at least 4 weeks after the last dose.

Lactation: Breastfeeding is not recommended during treatment with Upadacitinib, as upadacitinib may be excreted in human milk.

Fertility: No specific human fertility data; animal studies did not show adverse effects on fertility parameters at clinically relevant exposures.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

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

UNDESIRABLE EFFECTS:

Very Common (≥ 1/10):

- Upper respiratory tract infection

Common (≥ 1/100 to < 1/10):

- Nausea
- Cough
- Pyrexia (fever)
- Headache
- Acne
- Herpes zoster and herpes simplex (including oral herpes)
- Folliculitis
- Increased blood creatine phosphokinase
- Elevated liver enzymes / transaminases
- Neutropenia, lymphopenia
- Hyperlipidaemia / hypercholesterolaemia
- Bronchitis, pneumonia
- Fatigue, myalgia

Uncommon / Rare:

- Serious infections, including tuberculosis and opportunistic infections (e.g., cryptococcosis, oesophageal candidiasis)
- Hepatitis B reactivation
- Malignancies, including lymphoma and non-melanoma skin cancer
- Major adverse cardiovascular events (myocardial infarction, stroke)
- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) and arterial thrombosis
- Gastrointestinal perforation
- Hypersensitivity reactions, including anaphylaxis and angioedema
- Hypoglycaemia (in patients with diabetes)

Report suspected adverse reactions to the relevant national reporting system or the marketing authorisation holder.

PHARMACOLOGICAL PROPERTIES:

Pharmacodynamic Properties:

Pharmacotherapeutic group:

Immunosuppressants, selective immunosuppressants; **ATC code:** L04AF03.

Mechanism of Action:

Upadacitinib is a selective and reversible inhibitor of Janus kinase 1 (JAK1). JAK enzymes (JAK1, JAK2, JAK3, and TYK2) mediate intracellular signalling of cytokines and growth factors involved in haematopoiesis and immune cell function via the JAK-STAT (signal transducer and activator of transcription) pathway. By selectively inhibiting JAK1, upadacitinib modulates the signalling of cytokines implicated in the pathophysiology of inflammatory and immune-mediated diseases, including IL-6, IL-7, IL-15, IL-21, interferons, and GM-CSF; thereby reducing STAT phosphorylation and downstream inflammatory gene transcription.

Pharmacodynamic Effects:

- Dose-dependent inhibition of IL-6-induced STAT3 and IL-7-induced STAT5 phosphorylation.
- Transient, reversible decreases observed in circulating lymphocytes, neutrophils, and reticulocytes, generally returning toward baseline after treatment interruption.

- Increases in lipid parameters (total cholesterol, LDL-C, HDL-C) are observed, with LDL-C responsive to statin therapy.

Clinical Efficacy:

In pivotal Phase 3 trials across rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, ulcerative colitis, Crohn's disease, ankylosing spondylitis, non-radiographic axial spondylarthritis, polyarticular juvenile idiopathic arthritis, and giant cell arteritis, upadacitinib (15 mg and/or 30 mg and/or 45 mg once daily, depending on indication and treatment phase) demonstrated statistically significant improvements versus placebo or active comparator in disease-specific efficacy endpoints (e.g., ACR20/50/70 in RA/PsA, EASI-75/IGA in AD, clinical remission/endoscopic improvement in UC/CD, ASAS40 in AS/nr-axSpA, and sustained remission in GCA).

PHARMACOKINETIC PROPERTIES:

Absorption:

Following oral administration of the extended-release tablet, peak plasma concentrations are achieved within approximately 2–4 hours. Steady state is reached within approximately 4 days with once-daily dosing. Food has no clinically meaningful effect on upadacitinib exposure; tablets may be taken with or without food.

Distribution:

Upadacitinib is approximately 52% bound to plasma proteins. The apparent volume of distribution is approximately 51.5 L, indicating extravascular tissue distribution.

Metabolism:

Upadacitinib is metabolised primarily by CYP3A4, with minor contribution from CYP2D6. Unchanged upadacitinib is the predominant circulating moiety in plasma.

Elimination:

The terminal elimination half-life is approximately 8–14 hours. Upadacitinib is eliminated via both metabolic clearance (largely CYP3A4-mediated) and renal excretion, with approximately 24% of the dose excreted unchanged in urine and the remainder as metabolites in urine and faeces.

Special Populations:

- **Hepatic impairment:** exposure is not significantly altered in mild or moderate (Child-Pugh A/B) impairment; not studied/recommended in severe (Child-Pugh C) impairment.
 - **Renal impairment:** exposure increases with decreasing renal function; dose adjustment is required in select indications for severe renal impairment (see Section 4.2); not recommended in end-stage renal disease for certain indications.
 - **Elderly:** no clinically significant effect of age alone on pharmacokinetics; increased vigilance is recommended for infection, malignancy, and cardiovascular risk in patients ≥ 65 years.
 - **Paediatric patients:** pharmacokinetics have been characterised in weight-based dosing for pJIA and PsA, and in adolescents ≥ 12 years for AD.
- Clinical Implication of PK/PD Profile:**
- Extended release formulation permits convenient once-daily dosing while maintaining sustained JAK1 inhibition.
 - Minimal food effect supports flexible administration timing.
 - Predominantly hepatic (CYP3A4) metabolism underlies the potential for interaction with strong CYP3A4 inhibitors/inducers.

INSTRUCTIONS:

- Store below 30°C.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:

Upasit XR Tablet 15 mg : Pack of 3 x 10 Tablets.

Manufactured by:
Wenits Pharmaceuticals Pvt. Ltd.
Plot No. 129, Sundar Industrial Estate, Raiwind Road, Lahore, Pakistan.

FOR FURTHER INFORMATION PLEASE CONTACT:



Marketed by:
CCL Pharmaceuticals (Pvt.) Ltd.
62 Industrial Estate, Kot Lakhpat, Lahore, Pakistan.

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۳۰ درجہ سینٹی گریٹ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔