Upadacitinib (RINVOQ) in Crohn's Disease
Criteria for Use
February 2025

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

Exclusion Criteria

If the answer to ANY item below is met, then the patient should NOT receive upadacitinib.

- ☐ Uncontrolled, active, severe infection including evidence of *C. difficile* and undrained abscess (however, upadacitinib may be started / restarted once the infection treatment has been initiated).
- ☐ Untreated latent or active tuberculosis infection.
- ☐ Hepatitis B surface antigen (HBsAg)-positive and not on antiviral prophylaxis.[1] Upadacitinib may be initiated after starting antiviral prophylaxis.^1
- ☐ Untreated HIV infection. Treated, well-controlled, asymptomatic HIV-positive patients can be treated with upadacitinib.
- ☐ Malignancy within the previous 5 years other than successfully treated nonmelanoma skin cancer or cervical cancer unless it is documented that the treating gastroenterologist and oncologist agree that risk-benefits favor using the drug.
- ☐ At increased risk of thrombosis or major adverse cardiovascular events where potential harms are expected to outweigh the anticipated benefits.
- ☐ Lymphocytes < 500 cells/mm^3 confirmed by repeat testing, neutrophils < 1000 cells/mm^3, or hemoglobin < 8 g/dL. (Upadacitinib may be started / restarted once values normalize.)
- ☐ End stage renal disease (eGFR < 15 mL/min/1.73 m^2
- ☐ Severe hepatic impairment (Child-Pugh C).
- ☐ Concomitant live or live-attenuated vaccines or administration of inactivated, live, or live-attenuated vaccines less than 2 weeks before initiation of upadacitinib.^2
- ☐ Concomitant JAK inhibitors, biologic immunomodulators, or potent immunosuppressants such as azathioprine and cyclosporine.
- ☐ Concomitant strong CYP3A4 inducers.
- ☐ Pregnancy (during therapy and for 4 weeks after the last dose of upadacitinib).
- ☐ Breastfeeding / providing breastmilk to an infant (during therapy and for 6 days after the last dose).

Inclusion Criteria

All of the following criteria must be met:

- ☐ Prescribed^3 and monitored by a VA/VA Community Care gastroenterologist or locally designated Crohn's disease expert.
- ☐ Current or prior moderate to severe **Crohn's disease (CD)** confirmed by endoscopy or imaging.
- ☐ Completed tuberculosis (TB) test using tuberculin skin test or interferon-gamma release assay [IGRA].
- ☐ Completed hepatitis B screening (at minimum, HBsAg, total antibody-to-hepatitis-B-core-antigen (anti-HBc) and antibody to hepatitis B surface antigen [anti-HBs]).
- ☐ Current or past completion of hepatitis C screening. (Upadacitinib may be initiated while waiting for test results.)

Additional Inclusion Criteria

ONE of the following criteria must be met:

- ☐ **Tumor necrosis factor inhibitor (TNFI)** is medically inadvisable. Infliximab / biosimilar and adalimumab / biosimilar are the preferred TNFIs in CD.
- ☐ Primary nonresponse, inadequate partial response, or loss of response after 12 weeks of **TNFI** in the presence of adequate **TNFI** levels (mechanistic failure).
- ☐ Loss of response to **infliximab / biosimilar and another TNFI for CD** despite therapeutic drug monitoring (TDM)-based optimized dosing to address pharmacokinetic failure.^4,^5

See footnote 6 for sequencing CD drugs.

Additional Inclusion Criteria

Select if appropriate.

- ☐ If HBsAg-negative but anti-HBc-positive, a GI / liver or infectious diseases expert has been consulted for advice on whether to start antiviral prophylaxis or to preemptively monitor for HBV reactivation.
- ☐ For women who can become pregnant: Pregnancy status verified. Counseling provided on potential risks vs benefits of treatment and the use of effective contraception during therapy and for 4 weeks after discontinuation of therapy.

Other Justification

- ☐ _____

Footnotes

1. Antiviral prophylaxis for HBV: Agents with high genetic barrier to resistance such as entecavir or tenofovir should be used.
2. When possible, vaccinations should be updated before the patient initiates upadacitinib. Unless contraindicated, recombinant zoster (SHINGRIX) vaccine should be completed or at least initiated by the end of the first year of treatment with upadacitinib, preferably when dosage is low, disease is stable, or at other times when a robust immune response to vaccination can be expected.
3. Prescribe at the FDA-recommended dose for ulcerative colitis, adjusting for severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m^2), mild to moderate hepatic impairment (Child-Pugh A or B), and strong CYP3A4 inhibitors.

[4] Loss of response refers to active disease confirmed by endoscopy, imaging, or biochemical assessment.

[5] Pharmacokinetic failure resulting in low TNFI levels may be immune-mediated or non–immune-mediated.
If **TNFI levels are undetectable with high antidrug antibody (AdAb) titers** (i.e., immune-mediated pharmacokinetic failure): In CD, a switch from infliximab / biosimilar to a second TNFI is preferred over a switch to another drug class (such as vedolizumab, risankizumab-rzaa, or upadacitinib). Infliximab / biosimilar and adalimumab / biosimilar are the preferred TNFIs in CD.
If **TNFI levels are undetectable with low AdAb titers** (i.e., also immune-mediated pharmacokinetic failure), optimize dosing (i.e., shorten dosing interval, increase dose, or both; add a conventional immunomodulator if not already started).
If **trough TNFI levels are subtherapeutic with low or high AdAb titers**, optimal management is uncertain.
If **TNFI trough levels are subtherapeutic with no AdAbs** (i.e., non–immune-mediated pharmacokinetic failure due to rapid drug clearance), shorten the TNFI dosing intervals, increase the dose, or both.

[6] **Sequencing CD Drugs (1L = First-line, 2L = Second-line, etc.)**
1L: Infliximab or adalimumab
2L / 3L: Vedolizumab, upadacitinib, or risankizumab-rzaa (one drug should be risankizumab-rzaa as 2L or 3L drug)
4L: Mirikizumab-mrkz or ustekinumab

Supplemental Information

This supplemental information is provided to assist in adjudication of requests for upadacitinib in CD.

Section	Criterion	Issues for Consideration
Inclusion Criteria	Completed tuberculosis (TB) test using tuberculin skin test or interferon-gamma release assay [IGRA].	Routine retesting is not required for prescription renewals. Retesting in high-risk patients should be considered.
	Completed hepatitis B screening (at minimum, HBsAg, total anti-HBc and antibody to hepatitis B surface antigen [anti-HBs]).	Routine retesting is not required for prescription renewals. Retesting in high-risk patients should be considered. Anti-HBs may help to identify patients who require initial or booster vaccination (anti-HBs titers >= 10 IU/L are generally considered protective) or HBsAg-negative patients without past vaccination who have occult HBV from past infection (anti-HBs positive and lost anti-HBc).
	Current or past completion of hepatitis C screening. (Upadacitinib may be initiated while waiting for test results.).	Routine retesting is not required for prescription renewals. Retesting in high-risk patients should be considered.
Additional Inclusion Criteria	If HBsAg-negative but antibody-to-hepatitis-B-core-antigen (anti-HBc)-positive, a gastroenterologist / hepatologist or infectious diseases expert has been consulted for advice on whether to start antiviral prophylaxis or to preemptively monitor for HBV reactivation.	In patients who are HBsAg-negative but **anti-HBc-positive**, the presence of antibody to hepatitis B surface antigen (anti-HBs) does not guarantee protection against HBV reactivation, and the available evidence is insufficient to support the use of anti-HBs titers in deciding whether to give antiviral prophylaxis. Management depends on the patient's risk of HBV reactivation. [Reddy K, et al. American Gastroenterological Association Institute Guideline on the Prevention and Treatment of Hepatitis B Virus Reactivation During Immunosuppressive Drug Therapy. Gastroenterology. 2015;148(1):215–219. doi: https://doi.org/10.1053/j.gastro.2014.10.039 Ekpanyapong S, Reddy KR. Hepatitis B Virus Reactivation: What Is the Issue, and How Should It Be Managed? Clin Liver Dis. 2020 Aug;24(3):317-333. doi: 10.1016/j.cld.2020.04.002.]

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