

Tofacitinib (XELJANZ) in Ulcerative Colitis

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 ANY of the following criteria are met, the patient should NOT receive tofacitinib.

- Uncontrolled, active, severe infection including evidence of *C. difficile* and undrained abscess (however, tofacitinib may be started / restarted once the infection treatment has been initiated).^1
- Untreated latent or active tuberculosis infection.
- Hepatitis B surface antigen (HBsAg)-positive and not on antiviral prophylaxis.^2 Tofacitinib may be initiated after starting antiviral prophylaxis.
- Untreated HIV infection. Treated, well-controlled, asymptomatic HIV-positive patients can be treated with tofacitinib.
- Malignancy within the previous 5 years other than successfully treated nonmelanoma skin cancer or successfully treated cervical cancer, unless 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/mm³, neutrophils < 1000 cells/mm³, or hemoglobin < 9 g/dL. (Tofacitinib may be started / restarted once the lymphopenia, neutropenia and/or anemia resolve.)
- Severe hepatic impairment (Child-Pugh class C).
- Concomitant therapy with biologic disease-modifying antirheumatic drugs (bDMARDs), other immunosuppressive biologics, potent immunosuppressants (e.g., azathioprine, cyclosporine, tacrolimus), or strong CYP3A4 inducers (e.g., rifampin).
- Pregnancy and females of reproductive potential not using adequate contraception.
- Lactation/providing breastmilk to an infant unless it occurs at least 18 hours after the most recent dose of tofacitinib.
- Concomitant live or live-attenuated vaccines or administration of inactivated, live, or live-attenuated vaccines less than 2 weeks before initiation of tofacitinib therapy.^3

Inclusion Criteria

ALL of the following criteria must be selected to meet criteria.

- Current or prior moderate to severe ulcerative colitis (UC) confirmed by endoscopy or imaging.
- Prescribed and monitored by a VA/VA Community Care gastroenterologist / hepatologist or locally-designated expert. ^4
- 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. (Tofacitinib may be initiated while waiting for test results.)

Additional Inclusion Criteria

ONE of the following must be selected to meet criteria:

- Tumor necrosis factor inhibitor (TNFI) is medically inadvisable. Infliximab / biosimilar is the preferred TNFI in UC.
- Primary nonresponse, inadequate partial response, or loss of response^5 after 12 weeks of one TNFI in the presence of adequate TNFI levels (mechanistic failure).
- Loss of response to a TNFI (infliximab / biosimilar is the preferred TNFI in UC) despite therapeutic drug monitoring (TDM)-based optimized dosing to address pharmacokinetic failure. ^5,^6

See footnote 7 for sequencing UC drugs.

Additional Inclusion Criteria

Select if applicable.

- 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.

Other Justification

Footnotes

- ¹ Use with extreme caution in people 65 years or older due to higher risks of serious infections, fatal infection and possibly increased mortality.
- ² Antiviral prophylaxis for HBV: Agents with high genetic barrier to resistance such as entecavir or tenofovir should be used.

- 3 When possible, vaccinations should be updated before the patient initiates tofacitinib. Unless contraindicated, recombinant zoster (SHINGRIX) vaccine should be completed or at least initiated by the end of the first year of treatment with tofacitinib, preferably when dosage is low, disease is stable, or at other times when a robust immune response to vaccination can be expected.
- 4 Prescribe at the FDA-recommended dose for ulcerative colitis, adjusting for CYP3A4 drug interactions, moderate or severe renal impairment, moderate hepatic impairment, and hematocytopenias.
- 5 Loss of response refers to active disease confirmed by endoscopy, imaging, or biochemical assessment.
- 6 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): Consider adding an immunomodulator. If the patient is on adalimumab, a switch to a second TNFI is preferred over a switch to another drug class. If on infliximab, switch to a non-TNFI (one of vedolizumab, tofacitinib, upadacitinib, etrasimod, ozanimod, or risankizumab). Infliximab / biosimilar is the preferred TNFI. A trial of just one TNFI may be sufficient (prefer not switching infliximab to adalimumab, which has lower efficacy in UC).

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.

7 **Sequencing UC Drugs (1L = First-line, 2L = Second-line, etc.)**

1L: Infliximab (preferred) or adalimumab (less effective alternative)

2L / 3L: Vedolizumab, tofacitinib, upadacitinib, etrasimod, ozanimod, or risankizumab-rzaa (one drug should be risankizumab-rzaa as 2L or 3L drug)

4L: Mirikizumab-mrkz, guselkumab, or ustekinumab

Supplemental Information

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

Section	Criterion	Issues for Consideration
Exclusion Criteria	Lymphocytes < 500 cells/mm ³ , neutrophils < 1000 cells/mm ³ , or hemoglobin < 9 g/dL (tofacitinib may be started / restarted once the lymphopenia, neutropenia and/or anemia resolve).	Lymphocyte count less than 500 cells/mm ³ confirmed by repeat testing; absolute neutrophil count less than 1000 cells/mm ³ before initiation of therapy or less than 500 cells/mm ³ during therapy; hemoglobin less than 9 g/dL before initiation of therapy or hemoglobin less than 8 g/dL or decrease of more than 2 g/dL during therapy.
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. (Tofacitinib may be initiated while waiting for test results.)	Routine retesting is not required for prescription renewals. Retesting in high-risk patients should be considered.
	Tofacitinib is prescribed at the FDA-recommended dose for ulcerative colitis, adjusting for CYP3A4 drug interactions, moderate or severe renal impairment, moderate hepatic impairment, and hematocytopenias.	Because of increased risks for major adverse cardiovascular events (MACE), thrombosis, and all-cause mortality, <i>tofacitinib should be discontinued in patients with ulcerative colitis who do not achieve a response after 16 weeks of induction with tofacitinib 10 mg twice daily (or extended-release tofacitinib 22 mg once daily)</i> . Those who achieve a response or remission after induction <i>should have their dose reduced to 5 mg twice daily (or 11 mg once daily of extended-release tofacitinib)</i> and use the lowest effective dose needed to maintain response. The use of 10 mg twice daily (or extended-release tofacitinib 22 mg once daily) beyond induction should be limited to patients with loss of response and the shortest duration clinically feasible.
Additional Inclusion Criteria	Infliximab / biosimilar is the preferred TNFI in UC.	Other options for UC in TNFI-naïve patients are adalimumab and golimumab. Adalimumab is less preferred than vedolizumab and tofacitinib in TNFI-exposed UC patients.
Additional Inclusion Criteria	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.	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. <i>Gastroenterology</i> . 2015;148(1):215–219. doi: https://doi.org/10.1053/j.gastro.2014.10.039

Section	Criterion	Issues for Consideration
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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.]

Revised:

- February 2025 (Sequenced drugs: added JAKi, S1PRM, and risankizumab to 2L prerequisites with vedolizumab (2L after TNFI); mirikizumab, guselkumab, and ustekinumab are now 3L. Clarified pharmacokinetic failure footnote. Added infliximab / biosimilar is preferred TNFI in UC. Added caveat to malignancy exclusion. Added vaccination / Shingrix footnote. Added routine retesting not needed for TB, HBV, HCV. Deleted reasons for drugs being medically inadvisable in Supplemental Information [refer to relevant prescribing information].)
- July 2022. Separated composite CFU by individual indications for Cerner purposes (no change in content).
- December 2021. Removed HCV exclusion criterion; changed inclusion criterion from *completed HCV screening* to *current or past completion of HCV screening*; moved selected footnotes to Supplemental Information. Incorporated December 2021 Boxed Warning and Warnings and Precautions regarding mortality, malignancy, MACE, and thrombosis.
- May 2020. Added pregnancy exclusion and updated infection screening.
- March 2020. Incorporates FDA prescribing information and 31 Oct 2019 EMA PRAC provisional recommendations regarding risks of pulmonary embolism and all-cause mortality.

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