Ustekinumab (STELARA) 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 are selected, the patient will NOT meet criteria for ustekinumab.

- ☐ Untreated latent or active tuberculosis infection
- ☐ Uncontrolled, active, severe infection including evidence of *C. difficile* and undrained abscess (however, ustekinumab may be started / restarted once the infection is controlled)
- ☐ Hepatitis B surface antigen (HBsAg)-positive and not on antiviral prophylaxis. ^1 Ustekinumab may be initiated after starting antiviral prophylaxis.
- ☐ Untreated HIV infection. Treated, well-controlled, asymptomatic HIV-positive patients can be treated with ustekinumab.
- ☐ Concomitant live or live-attenuated vaccines or administration of inactivated, live, or live-attenuated vaccines less than 2 weeks before initiation of ustekinumab.^2
- ☐ History or development of reversible posterior leukoencephalopathy syndrome (RPLS)
- ☐ Known or suspected noninfectious pneumonia (e.g., interstitial pneumonia, eosinophilic pneumonia, cryptogenic pneumonia)
- ☐ Administration of Bacillus Calmette-Guerin (BCG) vaccine including therapeutic intravesical BCG within 1 year prior to starting ustekinumab (1 year after therapy).

Use with caution in patients who have malignancy within the previous 5 years other than successfully treated nonmelanoma skin cancer or successfully treated cervical cancer.

Inclusion Criteria

All the following must be selected to meet criteria.

- ☐ Prescribed and monitored by a VA/VA Community Care gastroenterologist or locally-designated expert.
- ☐ Current or prior moderate to severe **ulcerative colitis (UC)** 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. (Ustekinumab may be initiated while waiting for test results.)
- ☐ **One of vedolizumab, tofacitinib, upadacitinib, etrasimod, or ozanimod** was tried (unless medically inadvisable) and not tolerated or not adequate, or lost response^3,^4
- ☐ **Risankizumab-rzaa** was tried (unless medically inadvisable) and not tolerated or not adequate, or lost response^3,^4

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^4 after 12 weeks of **one TNFI** therapy in the presence of adequate TNFI levels (mechanistic failure).
- ☐ Loss of response^4 to a **TNFI (infliximab/biosimilar** is the preferred TNFI in UC) despite therapeutic drug monitoring (TDM)-based optimized dosing to address pharmacokinetic failure.^5

See footnote 6 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: Counseling provided on potential risks vs benefits of treatment and the use of effective contraception.

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 ustekinumab. Unless contraindicated, recombinant zoster (SHINGRIX) vaccine should be completed or at least initiated by the end of the first year of treatment with ustekinumab, preferably when dosage is low, disease is stable, or at other times when a robust immune response to vaccination can be expected.

[3] Applies only to new starts for ustekinumab. Patients on ustekinumab who are stable (responded to induction and/or controlled on maintenance therapy) should not be switched to a criteria-required prior drug for nonmedical reasons.

[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): 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-rzaa). 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.

[6] **Sequencing UC Drugs (1L = First-line, 2L = Second-line, etc.)**
1L: Infliximab or adalimumab
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 ustekinumab.

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. (Ustekinumab 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	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 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.]

Revised:

- February 2025 (Sequenced drugs: added JAKi, S1PRM, and risankizumab-rzaa to 2L prerequisites with vedolizumab; mirikizumab-mrkz, 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 2024 (Added risankizumab-rzaa prerequisite. Edited for Cerner / Oracle specs. Separated composite CFU into separate CFU for each indication.)
- 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.)
- June 2020 (updated infection and malignancy screening).
- March 2020 (extracted from Anti-Interleukin Biologics in Psoriasis and Psoriatic Arthritis Criteria for Use; Cerner reformatted; updated PsO and PsA; added CD and UC).
- December 2019 (Updated and streamlined).

Original: July 2019 (Anti-Interleukin Biologics in Psoriasis and Psoriatic Arthritis CFU).

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