Upadacitinib (RINVOQ) in Ulcerative Colitis
National Drug Monograph Addendum
May 2023

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

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description / Mechanism of Action

- Upadacitinib is the second Janus kinase inhibitor (JAKI) approved for the treatment of ulcerative colitis (UC) and is relatively selective for JAK1 and JAK2.[1]
- Lower activity at JAK2 receptors might theoretically reduce the risk of myelosuppression.
- Upadacitinib is also approved for rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, ankylosing spondylitis, and nonradiographic axial spondyloarthritis in the US.

Indication Under Review in This Document

- Treatment of adults with moderately to severely active UC who have had an inadequate response or intolerance to one or more tumor necrosis factor inhibitors (TNFIs).
- *Limitation of Use*: Upadacitinib is not recommended for use in combination with other JAKIs, biologic disease-modifying antirheumatic drugs, or with potent immunosuppressants such as azathioprine and cyclosporine.

Pretreatment Tests and Evaluations

- Tuberculosis (TB) screening
- Viral hepatitis screening (hepatitis B, hepatitis C)
- Complete blood count (noting neutrophils, lymphocytes, hemoglobin)
- Liver panel
- Pregnancy status
- Update immunizations, including for varicella zoster or herpes zoster prophylaxis as per immunization guidelines

Dosage Regimen and Dosage Form Under Review

- *Induction*: 45 mg once daily for 8 weeks. (Note: This dose is higher than doses used for previously approved indications.)
- *Maintenance*: 15 mg once daily. A dose of 30 mg once daily may be considered for patients with refractory, severe, or extensive disease. Discontinue upadacitinib if an adequate response is not achieved with 30 mg. Use lowest effective dosage needed to maintain response.
- *Extended-release tablets*: 15 mg, 30 mg, and 45 mg.

Laboratory Monitoring During Therapy

- Lipid panel (total cholesterol, LDL, HDL) about 12 weeks after initiation of therapy then as per lipid guidelines.
- Complete blood count as per routine management
- Latent TB testing, TB activation
- Liver panel as per routine management
- Viral hepatitis reactivation as per guidelines

Efficacy Considerations

- No active-controlled trials have been performed.
- Three phase 3, placebo-controlled, randomized clinical trials (RCTs) — two replicate induction trials (U-ACHIEVE induction [UC1] and U-ACCOMPLISH [UC2]) and one maintenance trial (U-ACHIEVE maintenance [UC3]) — showed clinical remittive and quality of life efficacy of upadacitinib in moderate to severe, active UC.[2,3,4,5]
- A phase 2b, dose- and placebo-controlled RCT (U-ACHIEVE substudy 1) provided supportive evidence of induction efficacy.[6,7] This study showed that, compared with lower doses of upadacitinib (7.5 mg, 15 mg, and 30 mg daily), 45 mg once daily produced the best benefit-risk profile for induction. For maintenance, both 15 mg and 30 mg were selected because of the potential for a better long-term safety profile.
- An FDA review of upadacitinib in UC was not available to date.

Phase 3 Randomized Clinical Trials

Methods

- Table 1 summarizes the methods of the phase 3 RCTs and Table 2 provides the patient characteristics.

Table 1 Methods of Phase 3 RCTs

Topic	UC1 and UC2 (Induction)	UC3 (Maintenance)
Study Design	MN DB PC RCT 2:1 randomization stratified by history of biologic failure, baseline CS use, baseline Adapted Mayo score (≤ 7 vs > 7), and further stratified by number of prior biologics for patients with biologic failure or by previous biologic use for patients without prior biologic failure.	RCT 1:1:1 randomization stratified by previous biologic failure, clinical remission status, and CS use. Week-8 clinical responders to placebo induction continued PBO. Week-8 clinical responders to upadacitinib 45 mg QD were randomized 1:1 to 52 weeks of upadacitinib 15 or 30 mg QD or placebo. 21 patients enrolled from the phase 2b study, 278 from UC1, and 152 from UC2.
Major Entry Criteria	Age 16–75 y Confirmed diagnosis of UC for ≥ 90 d Active disease (Mayo score of 5–9 without PGA; Mayo endoscopic subscore of 2 or 3) Previous inadequate response, loss of response or intolerance to ≥ 1 oral 5-ASA, corticosteroid, immunosuppressant, or biologic (infliximab, adalimumab, golimumab, vedolizumab, or ustekinumab). *Exclusion Criteria* Indeterminate colitis, fulminant colitis, toxic megacolon, rectum-only disease, active infection, previous exposure to JAKIs.	

Topic	UC1 and UC2 (Induction)	UC3 (Maintenance)
Interventions	• Upadacitinib 45 mg QD • Placebo *Concomitant UC Therapy*: Stable doses of prednisone ≤ 30 mg/d or equivalent, antibiotics, 5-ASAs, or methotrexate.	• Upadacitinib 15 mg QD • Upadacitinib 30 mg QD • Placebo *Concomitant UC Therapy*: Corticosteroids were tapered per protocol at Week 0. *Rescue Therapy*: Initiation or increased dose of corticosteroids, 5-ASAs, methotrexate, or antibiotics.
Primary Efficacy Measure(s)	Clinical remission at Week 8 (defined as Adapted Mayo score ≤ 2, with SFS ≤ 1 and not greater than baseline, RBS = 0, and endoscopic subscore ≤ 1 without friability)	Clinical remission at Week 52 per Adapted Mayo score.
Comments	The definition of clinical remission as per Adapted Mayo score (without PGA and with RBS = 0) is more stringent and may have underestimated efficacy vs previous studies with infliximab, adalimumab, ustekinumab, and vedolizumab.[2,13] Other drugs that have been evaluated using more stringent definitions of clinical remission but less stringent than with upadacitinib (i.e., used Total / Complete Mayo score with RBS = 0 but included PGA) are tofacitinib and ozanimod.[8,9,13] Excluding PGA reduced subjectivity in scoring.	

5-ASA, 5-aminosalicyclate acid; **PGA**, Physician's Global Assessment; **RBS**, Rectal bleeding score; **SFS**, Stool frequency score

Table 2 Baseline Patient Characteristics

Characteristic	UC1 + UC2	UC3
N	988	451
Male, %	62	59
White, %	67	65
Asian, %	28	30
Age, y	42	40
Immunosuppressant / Methotrexate use, %	1	< 1
Aminosalicylate use, %	68	67
Corticosteroid use, %	37	38
Baseline corticosteroid dose, mg	20	17
Previous biologic failure,† %	51	50
1 Previous biologic, %	20	21
2 Previous biologic, %	20	20
3 Previous biologic, %	11	9
≥ 4 Previous biologic, %	3	2

† Biologic failure referred to inadequate response, loss of response, or intolerance

Results

Selected key efficacy results

- Selected results are summarized in Table 3 for the UC1 and UC2 induction trials and in Table 4 for the UC3 maintenance trial.

Table 3 Efficacy results from induction trials at Week 8

Outcome	Study	UPA 45 mg QD	Placebo	Relative Risk (95% CI)	AAE per 1000 (95% CI)	NNT (95% CI)	Q
Clinical remission, n/N (%)	UC1	83/319 (26)	7/154 (5)	5.7 (2.7, 12.1)			
	UC2	114/341 (33)	7/174 (4)	8.3 (4.0, 17.4)			
	Pooled	197/660 (30)	14/328 (4)	7.0 (4.1, 11.8)	256 (215, 297)	4 (4, 5)	M[α]
Endoscopic remission, n/N (%)	UC1	44/319 (14)	2/154 (1)	10.6 (2.6, 43.2)			
	UC2	62/341 (18)	3/174 (2)	10.5 (3.4, 33.1)			
	Pooled	106/660 (16)	5/328 (2)	10.5 (4.3, 25.6)	145 (114, 176)	7 (6, 9)	M[α]

Source: 2

AAE, Anticipated absolute effect for achieving the outcome; **CFB**, Change from baseline; **NNT**, Number needed to treat for one additional patient to benefit; **Q**, GRADE quality of evidence (H = High, M = Moderate, L = Low, VL = Very low); **UPA**, Upadacitinib

[α] Downgraded for imprecision (wide CIs and/or optimal information size not met).

Table 4 Efficacy results from UC3 maintenance trial at Week 52

Outcome	UPA 15 mg QD	UPA 30 mg QD	Placebo	RR-15 mg (95% CI)	RR-30 mg (95% CI)	ARD-15 mg (95% CI)	ARD-30 mg (95% CI)	Q
Clinical remission, n/N (%)	63/148 (42)	80/154 (52)	18/149 (12)	3.5 (2.2, 5.6)	4.3 (2.7, 6.8)	30.7 (21.7, 39.8)	39.0 (29.7, 48.2)	M[α]
Maintenance of clinical remission, n/N (%)	28/47 (59)	40/58 (70)	12/54 (22)	2.7 (1.5, 4.6)	3.1 (1.8, 5.3)	37.4 (20.3, 54.6)	47.0 (30.7, 63.3)	M[α]
Corticosteroid-free clinical remission, n/N (%)	27/47 (57)	39/58 (68)	12/54 (22)	2.6 (1.5, 4.5)	3.0 (1.8, 5.1)	35.4 (18.2, 52.7)	45.1 (28.7, 61.6)	M[α]
Endoscopic remission, n/N (%)	36/148 (24)	40/154 (26)	8/149 (6)	4.5 (2.2, 9.4)	4.8 (2.3, 10.0)	18.7 (11.0, 26.4)	19.4 (11.7, 27.2)	M[α]

Maintenance of clinical remission was defined as clinical remission per Adapted Mayo score at Week 52 in those who achieved clinical remission at the end of the induction studies. **Corticosteroid-free clinical remission** was defined as clinical remission per Adapted Mayo score at Week 52 and were corticosteroid-free for ≥ 90 days prior to Week 52 in those who achieved clinical remission at the end of the induction studies. **ARD**, Absolute risk difference; **Q**, GRADE quality of evidence (H = High, M = Moderate, L = Low, VL = Very low); **RR**, Relative risk; **UPA**, Upadacitinib. [α] Downgraded for imprecision (wide CIs and/or optimal information size not met).

Secondary efficacy results

- *UC1 and UC2 (Induction).* Upadacitinib 45 mg showed statistically significant benefits in all secondary efficacy measures including endoscopic remission, endoscopic improvement, clinical response, clinical response at Week 2, histologic-endoscopic mucosal improvement, no bowel urgency, no abdominal pain, histologic improvement, change from baseline in the Inflammatory Bowel Disease Questionnaire (IBDQ) total score (a measure of quality of life), mucosal healing, and change from baseline in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score (also a measure of quality of life). The minimal clinically important change of ≥ 16 points in total IBDQ score was met in the upadacitinib and placebo groups.
- *UC3 (Maintenance)*. Both the 15 mg and 30 mg doses of upadacitinib showed significant benefits in all secondary efficacy measures including maintenance of clinical remission, corticosteroid-free clinical remission, maintenance of endoscopic improvement, maintenance of clinical response, and quality of life measures. As seen in UC1 and UC2, the improvements in IBDQ total scores from baseline were clinically important (≥ 16 points) in all treatment groups including placebo.

Subgroup Analyses (UC1, UC2, and UC3)

- No patient predictive factors were identified in subgroup analyses including evaluations by the presence or absence of previous biologic failure.
- Clinical remission rates were numerically lower in patients with previous biologic failure than those without.

Onset of Treatment Benefit and Duration of an Adequate Therapeutic Trial

- Onset of effects (earliest significant treatment difference) occurred at Week 2 with upadacitinib 45 mg based on clinical remission and clinical response rates.[2,10]
    - A post hoc analysis showed significant treatment differences as early as Day 1 based on achieving stool frequency score (SFS) of ≤ 1, SFS of 0 (normal number of stools), rectal bleeding score (RBS) of 0 (zero), and a 2-item patient-reported outcome (PRO 2) consisting of SFS ≤ 1 and RBS = 0.[10]
- The duration of an adequate therapeutic trial (time to maximal or near-maximal response) seems to be 16 weeks, based on an extended induction substudy. Of 125 induction nonresponders (failed to achieve clinical response) to upadacitinib 45 mg at Week 8, 73 (58.4%) achieved a clinical response at Week 16.[10]

    PBM Note: Unlike tofacitinib, upadacitinib did not gain FDA approval for an extended induction dosage regimen.

Durability of Response

- Of corticosteroid-treated patients randomized to placebo in the UC3 maintenance trial, 31.7% were in corticosteroid-free clinical remission at Week 12. Rates decreased thereafter.[2]

Safety Considerations

Safety Profile from US Prescribing Information

- **Boxed Warnings, Contraindications, and Other Warnings / Precautions** are the same as for the other approved indications for upadacitinib.
- **Common Adverse Events in Patients with UC** (≥ 5%):
    - *Induction Therapy*: Upper respiratory tract infection, acne, increased blood creatine phosphokinase, neutropenia.
    - *Maintenance Therapy*: Upper respiratory tract infection, increased blood creatine phosphokinase, neutropenia, elevated liver enzymes, rash.

Safety Results from UC Clinical Trials

- The overall safety profile and laboratory abnormalities of upadacitinib in patients with UC were generally similar to those in patients with rheumatoid arthritis and atopic dermatitis.
- In UC3, there were more reports of the following adverse events on upadacitinib 15 mg and 30 mg vs placebo, respectively[2]:
    - Venous thromboembolism: 0% and 1% vs 0%
    - Herpes zoster infection: 4% and 4% vs 0%
    - Hepatic disorder (all mild–moderate, mostly transaminase elevations): 7% and 5% vs 2%
    - Neutropenia: 3% and 6% vs 1%
    - CPK elevation: 6% and 8% vs 2%
- In UC3, the rate of worsening UC was higher with upadacitinib 15 mg (13%) than 30 mg (7%) and was 30% with placebo.[2]
- Rates were low and similar among upadacitinib 15 mg and 30 mg vs placebo for serious infection, opportunistic infection (excluding tuberculosis and herpes zoster), malignancy, nonmelanoma skin cancer, adjudicated gastrointestinal perforation, and adjudicated MACE.[2]

Evidence Gaps

- Survival / Mortality
- Hospitalization or readmission
- Functional ability / Disability
- Patient Satisfaction
- Longer term (> 1 year) safety and effectiveness experience
- Efficacy and safety in UC patients with prior JAKI exposure

Network Meta-analyses

- Four network meta-analyses have included upadacitinib UC trials and are summarized in Table 5 to Table 10.[11,12,13,14]

Table 5 Induction of Clinical Remission: Summary of Network Meta-analyses

Reference	Time Point, Patient Group	Drug Ranked Best (Worst)	UPA Superior to	UPA Similar to	UPA Inferior to
Burr, et al. (2022)[11]	Weeks 6–14, All patients	**UPA** 45 mg (ADA 80/40 mg)	TOFA 10 mg,* GOL 400/200 mg, OZA 1 mg, VEDO 300 mg, ADA 160/160 mg, GOL 200 / 100 mg, UST 130 mg, UST 6 mg/kg, ADA 160/80 mg, ADA 80/40 mg	INF 5 mg/kg INF 10 mg/kg	—
	Weeks 6–14, TNFI-naïve patients	**UPA** 45 mg (ADA 80/40 mg)	VEDO 300 mg, OZA 1 mg, GOL 400/200 mg, TOFA 10 mg,* UST 130 mg, GOL 200/100 mg, ADA 160/80 mg, UST 6 mg/kg, ADA 80/40 mg	INF 5 mg/kg INF 10 mg/kg	—
	Weeks 6–14, TNFI-exposed patients	**UPA** 45 mg (ADA 160/80 mg)	TOFA 10 mg,* UST 130 mg, VEDO 300 mg, OZA 1 mg, ADA 160/80 mg	UST 6 mg/kg	—
Lasa, et al. (2022)[12]	Weeks 6–14, All patients	**UPA** (INF)	OZA, TOFA,** UST, VEDO, GOL, ADA, INF	—	—
Attauabi, et al. (2023)[13]	Week 2, All Patients	**UPA** (UST)	INF, GOL, ADA, VEDO, UST	—	—
	Week 6, All Patients	**UPA** (GOL IV)	INF, VEDO, ADA, GOL IV	GOL SC	—

ADA, Adalimumab; **GOL**, Golimumab; **INF**, Infliximab; **OZA**, Ozanimod; **TOFA**, Tofacitinib; **UPA**, Upadacitinib; **UST**, Ustekinumab; **VEDO**, Vedolizumab

* Upadacitinib vs tofacitinib odds ratio (OR) (95% CI) for failure to achieve clinical remission: 0.86 (0.76, 0.96) in all patients, 0.79 (0.67, 0.94) for TNFI-naïve patients, and 0.88 (0.80, 0.98) for TNFI-exposed patients.

** Upadacitinib vs tofacitinib odds ratio (95% CI) for achieving clinical remission: 2.8 (1.28, 6.31)

Table 6 Maintenance of Remission: Summary of Network Meta-analyses

Reference	Time Point, Patient Group	Drug Ranked Best (Worst)	UPA Superior to	UPA Similar to	UPA Inferior to
Maintenance of Clinical Remission					
Lasa, et al. (2022)[12]	Weeks 26–66, All patients	**UPA** (GOL)	OZA, UST, GOL	TOFA, VEDO	—
Maintenance of GC-free Remission (Randomized Responder Trials)					
Lasa, et al. (2022)[12]	Weeks 26–66, All patients	**UPA** (GOL)	OZA, VEDO, GOL	TOFA, UST	—

GOL, Golimumab; **OZA**, Ozanimod; **TOFA**, Tofacitinib; **UPA**, Upadacitinib; **UST**, Ustekinumab; **VEDO**, Vedolizumab

Table 7 Serious Adverse Events: Summary of Network Meta-analyses

Reference	Drug Ranked Safest (Least Safe)	UPA Safer Than	UPA Similar to	UPA Less Safe Than
Burr, et al. (2022)[11]	GOL 200/100 mg† (OZA 1 mg)	—	GOL 200/100 mg, UST 6 mg/kg, ADA 80/40 mg, UST 130 mg, GOL 400/200 mg, VEDO 300 mg, TOFA 10 mg, ADA 160/80 mg, INF 5 mg/kg, INF 10 mg/kg, OZA 1 mg	—
Lasa, et al. (2022)[12]	VEDO (OZA)	—	OZA, TOFA, UST, VEDO, GOL, ADA, INF	—

NR, Not reported

† Golimumab and vedolizumab were significantly less likely than placebo to cause serious adverse events (HR, 95% CI): 0.45 (0.21, 0.97) and 0.60 (0.39, 0.92), respectively.

Table 8 Discontinuations Due to Adverse Events: Network Meta-analyses

Reference	Drug Ranked Safest (Least Safe)	UPA Safer Than	UPA Similar to	UPA Less Safe Than
Burr, et al. (2022)[11]	**UPA** 45 mg† (ADA 160/80 mg)	INF 5 mg/kg, INF 10 mg/kg, VEDO 300 mg, ADA 80/40 mg, ADA 160/80 mg	GOL 400/200 mg, GOL 200/100 mg, TOFA 10 mg, OZA 1 mg	None

† Although ranked the safest for discontinuations due to adverse events, upadacitinib 45 mg had a significantly higher risk of adverse events relative to all other drugs except adalimumab 80/40 mg.

Table 9 Infections: Summary of Meta-analyses

Reference	Infection Outcome	Drug Ranked Safest (Least Safe)	UPA Safer Than	UPA Similar to	UPA Less Safe Than
Burr, et al. (2022)[11]	Infections	VEDO 300 mg (TOFA 10 mg)	No data for UPA	No data for UPA	No data for UPA
Din, et al. (2022)[14]	Herpes zoster	RIS (UPA)	None	VEDO, GOL, UST, INF, CER, OZA, ADA, TOFA	RIS

ADA, Adalimumab; **CER**, Certolizumab; **GOL**, Golimumab; **INF**, Infliximab; **OZA**, Ozanimod; **RIS**, Risankizumab; **TOFA**, Tofacitinib; **UPA**, Upadacitinib; **UST**, Ustekinumab; **VEDO**, Vedolizumab

Table 10 Other Considerations About the Network Meta-analyses

Consideration	Burr, et al. (2022)	Lasa, et al. (2022)	Attauabi, et al. (2023)	Din, et al. (2022)
Limitations	Included the two phase 3 UPA induction trials before they were fully published and peer reviewed. Included phase 3 RCTs involving outpatients. Used non-GRADE quality assessments based only on risk of bias.	Unclear if MESH terms were used in searches. Variable study designs. Confidence in estimates was provided for each of the drug comparisons overall but not by outcome.† Included the three phase 3 UPA trials before they were fully published and peer reviewed.	Inability to adjust analyses for patient-level variables that may affect drug onset; variable study designs; high interstudy heterogeneity; paucity of biologic-exposed patient data.	Only 52% of induction RCTs had low risk of bias. Differences in design of RCTs could have affected differences in risk of herpes zoster and transitivity. Rare herpes zoster events.
Funding	None	None	None	None
Author(s) COI with Abbvie	None	Yes	Yes	Yes

† Confidence in estimates was high for all UPA–drug pair comparisons except it was moderate in comparisons with INF and VEDO.

Other Therapeutic Options

- Alternative treatments for patients with moderate to severe, active UC are summarized in Table 11.

Table 11 Treatment Alternatives for Moderate to Severe UC

Drug	On VANF	CFU Place in Therapy	FDA Place in Therapy	Guideline Place in Therapy	Safety Considerations	Other Considerations
Janus Kinase Inhibitors						
Upadacitinib	No	TBD	Inadequate response or intolerance to ≥ 1 TNFI	NA	Safety considerations are similar to those for tofacitinib, except it is advised to avoid pregnancy during upadacitinib therapy and for 4 weeks after the end of therapy.	Somewhat less effective in TNFI-exposed than TNFI-naïve patients. In clinical trials, prior biologics included non-TNFIs. No approved extended induction regimen. Other approved uses: RA, PsA, AD, AS, and nrAxSp.
Tofacitinib	No	After vedolizumab if TNFI is medically inadvisable OR After TNFIs	Inadequate response or intolerance to ≥ 1 TNFI	*Infliximab-exposed:* Preferred over vedolizumab particularly for primary nonresponse to a TNFI (+ IMM) due to mechanistic failure.	Boxed warnings for serious infections, mortality, malig-nancies, MACE, and thrombosis. Myelosuppressive. Herpes zoster infection Routine lab monitoring required (Hg, neutrophils, lymphocytes, liver enzymes, lipids).	Similarly effective in TNFI-naïve and TNFI-exposed patients. Clinical trials did not include non-TNFI biologic failures. Has an approved extended induction regimen.

Drug	On VANF	CFU Place in Therapy	FDA Place in Therapy	Guideline Place in Therapy	Safety Considerations	Other Considerations
					DDIs‡: Live vaccines, CYP3A4 inducers / inhibitors, potent cIMMs (e.g., AZP, CSA). Pregnancy: *Consider* pregnancy prevention in patients with reproductive potential.	Onset of significant symptomatic improvement was as early as 3 days (based on RBS = 0) in phase 3 RCTs[15] (vs 1 day for upada-citinib – see page 5). Orally administered. Lacks antidrug antibodies. Other approved uses: RA, PsA, AS, and PJIA.
Tumor Necrosis Factor Inhibitors						
Infliximab / biosimilars	Yes, PA-F (infliximab-abda)	No CFU	Inadequate response to conventional therapy	1st-line option. Preferred TNFI.	Boxed Warnings for serious infections and malignancy. Providers are familiar with use of TNFIs. DDIs‡: Live vaccines, anakinra, abatacept, rituximab, tocilizumab, other biologics for UC	Concomitant cIMM is recommended to reduce antidrug antibodies. TDM is conditionally recommended.[16] Infliximab / biosimilars require in-clinic IV infusions. Other approved uses: RA, PsO, PsA, AS, CD; adalimumab also approved for UV and HS.
Adalimumab / biosimilars	Yes, PA-F	No CFU	Potential 1st-line	Less preferred TNFI.†		
Golimumab	No	No CFU	GC depend-ence or inadequate response or intolerance to oral 5-ASA, oral GC, AZP, or 6MP	Least preferred TNFI.		
Integrin Receptor Inhibitors						
Vedolizumab	Yes, PA-F	After TNFIs	Potential 1st-line	1st-line alternative in patients for whom infliximab / biosimilar is medically inadvisable *TNFI-exposed:* Alternative after tofacitinib and/or ustekinumab	Purported to have lower risks of serious infection, malig-nancy, and immuno-genicity than TNFIs.[17] Can be given with live vaccines if benefits outweigh risks.	May be ineffective in TNFI-exposed patients.[11] Relatively gut-selective; ineffective for extraintestinal (e.g., skin or joint) manifesta-tions. Requires in-clinic IV infusions.
Interleukin-12/23 Inhibitors						
Ustekinumab	No	After vedolizumab if TNFI is medically inadvisable OR After TNFIs	Potential 1st-line	*TNFI-exposed:* Preferred over vedolizumab particularly for primary nonresponse to a TNFI (+ IMM) due to mechanistic failure.	Purported to have lower risks of serious infection, malignancy, and immunogenicity than TNFIs.[17] DDIs‡: Live vaccines	May be preferred over vedolizumab in patients with co-occurring skin or joint inflamma-tion. Other approved uses: PsO, PsA, CD

Drug	On VANF	CFU Place in Therapy	FDA Place in Therapy	Guideline Place in Therapy	Safety Considerations	Other Considerations
Sphingosine 1-Phosphate Receptor Modulator						
Ozanimod	No	No CFU	Potential 1st-line	NA	Multiple contraindications (MI, UA, CVA, HF, AVB, SSS, SAB, sleep apnea, MAOIs) and other safety concerns. DDIs‡: Live vaccines, alemtuzumab, CYP2C8 inducers and inhibitors; QT-prolonging drugs; MAOIs; tyramine; serotonin or norepinephrine reuptake inhibitors.	Not recommended for use with non-GC cIMMs (e.g., AZP, 6MP, MTX). *TNFI-exposed*: Did not improve clinical remission in this subgroup. *Biologic-naïve*: Limited long-term safety experience discourages its potential use as a 1st-line treatment alternative. Orally administered. Lacks antidrug antibodies. Other approved use: MS

Guideline Source: 18

6MP, 6-Mercaptopurine; AVB, Atrioventricular block; AZP, Azathioprine; CFU, Criteria for Use; CSA, Cyclosporine A; cIMMs, Conventional immunomodulators; CVA, Cerebrovascular accident (stroke, transient ischemic attack); DDI, Drug-drug interaction; GC, Glucocorticoid; HF, Heart failure; HS, Hydradenitis suppurativa; MACE, Major adverse cardiovascular events; MAOIs, Monoamine oxidase inhibitors; MI, Myocardial infarction; MS, Multiple sclerosis; MTX, Methotrexate; NDM, National drug monograph; PGA, Physician Global Assessment; RBS, Rectal bleeding score; SAB, Sinoatrial block; SSS, Sick sinus syndrome; TNFI, Tumor necrosis factor inhibitor; UA, Unstable angina; UV, Uveitis; WP, Warnings and Precautions

† Adalimumab may be suggested over infliximab/BSM for patients who prefer SC injections, particularly those with less severe disease.[18] In TNFI-exposed UC patients, adalimumab may be ineffective.[11]

‡ DDIs for which concomitant use is not recommended.

Projected Place in Therapy

- **Potential Place in Therapy Based on the Evidence**. Although no head-to-head trials were available, moderate-quality evidence from three placebo-controlled trials supports the use of upadacitinib for induction and maintenance of clinical remission in patients with moderate to severe, active UC who had an inadequate response, loss of response or intolerance to conventional therapies or biologics for UC. Clinical and endoscopic remission benefits were small to moderate and associated with clinically meaningful improvements in health-related quality of life. Upadacitinib showed a rapid onset of effects with a significant treatment difference in achieving clinical remission as early as Week 2. In indirect comparisons, two network meta-analyses suggest that upadacitinib may be significantly more effective in inducing clinical remission than other UC therapies including tofacitinib.[11,12] Upadacitinib was also more effective than tofacitinib in TNFI-naïve and TNFI-exposed patients. [11] Network meta-analyses suggest that upadacitinib has the lowest probability of discontinuations due to adverse events relative to infliximab, vedolizumab, and adalimumab (tofacitinib had no data)[11] and higher risk of adverse events than all other drugs except adalimumab 80/40 mg.[11] Upadacitinib and tofacitinib seem similar in maintenance of clinical remission and glucocorticoid-free remission[12] and in risks of serious adverse events[12] and herpes zoster.[14] The two potential advantages of upadacitinib over tofacitinib — better induction of clinical remission and faster symptomatic onset by a difference of 2 days — are inconclusive because they are based on indirect

comparisons. As of the date of this review, drug acquisition costs for maintenance therapy was 3.8 times higher with upadacitinib than tofacitinib.

- **Potential Place in Therapy in VHA**. Upadacitinib may be an alternative to (at the same level as) tofacitinib in patients with moderate to severe, active UC who have an inadequate response to vedolizumab if TNFIs are medically inadvisable or in those who have nonresponse, inadequate response, loss of response, or intolerance to TNFIs. One issue to consider when choosing among oral agents for TNFI-exposed patients is that upadacitinib and tofacitinib showed efficacy whereas ozanimod did not.

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