Upadacitinib (RINVOQ) in Crohn's Disease
National Drug Monograph Addendum
August 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 a Janus kinase inhibitor (JAKI) relatively selective for JAK1 and JAK2 receptors.[1]
- It is the first oral targeted small molecule approved in the US for Crohn's disease (CD).
- The other approved indications for upadacitinib are rheumatoid arthritis, psoriatic arthritis, atopic dermatitis, ankylosing spondylitis, nonradiographic axial spondyloarthritis, and ulcerative colitis.

Indication Under Review in This Document

- Treatment of adults with moderately to severely active Crohn's disease 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 therapies for Crohn's disease, or with potent immunosuppressants such as azathioprine and cyclosporine.

Dosage Regimen and Dosage Forms Under Review

- *Induction*: 45 mg once daily for 12 weeks.
- *Maintenance*: 15 mg once daily. A dosage 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 daily. Use the lowest effective dosage needed to maintain response.
- Extended-release tablets: 15 mg, 30 mg, 45 mg

PBM Note: The duration of the induction regimen in Crohn's disease is longer than that for ulcerative colitis (12 weeks vs 8 weeks, respectively).

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.
- A 52-week, dose-ranging phase 2 induction and maintenance therapy RCT (CELEST) provided supportive evidence of efficacy of a upadacitinib immediate-release formulation mainly in achieving endoscopic

remission.[2,3,4] This RCT involved patients with moderate to severe CD who had an inadequate response or intolerance to immunosuppressants or TNFIs. Patients who completed the CELEST trial were eligible to enter a 96-month, phase 2, open-label extension study (CELEST OLE).[5]

- The CELEST trial showed that a dose of 12 mg twice daily was more consistently effective and produced higher trough drug levels than 24 mg once daily. This observation and exposure-response pharmacokinetic modeling led to the development of the once-daily extended-release tablets, which were used in CELEST OLE and subsequent phase 3 RCTs.[6]

- There were three phase 3 RCTs of upadacitinib in patients with moderate to severe CD: two induction RCTs (U-EXCEED and U-EXCEL) and one ongoing dose- and placebo-controlled maintenance RCT with a long-term extension.[7,8]
  - U-EXCEED evaluated upadacitinib in patients with moderate to severe, active CD who had an inadequate response or intolerance to biologic therapy.[7]
  - U-EXCEL evaluated upadacitinib in patients with moderate to severe CD who had an inadequate response or intolerance to conventional and/or biologic therapies.**Error! Bookmark not defined.**
  - Both induction trials used the co-primary endpoints of clinical remission and endoscopic response at Week 12.
  - *Clinical remission* was defined as a Crohn's Disease Activity Index (CDAI) of < 150 for the US FDA and stool frequency ≤ 2.8 daily and average daily abdominal pain score of ≤ 1.0 with neither worse than baseline (SF / AP, aka PRO-2) for the EU European Medicines Agency. This monograph focuses on the US FDA definition.
  - *Endoscopic response* was defined as a decrease from baseline in simple endoscopic score for Crohn's disease (SES-CD, range 0–600) of > 50% or, in patients with a baseline SES-CD of 4, at least a 2-point reduction from baseline.
  - *Clinical response* was defined as ≥ 30% decrease in SF and/or AP or decrease from baseline in CDAI of ≥ 100 points.

Phase 3 Randomized Clinical Trials

Methods

- Table 1 summarizes the methods of the phase 3 RCTs.

Table 1 Methods of Phase 3 RCTs

Topic	U-EXCEED	U-EXCEL	U-ENDURE
Study Design	12-wk MC DB PC RCT (2:1) with 12-wk DB Extended Treatment for Wk-12 IRs 2:1 randomization stratified by baseline CS use, SES-CD < 15 / ≥ 15, and number of prior biologics with inadequate response or intolerance (1 or > 1)	12-wk MC DB PC RCT 2:1 randomization stratified by baseline CS use, SES-CD < 15 / ≥ 15, and number of prior biologics with inadequate response or intolerance (0, 1, > 1)	52-wk MC DB Dose-controlled and PC RCT, re-randomized to maintenance therapy; long-term extension 1:1:1 re-randomization stratified by previous failure of biologics, SF/AP clinical remission, and endoscopic response. 3 substudies
Major Entry Criteria	*Inclusion:* Age 18–75 yrs; confirmed diagnosis of CD for ≥ 3 mos; confirmed diagnosis of moderate to severe CD based on SF (≥ 4/d) and AP (score of ≥ 2); evidence of mucosal inflammation based on SES-CD on endoscopy; inadequate response or intolerance to biologic therapy	*Inclusion:* Same as for U-EXCEED except patients had to have had an inadequate response or intolerance to conventional and/or biologic therapies *Exclusion:* Same as for U-EXCEED	*Inclusion:* Age 18–75 yrs; achieved clinical response in either induction study Substudy 1: Completers of either induction trial Substudy 2: Completers of substudy 1 and achieved clinical response Substudy 3: Ongoing patient in

Topic	U-EXCEED	U-EXCEL	U-ENDURE
	(infliximab, adalimumab, certolizumab, vedolizumab, and ustekinumab) *Exclusion:* UC or indeterminate colitis; not on stable doses of CD immunomodulators (e.g., 5-ASAs, CS, MTX) or antibiotics; ongoing complications of CD; other manifestation of CD that might require surgery; ostomy or ileoanal pouch		substudy 2 for ≥ 12 mos; in stable remission for ≥ 6 months (CDAI < 150; CRP < 5 mg/L and FCP < 250 mg/kg; AND no locally acting [rectal or suppository] or systemic CS for CD ≥ 90 d prior to entry). *Exclusion:* Active or chronic recurring infections; untreated, unresolved serious infection, high-grade colonic dysplasia or malignancy on endoscopy
Interventions	*DB Induction, 12 wks* • Upadacitinib ER 45 mg QD • Placebo Allowed Co-therapies: stable doses of CD-related antibiotics, 5-ASAs, or MTX; CS up to 30 mg/d prednisone equivalent with tapering started at Wk 4.	*DB Induction, 12 wks* • Upadacitinib ER 45 mg QD • Placebo Allowed Co-therapies: Same as for U-EXCEED.	*Substudy 1 (Maintenance, 52 wks)* • Upadacitinib ER 15 mg QD • Upadacitinib ER 30 mg QD • Placebo *Substudy 2 (LTE, 240 wks)* • Upadacitinib 15 mg QD • Upadacitinib 30 mg QD • Placebo *Substudy 3 (OL Dose Optimization, 48 wks)* • Upadacitinib dose A
Primary Efficacy Measure(s)	Co-primary at Wk 12: Clinical remission defined as • CDAI < 150 in US; and • SF ≤ 2.8 / AP ≤ 1.0 in EU Endoscopic response, defined as CFB in SES-CD of > 50% (or CFB of ≥ 2 points if baseline SES-CD was 4)	Same as for U-EXCEED	CDAI Clinical remission Endoscopic response Adverse events

Sources: 7,**Error! Bookmark not defined.**
AP, Abdominal pain score; CDAI, Crohn's disease activity index; CFB, Change from baseline; IR, Inadequate responder based on failure to achieve clinical response; LTE, Long-term extension; OL, Open-label; SES-CD, Simple endoscopic score for Crohn's disease; SF, Stool frequency score

Table 2 Baseline Patient Characteristics

Characteristic	U-EXCEED (N = 624)	U-EXCEL (N = 526)	U-ENDURE (N = 502)
Age, mean, y	39.0	39.6	37.7
Age ≥ 65 y, %	—	3.8	—
Male, %	53.5	53.8	56.4
White	75.2	73.8	69.9
Asian	18.9	20.7	24.5
Corticosteroid use, %	37	36.1	37.2
5-ASA use, %	15	24	18.9
Methotrexate use, %	7	3	—
No previously failed biologics, %	—	54.6	24.9
1 previously failed biologic, %	39.4	16.3	39.0
> 1 previously failed biologic, %	60.6	29.1	61.0

Sources: 1,7,Error! Bookmark not defined.
CDAI, Crohn's disease activity index; **NR**, Not reported; **SF 2.8 / AP 1.0**, Stool frequency ≤ 2.8 daily / abdominal pain average score of ≤ 1.0

Preliminary Primary Results

- Primary efficacy data for US FDA outcomes are summarized in Table 3 and Table 4.

Table 3 Selected Week-12 Efficacy Results from Induction Trials

Outcome	UPA 45 mg	PBO	Relative Risk (95% CI)	Difference (95% CI)
Biologic Failures (U-EXCEED)				
CDAI Clinical remission, n/N (%)	126/324 (38.9)	36/171 (21.1)	1.8 (1.34, 2.55)	17.9 (10.0, 25.8)
Endoscopic response, n/N (%)	112/324 (34.6)	6/171 (3.5)	9.9 (4.43, 21.93)	31.2 (25.5, 37.0)
Conventional Therapy and/or Biologic Failures (U-EXCEL)				
CDAI Clinical remission, n/N (%)	173/350 (49.5)	51/176 (29.1)	1.7 (1.32, 2.20)	20.8 (12.7, 28.8)
Endoscopic response, n/N (%)	159/350 (45.5)	23/176 (13.1)	3.5 (2.33, 5.18)	33.0 (26.2, 39.9)
Without Previous Biologic Failure (U-EXCEL)				
CDAI Clinical remission, n/N (%)	80/160 (50)	28/81 (35)	1.4 (1.03, 2.03)	15.4 (2.5, 28.4)
Endoscopic response, n/N (%)	82/160 (51)	12/81 (15)	3.5 (2.01, 5.96)	36.4 (25.5, 47.4)
With Previous Biologic Failure (U-EXCEL)				
CDAI Clinical remission, n/N (%)	57/135 (42)	4/62 (7)	6.5 (2.49, 17.23)	35.8 (25.4, 46.1)
Endoscopic response, n/N (%)	53/135 (39)	6/62 (10)	4.1 (1.84, 8.93)	29.6 (18.5, 40.6)

Sources: 1,7,Error! Bookmark not defined.
CDAI, Crohn's disease activity index; **UPA**, Upadacitinib

- In U-EXCEL, upadacitinib was superior to placebo in achieving SF/AP (PRO-2) clinical remission (the EU co-primary outcomes): 50.7% (177/350) vs 22.2% (39/176), respectively.**Error! Bookmark not defined.**

Table 4 Absolute Effects for Achieving Co-primary Outcomes at Week 12

Outcome Measure	AAE per 1000 pts (95% CI)	NNT (95% CI)	Q
Biologic Failures (U-EXCEED)			
CDAI Clinical remission	178 (97, 259)	6 (4, 11)	M†
Endoscopic response	311 (252, 369)	4 (3, 4)	M†
Conventional Therapy and/or Biologic Failures (U-EXCEL)			
CDAI Clinical remission	204 (119, 290)	5 (4, 9)	M†
Endoscopic response	324 (251, 396)	4 (3, 4)	M†

AAE, Anticipated absolute effect for achieving the outcome; **NNT**, Number needed to treat for one additional patient to benefit; **Q**, GRADE quality of evidence (M = Moderate)
† Downgraded for imprecision (optimal information size not met or wide confidence intervals)

  - The magnitude of treatment effects were similar in the biologic failure population of U-EXCEED and the conventional and/or biologic therapy failure population of U-EXCEL.
  - In U-EXCEL, the effect size for CDAI clinical remission was unexpectedly lower in the subgroup of patients without vs those with previous biologic failure (15.4 vs 35.8 percentage points, respectively), although the 95% CIs overlapped. Patients without previous biologic failure had a higher endoscopic response rate than those with previous biologic failure (36.4 vs 29.6 percentage points) but the 95% CIs overlapped.

Secondary Efficacy Results in Induction Trials

U-EXCEED

- Upadacitinib was significantly better than placebo in the following outcomes at Week 12: corticosteroid-free clinical remission rate, change from baseline (CFB) in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) total score, CFB in the Inflammatory Bowel Disease Questionnaire (IBDQ) total score, and clinical response 100 (≥ 100-point decrease from baseline in CDAI; CR-100).
- Upadacitinib was also superior in achieving clinical response 100 (≥ 100-point decrease from baseline in CDAI; CR-100) at Week 2 and CDAI clinical remission at Week 4.

- Upadacitinib was not significantly different from placebo in the rate of hospitalizations due to CD at Week 12 and the rate of resolution of extraintestinal manifestations (EIMs) at Week 12 (in the subgroup with EIMs at baseline).

U-EXCEL

- Secondary efficacy results in U-EXCEL were consistent with all secondary outcomes in U-EXCEED.
- In addition, upadacitinib was superior to placebo at Week 12 in the rate of endoscopic remission and in corticosteroid-free SF/AP clinical remission rate.
- Upadacitinib was not significantly different from placebo in the rate of SF/AP clinical remission at Week 4.

Maintenance Trial (U-ENDURE)

- Upadacitinib 30 mg and 15 mg were each significantly better than placebo in the maintenance of CDAI clinical remission at Week 52 (55% of 119 patients, 42% of 113 patients, and 14% of 111 patients, respectively).[1] Upadacitinib was also superior in maintaining endoscopic response (41%, 28%, and 7%, respectively).[1]
- The treatment effect (difference between upadacitinib and placebo) for maintenance of CDAI clinical remission at Week 52 was larger with the higher dose of upadacitinib (30 mg) than the lower dose (15 mg): 40% (95% CI 29, 51) and 29% (18, 39), respectively. However, the 95% CIs overlapped and the trial may not have been designed to compare the two doses.
- The treatment effects for endoscopic response relative to placebo showed a similar pattern; larger for the 30-mg than the 15-mg dose: 34% (25, 44) vs 22% (13, 32), respectively.[1]
- In the subgroup of patients with biologic failure, the rate of maintaining CDAI clinical remission was 1.5 times higher with upadacitinib 30 mg than 15 mg: 54% of 90 patients vs 35% of 85 patients, respectively, (and 13% of 87 placebo patients). The 30-mg dose was 1.9 times better than the 15-mg dose in maintaining endoscopic response: 42% and 22%, respectively (and 5% on placebo).
- Corticosteroid-free clinical remission was maintained at Week 52 in 53% of 119 patients, 42% of 113 patients, and 14% of 111 patients in the upadacitinib 30 mg, 15 mg, and placebo groups, respectively.[1] Rates were 1.5 times higher with the 30-mg dose than the 15-mg dose in the subgroup of prior biologic failures (52% of 90 patients and 35% of 85 patients, respectively).[1]

Safety Considerations

Safety Profile from US Prescribing Information

- Overall, the safety profile of upadacitinib in patients with Crohn's disease was consistent with that seen in other indications.
- *Gastrointestinal Perforations.* Of 938 patients treated with upadacitinib 45 mg in induction trials, gastrointestinal perforation was reported in 4 patients (2 per 100 patient-years [PY]) and at similar rates among treatment groups during the 12-week placebo-controlled periods (1 per 100 PY for 30 mg and 15 mg vs no patients on placebo). The exposure-adjusted incidence rates during the maintenance / long-term extension study were < 1 per 100 PY for upadacitinib 30 mg and 15 mg and 1 per 100 PY on placebo.

Evidence Gaps

- Survival / Mortality
- Patient Satisfaction – Oral upadacitinib vs injectable therapy

Network Meta-analyses

- Three network meta-analyses have included upadacitinib trials (Table 8).[9,10,11]

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

Reference	Time Point, Patient Group	Drug Ranked Best (Worst)	UPA Superior to (QE)	UPA Similar to (QE)	UPA Inferior to
UPA 45 mg					
Barberio, et al. (2023)[9]	4–16 wks All patients	INF 5 mg/kg (CER 400 mg)	ADA 80/40 mg (M),† UST 130 mg (H),† VEDO 300 mg (H), CER 400 mg (H)	INF 5 mg/kg (M), RIS 600 mg (M), RIS 1200 mg (M), ADA 160/80 mg (M), ADA 160/160 mg (M), UST 6 mg/kg (H), INF 10 mg/kg (M)	—
	4–16 wks Biologic-exposed	RIS 600 mg (—)	UST 130 mg (H),† VEDO 300 mg (H), ADA 80/40 mg (M),† ADA 160/160 mg (M)	Supplemental results not available	Supplemental results not available
UPA 24 mg BID					
Rokkas, et al. (2021)[10]	4–16 wks All patients	UPA 6 mg BID; **UPA 24 mg BID** was second best. (TOFA 15 mg BID)	UPA 3 mg BID, UPA 12 mg BID, TOFA 15 mg BID	FIL, TOFA 1 mg BID, UPA 24 mg QD, TOFA 5 mg BID, TOFA 10 mg BID	—

ADA, Adalimumab; **INF**, Infliximab; **FIL**, Filgotinib; **H**, High; **M**, Moderate; **QE**, Quality of evidence, available only in Barberio, et al. (2023), was based on the Confidence in Network Meta-Analysis (CINeMA) method; **RIS**, Risankizumab; **TOFA**, Tofacitinib; **UPA**, Upadacitinib; **UST**, Ustekinumab; **VEDO**, Vedolizumab

† Less than recommended induction dose

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

Reference	Time Point, Patient Group	Drug Ranked Best (Worst)	UPA 30 mg QD Superior to	UPA 30 mg QD Similar to	UPA 30 mg QD Inferior to
Maintenance of Clinical Remission					
Barberio, et al. (2023)[9]	22–60 wks All re-randomized patients	UPA 30 mg QD (INF 5 mg/kg Q8W)	UPA 15 mg QD, VEDO 300 mg Q8W, UST 90 mg Q8W, VEDO 180 mg Q2W, RIS 360 mg Q8W, VEDO 300 mg Q4W, UST 90 mg Q12W, INF 5 mg/kg Q8W	ADA 40 mg QW, INF 10 mg/kg Q8W, ADA 40 mg Q2W, INF 120–240 mg Q2W, CER 400 mg Q4W, RIS 180 mg Q8W	—

Abbreviations: See Table 5 footnotes.

Table 7 Herpes Zoster Infections in Inflammatory Bowel Disease: Summary of Meta-analysis

Reference	Infection Outcome	Drug Ranked Safest (Least Safe)	UPA Safer Than	UPA Similar to	UPA Less Safe Than
Din, et al. (2022)[11]	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

† Not approved for Crohn's disease in the US

- Only the NMA of JAKIs in CD provided relative treatment rankings that jointly considered efficacy and tolerability. Upadacitinib 24 mg BID was included in the cluster of drugs with the best performance based on efficacy and tolerability (Table 8).

Table 8 Summary of Clustered Ranking Plot: Joint Efficacy–Tolerability Relative Rankings of JAKIs

Cluster†	SUCRA for Efficacy	SUCRA for Tolerability§	Drugs in Cluster†
4 (Best)	80–100	45–60	FIL 200 mg **UPA 24 mg BID** UPA 6 mg
3	60–80	35–40	TOFA 1 mg
2	35–50	30–45	UPA 12 mg PBO TOFA 15 mg TOFA 5 mg
1	20–40	55–65	TOFA 10 mg UPA 3 mg UPA 24 mg QD

Source: 10

FIL, Filgotinib; **SUCRA**, Surface under cumulative ranking value (range, 0%–100%), which refers to the probability that a treatment is the best or safest intervention; **TOFA**, Tofacitinib; **UPA**, Upadacitinib

† Cluster numbers reflect those used in the report. Drugs in a cluster may be considered to have similar performance.

§ Tolerability was inferred from discontinuations due to adverse events

Table 9 Other Considerations About the Network Meta-analyses

Consideration	Barberio, et al. (2023)	Rokkas, et al. (2021)	Din, et al. (2022)
Limitations	The U-EXCEL induction RCT and U-ENDURE maintenance RCT were unpublished.	Only the phase 2 RCT of upadacitinib was included. Compared only JAKIs. Included a total of only 4 RCTs. No evaluation of the confidence rating of evidence for all comparisons across the network.	Included only the U-EXCEED induction RCT. The results pertain to short-term therapy and CD and UC combined. Low risk of bias in only 52% of induction RCTs. Different study methods. Rare events. No evaluation of the confidence rating of evidence for all comparisons across the network.
Funding	None	Not reported	None
Author(s) COI with AbbVie	None	None	Yes

Other Considerations

Onset of Treatment Benefit and Duration of an Adequate Therapeutic Trial

- Onset of CDAI-100 clinical response (earliest significant treatment difference) was 2 weeks in both induction trials.[1]
- Onset of statistically significant treatment difference vs placebo in CDAI clinical response is summarized in Table 10.

Table 10 Onset of Treatment Benefit

Intervention	Trial	CD Population	Onset, CDAI-100 Response	Onset, CDAI-70 Response
Upadacitinib	U-EXCEED (Induction)	Biologic IR or INTOL	Week 2†	—
	U-EXCEL (Induction)	cIMM and/or Biologic IR or INTOL	Week 2†	—
Ustekinumab	UNITI-1 (Induction)[12]	Biologic IR or INTOL	Week 6†	Week 3†
	UNITI-2 (Induction)[12]	cIMM IR or INTOL	Week 6†	Week 3†
Risankizumab	ADVANCE (Induction)[13]	cIMM OR Biologic IR or INTOL	Week 4†	—
	MOTIVATE (Induction)[13]	Biologic IR or INTOL	Week 4†	—
Vedolizumab	GEMINI 2 (Induction, maintenance)	cIMM or TNFI IR, LOR, or INTOL	~Week 10§	—
	GEMINI 3 (Induction)	cIMM or TNFI IR, LOR, or INTOL	Week 6†	—

cIMM, Conventional immunomodulator; **INTOL**, Intolerance; **IR**, Inadequate response; **LOR**, Loss of response; **NSD**, No statistically significant difference

† First assessment time point. Statistical testing for any treatment differences was not assessed before this time.

§ Time of apparent separation in treatment effects. No statistical testing was done. There was NSD at Week 6, the first assessment time point.

Durability of Response

- No available data.

Other Therapeutic Options

- The 2021 American Gastroenterology Association (AGA) guideline recommendations on the management of CD[14,15] and other treatments for moderate to severe, active CD were summarized in the *Risankizumab-rzaa SKYRIZI in Crohn's Disease Monograph Feb 2023* available at PBM Formulary Management - Drug Monographs - All Documents (sharepoint.com).
- The AGA guidelines and other guidelines on management of CD published in the past 5 years[16,17,,18,19,20] do not cover upadacitinib and preceded FDA approval of upadacitinib for CD.
- Alternative treatments are limited in number. Other FDA-approved agents for induction of remission in patients with CD are TNFIs (adalimumab, infliximab), vedolizumab, ustekinumab, and risankizumab-rzaa. Upadacitinib is the only approved agent limited to second-line use; i.e., in patients with inadequate response or intolerance to TNFIs.

Projected Place in Therapy

- **Potential Place in Therapy Based on the Evidence**. Based on the FDA-approved indication, upadacitinib may be used for the treatment of patients with moderate to severe, active CD who have had an inadequate response or intolerance to TNFIs. Otherwise, the potential place in therapy of upadacitinib in the treatment of CD is uncertain. No head-to-head trials were available. The moderate-quality evidence from the placebo-controlled trials supported the use of upadacitinib for induction and maintenance of CDAI clinical remission and endoscopic response in patients who have had an inadequate response or intolerance to conventional agents and/or biologic therapies. Overall, treatment effects of upadacitinib relative to placebo based on CDAI clinical remission seemed to be small to medium, and endoscopic response benefits seemed to be medium. These clinical and endoscopic benefits appeared to be clinically meaningful, although upadacitinib induction did not significantly improve CD-related hospitalization rates. Limited network meta-analyses suggested that upadacitinib may be better than vedolizumab for induction therapy. These findings need confirmation in directly comparative trials. Onset of clinical response was about 2 weeks with upadacitinib and 3, 4, and 10 weeks with ustekinumab, risankizumab-rzaa, and vedolizumab, respectively, although these agents have not been directly compared.
- **Potential Place in Therapy in VHA**. Upadacitinib may be used for induction and maintenance therapy of patients with moderate to severe, active luminal CD who have an inadequate response or intolerance to one or more TNFIs unless TNFIs are medically inadvisable. Upadacitinib may be less preferred than

risankizumab-rzaa and ustekinumab in patients who have co-existing plaque psoriasis, and preferred over vedolizumab in patients with extraintestinal involvement.

Prepared: August 2023.

Contact person: Francine Goodman, PharmD, BCPS, National PBM Clinical Pharmacy Program Manager, Formulary Management, VA Pharmacy Benefits Management Services (12PBM)

References

[1] RINVOQ (upadacitinib) extended-release tablets [prescribing information online]. North Chicago, IL: AbbVie. May 2023. Available at: Microsoft Word - 484789.docx (rxabbvie.com). Accessed 22 May 2023.

[2] Sandborn WJ, Feagan BG, Loftus EV Jr, Peyrin-Biroulet L, Van Assche G, D'Haens G, Schreiber S, Colombel JF, Lewis JD, Ghosh S, Armuzzi A, Scherl E, Herfarth H, Vitale L, Mohamed MF, Othman AA, Zhou Q, Huang B, Thakkar RB, Pangan AL, Lacerda AP, Panes J. Efficacy and Safety of Upadacitinib in a Randomized Trial of Patients With Crohn's Disease. Gastroenterology. 2020 Jun;158(8):2123-2138.e8. doi: 10.1053/j.gastro.2020.01.047.

[3] D'Haens G, Panés J, Louis E, Lacerda A, Zhou Q, Liu J, Loftus EV Jr. Upadacitinib Was Efficacious and Well-tolerated Over 30 Months in Patients With Crohn's Disease in the CELEST Extension Study. Clin Gastroenterol Hepatol. 2022 Oct;20(10):2337-2346.e3. doi: 10.1016/j.cgh.2021.12.030.

[4] Aguilar D, Revilla L, Garrido-Trigo A, Panés J, Lozano JJ, Planell N, Esteller M, Lacerda AP, Guay H, Butler J, Davis JW, Salas A. Randomized Controlled Trial Substudy of Cell-specific Mechanisms of Janus Kinase 1 Inhibition With Upadacitinib in the Crohn's Disease Intestinal Mucosa: Analysis From the CELEST Study. Inflamm Bowel Dis. 2021 Nov 15;27(12):1999-2009. doi: 10.1093/ibd/izab116.

[5] A Study to Evaluate the Long-Term Efficacy, Safety, and Tolerability of Repeated Administration of Upadacitinib (ABT-494) in Participants With Crohn's Disease. Available at: https://clinicaltrials.gov/ct2/show/NCT02782663. Accessed: 22 May 2023.

[6] Mohamed MF, Klünder B, Lacerda AP, Othman AA. Exposure-Response Analyses for Upadacitinib Efficacy and Safety in the Crohn's Disease CELEST Study and Bridging to the Extended-Release Formulation. Clin Pharmacol Ther. 2020 Mar;107(3):639-649. doi: 10.1002/cpt.1668.

[7] Loftus EV Jr, Panés J, Lacerda AP, Peyrin-Biroulet L, D'Haens G, Panaccione R, Reinisch W, Louis E, Chen M, Nakase H, Begun J, Boland BS, Phillips C, Mohamed MF, Liu J, Geng Z, Feng T, Dubcenco E, Colombel JF. Upadacitinib Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2023 May 25;388(21):1966-1980. doi: 10.1056/NEJMoa2212728.

[8] A Maintenance and Long-Term Extension Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Participants With Crohn's Disease Who Completed the Studies M14-431 or M14-433. Available at: https://clinicaltrials.gov/ct2/show/NCT03345823. Accessed: 22 May 2023.

[9] Barberio B, Gracie DJ, Black CJ, Ford AC. Efficacy of biological therapies and small molecules in induction and maintenance of remission in luminal Crohn's disease: systematic review and network meta-analysis. Gut. 2023 Feb;72(2):264-274. doi: 10.1136/gutjnl-2022-328052.

[10] Rokkas T, Ekmektzoglou K, Niv Y. Comparative Efficacy and Tolerability of Janus Kinase Inhibitor Therapies for Moderate to Severe Crohn's Disease: A Network Meta-analysis. J Gastrointestin Liver Dis. 2021 Sep 21;30(3):388-397. doi: 10.15403/jgld-3804.

[11] Din S, Selinger CP, Black CJ, Ford AC. Systematic review with network meta-analysis: Risk of Herpes zoster with biological therapies and small molecules in inflammatory bowel disease. Aliment Pharmacol Ther. 2023 Mar;57(6):666-675. doi: 10.1111/apt.17379.

[12] Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, Blank MA, Johanns J, Gao LL, Miao Y, Adedokun OJ, Sands BE, Hanauer SB, Vermeire S, Targan S, Ghosh S, de Villiers WJ, Colombel JF, Tulassay Z, Seidler U, Salzberg BA, Desreumaux P, Lee SD, Loftus EV Jr, Dieleman LA, Katz S, Rutgeerts P; UNITI–IM-UNITI Study Group. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2016 Nov 17;375(20):1946-1960. doi: 10.1056/NEJMoa1602773.

[13] D'Haens G, Panaccione R, Baert F, Bossuyt P, Colombel JF, Danese S, Dubinsky M, Feagan BG, Hisamatsu T, Lim A, Lindsay JO, Loftus EV Jr, Panés J, Peyrin-Biroulet L, Ran Z, Rubin DT, Sandborn WJ, Schreiber S, Neimark E, Song A, Kligys K, Pang Y, Pivorunas V, Berg S, Duan WR, Huang B, Kalabic J, Liao X, Robinson A, Wallace K, Ferrante M. Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials. Lancet. 2022 May 28;399(10340):2015-2030. doi: 10.1016/S0140-6736(22)00467-6.

[14] Feuerstein JD, Ho EY, Shmidt E, Singh H, Falck-Ytter Y, Sultan S, Terdiman JP; American Gastroenterological Association Institute Clinical Guidelines Committee. AGA Clinical Practice Guidelines on the Medical Management of Moderate to

Severe Luminal and Perianal Fistulizing Crohn's Disease. Gastroenterology. 2021 Jun;160(7):2496-2508. doi: 10.1053/j.gastro.2021.04.022.

[15] American Gastroenterological Association. Medical Management of Adult Outpatients With Moderate to Severe Lunminal Crohn's Disease: Clinical Decision Support Tool. Gastroenterology. 2021 Jun;160(7):2509-2510. doi: 10.1053/j.gastro.2021.04.058.

[16] Macaluso FS, Papi C, Orlando A, Festa S, Pugliese D, Bonovas S, Pansieri C, Piovani D, Fiorino G, Fantini MC, Caprioli F, Daperno M, Armuzzi A; Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD); Working panel; Review panel. Use of biologics for the management of Crohn's disease: IG-IBD clinical guidelines based on the GRADE methodology. Dig Liver Dis. 2023 Apr;55(4):442-453. doi: 10.1016/j.dld.2023.01.155..

[17] Bonovas S, Piovani D, Pansieri C, Macaluso FS, Orlando A, Festa S, Papi C, Pugliese D, Armuzzi A. Use of biologics for the management of Crohn's disease: IG-IBD technical review based on the GRADE methodology. Dig Liver Dis. 2023 Mar 22:S1590-8658(23)00484-X. doi: 10.1016/j.dld.2023.02.019.

[18] Torres J, Bonovas S, Doherty G, Kucharzik T, Gisbert JP, Raine T, Adamina M, Armuzzi A, Bachmann O, Bager P, Biancone L, Bokemeyer B, Bossuyt P, Burisch J, Collins P, El-Hussuna A, Ellul P, Frei-Lanter C, Furfaro F, Gingert C, Gionchetti P, Gomollon F, González-Lorenzo M, Gordon H, Hlavaty T, Juillerat P, Katsanos K, Kopylov U, Krustins E, Lytras T, Maaser C, Magro F, Marshall JK, Myrelid P, Pellino G, Rosa I, Sabino J, Savarino E, Spinelli A, Stassen L, Uzzan M, Vavricka S, Verstockt B, Warusavitarne J, Zmora O, Fiorino G. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. J Crohns Colitis. 2020 Jan 1;14(1):4-22. doi: 10.1093/ecco-jcc/jjz180.

[19] Amiot A, Bouguen G, Bonnaud G, Bouhnik Y, Hagege H, Peyrin-Biroulet L; French National Consensus Clinical guidelines for the management of IBD study group. Clinical guidelines for the management of inflammatory bowel disease: Update of a French national consensus. Dig Liver Dis. 2021 Jan;53(1):35-43. doi: 10.1016/j.dld.2020.10.018.

[20] Panaccione R, Steinhart AH, Bressler B, Khanna R, Marshall JK, Targownik L, Afif W, Bitton A, Borgaonkar M, Chauhan U, Halloran B, Jones J, Kennedy E, Leontiadis GI, Loftus EV Jr, Meddings J, Moayyedi P, Murthy S, Plamondon S, Rosenfeld G, Schwartz D, Seow CH, Williams C, Bernstein CN. Canadian Association of Gastroenterology Clinical Practice Guideline for the Management of Luminal Crohn's Disease. Clin Gastroenterol Hepatol. 2019 Aug;17(9):1680-1713. doi: 10.1016/j.cgh.2019.02.043.