Upadacitinib (RINVOQ) in Psoriatic Arthritis National Drug Monograph Addendum June 2022

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, a Janus kinase inhibitor (JAKI) with JAK1 selectivity,[1] is the third JAKI approved for the treatment of psoriatic arthritis (PsA).
- Lower activity at JAK2 receptors, which are thought to play a key role in hematopoietic signaling, theoretically might reduce the risk of myelosuppression.

Indication Under Review in This Document

- Treatment of adults with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNFIs.
    - *Limitations of Use*: Upadacitinib is not recommended in combination with other JAKIs, biologic disease-modifying antirheumatic drugs (DMARDs), or potent immunosuppressants, such as azathioprine and cyclosporine.

Dosage Regimen and Dosage Forms Under Review

Pre-treatment Assessments

- Refer to the prescribing information for important pre-treatment assessments.

Dosage for Psoriatic Arthritis

- *Adults*: 15 mg once daily.
- *Renal Impairment*: No dosage adjustment is needed.

Dosage Forms

- Extended-release tablets, 15 and 30 mg

Clinical Evidence Summary

Efficacy Considerations

- The efficacy of upadacitinib in patients with active psoriatic arthritis was mainly supported by two 24-week, phase 3, placebo-controlled, randomized clinical trials (RCTs) involving patients with inadequate response or intolerance to ≥ 1 nonbiologic immunomodulator (nbIMM) (SELECT-PsA 1)[2,3,4] or ≥ 1 biologic DMARD (SELECT-PsA 2).[5,6,7,8]

- SELECT-PsA 1 showed that upadacitinib 15 mg was not better, and upadacitinib 30 mg was significantly better, than adalimumab (40 mg subcutaneously every 2 weeks) in achieving at least a 20% improvement in American College of Rheumatology criteria (ACR20 response) in patients who had an inadequate response or intolerance to nbIMM therapy.
- Both SELECT-PsA 1 and SELECT-PsA 2 showed that upadacitinib (15 and 30 mg) produced significant benefits over placebo in achieving ACR20 response and in measures of disability, psoriasis symptoms, minimal disease activity response, enthesitis, dactylitis, and quality of life.
- SELECT-PsA 1 showed that upadacitinib in both doses significantly reduced radiographic progression of peripheral PsA in patients who had an inadequate response or intolerance to nbIMMs. Since SELECT-PsA 2 did not evaluate radiographic progression, there is a lack of evidence that upadacitinib reduces radiographic progression in patients who failed bDMARDs.
- Neither study required objective (e.g., magnetic resonance imaging) confirmation of axial inflammation. Only investigator-reported presence of spinal pain was assessed on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
- Ultimately only the 15-mg dose was approved for PsA because of a better balance of risks vs benefits across patients with PsA regardless of different baseline characteristics.[9] Therefore, the 15-mg dose is the focus of the review below. (Note that escalation of dosage from 15 mg to 30 mg was only approved for the treatment of atopic dermatitis.)
- Pooled data from both phase 3 trials showed that upadacitinib monotherapy was similar in efficacy to upadacitinib combination therapy with ≤ 2 nbIMMs (methotrexate, sulfasalazine, leflunomide, apremilast, hydroxychloroquine and two other non-US, less commonly used nbIMMs).

- Ongoing extension studies of up to 5 years' duration are ongoing.

SELECT-PsA 1 and SELECT-PsA 2 Trials

- Selected study characteristics are summarized in Table 1.

Table 1 SELECT-PsA 1 and 2 Trial Methods

Topic	SELECT-PsA 1	SELECT-PsA 2
Study Design	• Multinational, double-blind randomized clinical trial (RCT) • Randomization was stratified by extent of psoriasis (≥ 3% vs < 3% of body surface area); current use vs nonuse of ≥ 1 nbIMM; presence vs absence of dactylitis; and presence vs absence of enthesitis. • Sample size calculation was based on having at least 85% power to assess the noninferiority and superiority of each upadacitinib dose relative to adalimumab in terms of the Week-12 ACR20 response. • The safety protocol included an independent, blinded, cardiovascular adjudication committee.	• Multinational, double-blind RCT • Randomization was stratified by extent of psoriasis (≥ 3% vs < 3% of body surface area), current use of at least 1 "DMARD" and number of prior bDMARDs failed (1 vs > 1). • No formal statistical analyses were performed for long-term efficacy (56-week trial results).

Topic	SELECT-PsA 1	SELECT-PsA 2
Major Entry Criteria	• Diagnosis of PsA; ≥ 3 swollen joints; ≥ 3 tender joints • History of or current plaque psoriasis • Erosions present on radiography of hands or feet or a high-sensitivity C-reactive protein level greater than the laboratory-defined upper limit of normal • Inadequate response or intolerance to ≥ 1 nbIMM. • Biologic-naïve and JAKI-naïve	• Diagnosis of PsA; ≥ 3 swollen joints; ≥ 3 tender joints • History of or current plaque psoriasis • Inadequate response (after ≥ 12 wks) or intolerance to ≥ 1 bDMARD. Of 641 patients, the majority (61.0%) had failed one prior bDMARD, while 18.1% and 12.9% had failed two and ≥ 3 prior bDMARDs, respectively. Only 8% of patients had intolerance but not inadequate response to prior bDMARDs.
Interventions	• Upadacitinib 15 mg once daily • Upadacitinib 30 mg once daily • Placebo • Adalimumab 40 mg subcutaneously every other week. • At Week 24, placebo patients were rerandomized to receive upadacitinib 15 mg or 30 mg in a 1:1 ratio. • Up to Week 36, stable background therapy was allowed and could include NSAIDs, glucocorticoids, and ≤ 2 nbIMMs (csIMMs or apremilast). • Rescue Therapy: Starting at Week 16, inadequate responders (< 20% improvement from baseline to Weeks 12 and 16 in tender and swollen joint counts) could start or modify background therapy including "DMARDs," NSAIDs, acetaminophen, low-potency opioids or glucocorticoids or adjust the upadacitinib dose.	• Upadacitinib 15 mg once daily • Upadacinitib 30 mg once daily • Placebo • At Week 24, placebo patients were rerandomized to receive upadacitinib 15 mg or 30 mg in a 1:1 ratio. • At Week 24, patients were randomized in a 2:2:1:1 ratio to receive upadacitinib 15 mg once daily, upadacitinib 30 mg once daily, or placebo switched to either upadacitinib 15 mg or 30 mg. • Allowed stable background therapy could include NSAIDs, glucocorticoids (≤ 10 mg/day prednisone equivalent), and/or ≤ 2 nbIMMs (csIMMs or apremilast). • Rescue Therapy: Starting at Week 16, inadequate responders (< 20% improvement from baseline to Weeks 12 and 16 in tender and swollen joint counts) could start or adjust background therapies. Inadequate responders for two consecutive weeks starting at Week 36 discontinued study drug. Starting at Week 36, all patients could start or adjust background therapies.
Primary Efficacy Measures	• ACR20 response† with upadacitinib vs placebo at Week 12:	• ACR20 response† at Week 12.
Baseline Patient Characteristics	• 81.8% of patients were using a nbIMM at baseline, 63.6% MTX monotherapy, and 16.8% glucocorticoids. • Male 46.8%, mean age 50.8 y, White 88.9%, duration of PsA 6.0 y.	• 53.8% were on nbIMM monotherapy, 34.7% were using MTX monotherapy, 59.0% were on NSAIDs, and 9.2% were on glucocorticoids. • Male 45.7%, mean age 53.4 y, White 88.1%, duration of PsA diagnosis 10.1 y.

† ACR20 response was defined as at least 20% improvement from baseline in the tender and swollen joint counts and ≥ 20% improvement in at least three of five other domains of the American College of Rheumatology criteria.

Results

Primary and Secondary Outcome Measures

- In patients with nbIMM inadequate response or intolerance (SELECT-PsA 1), upadacitinib 15 mg was noninferior and nonsuperior to adalimumab in ACR20 response at Week 12 (Table 2). Upadacitinib at the higher dose (30 mg) showed a significant benefit over adalimumab in ACR20 response at Week 12: 332/423 (78.5%) vs 279/429 (65.0%), respectively (difference of 13.5 [95% CI 7.5, 19.4]; p < 0.001).

- Efficacy data for the approved dose of upadacitinib in patients with active PsA after nbIMM inadequate response or intolerance are summarized in Table 2.

Table 2 Efficacy results from SELECT-PsA 1 with focus on upadacitinib 15 mg vs adalimumab comparison

Outcome Measure	Time Point (Wk)	UPA15	PBO	ADA	Relative Risk vs ADA (95% CI)	Absolute Difference vs ADA (95% CI)	Q
ACR20 response, n/N (%)	12	303/429 (70.6)	153/423 (36.2)	279/429 (65.0)	1.1 (1.0, 1.2)	5.6 (–0.6, 11.8)†‡	H
CFB in HAQ-DI, LSM (95% CI) (N)	12	–0.42 (–0.47, –0.37) (404)	–0.14 (–0.18, –0.09) (392)	–0.34 (–0.38, –0.29) (406)	—	–0.08 (–0.15, –0.01)†‡	H
PASI75 response, n/N (%)	16	134/214 (62.6)	45/211 (21.3)	112/211 (53.1)	1.2 (1.0, 1.4)	—	M[α]
CFB in mTSS, LSM (95% CI) (N)	24	–0.04 (–0.16, 0.07) (391)	0.25 (0.13, 0.36) (372)	0.01 (–0.11, 0.13) (384)	—	—	M[β]
MDA, n/N (%)	24	157/429 (36.6)	52/423 (12.3)	143/429 (33.3)	1.1 (0.9, 1.3)	—	H
LEI-0, n/N (%)	24	145/270 (53.7)	78/241 (32.4)	125/265 (47.2)	1.1 (1.0, 1.3)	—	H
LDI-0, n/N (%)	24	104/136 (76.5)†	50/126 (39.7)	94/127 (74.0)	1.0 (0.9, 1.1)	—	M[α]
CFB in SF-36 PCS score, LSM (95% CI) (N)	12	7.9 (7.1, 8.6) (405)	3.2 (2.4, 4.0) (394)	6.8 (6.1, 7.6) (410)	—	—	H

Sources: 7

All differences between upadacitinib 15 mg and placebo in the table were significant ($p < 0.001$).

ADA, Adalimumab; **CFB**, Change from baseline; **HAQ-DI**, Health Assessment Questionnaire–Disability Index (minimal clinically important change [MCIC] of ≥ 0.35-unit decrease; **LDI-0**, Leeds Dactylitis Index score of 0, indicating resolution of dactylitis; **LEI-0**, Leeds Enthesitis Index score of 0, indicating resolution of enthesitis; **LSM**, Least square mean; **MDA**, Minimal disease activity, defined as meeting 5 of 7 criteria (tender joint count of ≤ 1, swollen joint count of ≤ 1, a Psoriasis Area and Severity Index score of ≤ 1 or an affected body surface area of ≤ 3%; patient assessment of pain score of ≤ 1.5; patient global assessment of disease activity score of ≤ 2; Health Assessment Questionnaire–Disability Index score of ≤ 0.5; and a score on the LEI of ≤ 1); **mTSS**, Modified total Sharp-van der Heijde Score (range 0 to 528; higher scores indicate greater damage); **PASI75**, At least 75% improvement from baseline in the Psoriasis Area and Severity Index; **Q**, GRADE quality of evidence for comparison between upadacitinib 15 mg and adalimumab (H = High, M = Moderate, L = Low, VL = Very low); **SF-36 PCS**, 36-item Short Form Health Survey Physical Component Summary (MCIC ≥ 2.5-point increase); **UPA15**, Upadacitinib 15 mg

† Multiplicity controlled end point

‡ No p-value was calculated because the hierarchical testing to control for multiplicity failed at testing for superiority of upadacitinib 15 mg vs adalimumab in ACR20 response.

[α] Downgraded for imprecision because optimal information size not met.

[β] Downgraded for imprecision (wide confidence intervals).

- Efficacy results for upadacitinib in patients with active PsA after biologic inadequate response or intolerance is summarized in Table 3.

Table 3 Efficacy results from SELECT-PsA 2

Outcome Measure	Time Point (Wk)	UPA15	PBO	Relative Risk (95% CI)	Absolute Difference (95% CI)	Q
ACR20 response, n/N (%)†	12	120/211 (56.9)	51/212 (24.1)	1.4 (1.8, 3.1)	32.8 (24.0, 41.6)	H
CFB in HAQ-DI, LSM (95% CI) (N)†	12	–0.30 (–0.37, –0.24) (199)	–0.10 (–0.16, –0.03) (180)	—	–0.21 (–0.30, –0.12)	H
CFB in SF-36 PCS score, LSM (95% CI) (N)†	12	5.1 (4.1, 6.2) (201)	1.6 (0.6, 2.7) (185)	—	3.5 (2.1, 5.0)	H
PASI75 response, n/N (%)†	16	68/130 (52.3)	21/131 (16.0)	3.3 (2.1, 5.0)	36.3 (25.6, 46.9)	M$^{\alpha}$
MDA, n/N (%)†	24	53/211 (25.1)	6/212 (2.8)	8.9 (3.9, 20.2)	22.3 (16.0, 28.6)	H
LEI-0, n/N (%)	12	52/133 (39.1)	29/144 (20.1)	1.9 (1.3, 2.9)	19.0 (8.4, 29.5)	L$^{\alpha\beta}$
LDI-0, n/N (%)	12	35/55 (63.6)	23/64 (35.9)	1.8 (1.2, 2.6)	27.7 (10.4, 45.0)	L$^{\alpha\beta}$

Sources: 5,8

Abbreviations: See Table 2**. NR**, Not reported; **Q**, GRADE quality of evidence (H = High, M = Moderate, L = Low, VL = Very low)

† Multiplicity controlled end point

$^{\alpha}$ Downgraded for imprecision because optimal information size was not met.

$^{\beta}$ Downgraded for risk of bias (subgroup analysis without stratified randomization).

- Based on the SELECT-PsA 1 results, upadacitinib 15 mg produced no significant benefit over adalimumab and had large effects in ACR20 response vs placebo.
    - The anticipated absolute effect for achieving ACR20 in 12 weeks with upadacitinib 15 mg was 65 with a 95% CI of 0 to 130 more per 1000 patients relative to adalimumab (Table 4). The 95% CI includes a worst case of no incremental ACR20 benefit over adalimumab.
    - The anticipated absolute effect for achieving ACR20 in 12 weeks with upadacitinib 15 mg was 362 (253, 434) more per 1000 patients versus placebo (Table 4).
- In patients with active PsA after bDMARD inadequate response or intolerance (SELECT-PsA 2), upadacitinib 15 mg produced small to moderate effects in ACR20 response vs placebo.
    - The anticipated absolute effect for achieving ACR20 in 12 weeks with upadacitinib 15 mg relative to placebo was 337 (192, 505) more per 1000 patients (Table 4).

Table 4 Absolute Effects for Achieving ACR20 at Week 12

Trial	Treatment Comparison	AAE, per 1000 pts (95% CI)	NNT (95% CI)
SELECT-PsA 1	UPA15 vs ADA	65 (0, 130) more	18 (NSD)
SELECT-PsA 1	UPA15 vs PBO	362 (253, 434) more	2 (2, 3)
SELECT-PsA 2	UPA15 vs PBO	337 (192, 505) more	4 (3, 5)

AAE, Anticipated absolute effect for achieving the outcome in the given time period; **NNT**, Number needed to treat for one additional patient to benefit

Upadacitinib 15 mg vs Adalimumab After nbIMM Inadequate Response or Intolerance (SELECT-PsA 1)

- No significant differences between upadacitinib 15 mg and adalimumab were seen in ACR50 response (37.5% vs 37.5%, respectively) and ACR70 response (15.6% vs 13.8%, respectively) at Week 12. Increases were seen over time. At Week 24, response rates were 52.4% vs 44.3% for upadacitinib 15 mg vs adalimumab, respectively, for ACR50 and 28.7% vs 22.6%, respectively, for ACR70.[2]
- Significant treatment differences favoring upadacitinib 15 mg were seen in the following multiplicity-controlled patient-reported outcomes: improvements from baseline in HAQ-DI from Weeks 12 to 56, pain from Weeks 20 to 56, and SF-36 Physical Component Summary (PCS) and Self-Assessment of Psoriasis Symptoms at Week 56.

  - Nominally significant treatment differences ($p \leq 0.05$, without multiplicity control) were seen in patient global assessment from Weeks 16 to 56; and itch, Work Productivity and Activity Impairment (WPAI) activity impairment, and WPAI presenteeism at Week 56.[4]
  - No significant differences between active treatments were seen in BASDAI, BASDAI-50 response (defined as ≥ 50% improvement from baseline in BASDAI), WPAI overall work impairment, and WPAI absenteeism.
  - Upadacitinib 15 mg was significantly better than adalimumab in the percentage of patients achieving the minimal clinically important change (MCIC) from baseline in HAQ-DI; however, there were no differences for all other MCIC responses (i.e., for patient global assessment, pain, fatigue, EQ-5D-5L, BASDAI, morning stiffness, and SF-36 PCS).
- The comparative effects of upadacitinib and adalimumab on radiographic progression is uncertain since they were not statistically compared for this outcome. Upadacitinib 15 mg produced a reduction (improvement) from baseline by 0.04 units in mTSS, whereas adalimumab produced a slight increase (worsening) of 0.01 units. Upadacitinib 30 mg also produced a slight increase (worsening) of 0.03 units. The 95% CIs for the mTSS changes of the three treatments overlapped.
- Comparative effects of the active drugs is also uncertain for resolution of enthesitis (Leeds Enthesitis Index of 0; LEI-0) and dactylitis (Leeds Dactylitis Index of 0, LDI-0). Upadacitinib produced numerically better LEI and LDI resolution responses than adalimumab (Table 2).

Upadacitinib 30 mg (Nonapproved Dose for PsA) vs Adalimumab (SELECT-PsA 1)

- The ACR50 response (51.8% vs 37.5%, respectively) and ACR70 response (25.3% vs 13.8%, respectively) at Week 12 were higher with upadacitinib 30 mg than adalimumab; however, treatment differences were inconclusive because no adjustment was made for multiplicity. At Week 24, responses were 60.5% vs 44.3%, respectively, for ACR50 and 36.4% vs 22.6%, respectively, for ACR70.[2]
- Upadacitinib 30 mg was significantly better than adalimumab in HAQ-DI improvements from Weeks 4 to 56 and in patient global assessment and pain improvements from Weeks 2 to 56.[4]
- Upadacitinib 30 mg was also better than adalimumab in the percentage of patients achieving MCICs in patient global assessment, pain, HAQ-DI, and SF-36 PCS at Week 12.
- No significant treatment differences were observed between upadacitinib 30 mg and adalimumab in Week-12 MCIC responses for fatigue, EQ-5D-5L, BASDAI, and morning stiffness.

Upadacitinib vs Placebo After nbIMM Inadequate Response or Intolerance (SELECT-PsA 1)

- Both doses of upadacitinib showed significant benefits vs placebo in all efficacy outcomes including radiographic progression (mTSS), resolution of enthesitis and dactylitis, and investigator-determined spinal pain (measured on the BASDAI and BASDAI-50 response) up to Week 24.[2,4] However, there is some uncertainty in the BASDAI results due to potential type 1 error (BASDAI was not one of the multiplicity-controlled secondary outcomes). Also, the presence of axial inflammation / involvement was not determined objectively at baseline. (However, the efficacy of upadacitinib for axial PsA could be extrapolated from its approval for ankylosing spondylitis in the EU.)

Upadacitinib vs Placebo After bDMARD Inadequate Response or Intolerance (SELECT-PsA 2)

- In patients who had active PsA after bDMARD inadequate response or intolerance, both doses of upadacitinib provided significant benefits vs placebo in all primary and multiplicity-controlled secondary outcomes, including ACR20, sIGA-0/1, PASI75 responses, and MDA.
- Additional secondary outcomes had nominally significant treatment differences (both doses vs placebo) in ACR50, ACR70, and Week-2 ACR20 and changes from baseline in HAQ-DI, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and SF-36 Physical Component Summary.[5]
- Both doses also showed nominally significant effects vs placebo in enthesitis and dactylitis resolution rates.[5]

Subgroup Analyses: Monotherapy vs Combination Therapy (Pooled SELECT-PsA 1 and 2 Data)

- Based on placebo-subtracted treatment effects, upadacitinib monotherapy and combination therapy (with csIMMs, apremilast, or other nonbiologic immunomodulators) were similar in
    - Week-12 ACR20, ACR50, and ACR70 efficacy,
    - Week-24 resolution of enthesitis and dactylitis,
    - Week-16 PASI-90 and PASI-100,
    - Week-24 minimal disease activity response,
    - change from baseline (CFB) to Week 12 in patient global assessment of pain, and
    - CFB to Week 12 in the Health Assessment Questionnaire – Disability Index.[5]
- Upadacitinib 30 mg monotherapy showed a significantly greater placebo-subtracted treatment effect in Week-16 PASI-75 relative to combination therapy.[5]

Onset of Treatment Benefit

- Upadacitinib 15 mg showed significant benefit over placebo in achieving ACR20 as early as Week 2 in both SELECT-PsA 1 and SELECT-PsA 2.[8]
- In SELECT-PsA 1, upadacitinib 15 mg and adalimumab produced similar ACR20 responses at Week 2.[2]

Duration of an Adequate Therapeutic Trial of Upadacitinib 15 mg

- Results of a pharmacokinetic study evaluating exposure-response relationships using data from both phase 3 RCTs suggested that 12 weeks may represent an adequate trial of upadacitinib 15 mg. Exposure-response analyses suggested that the effects of upadacitinib 15 mg plateaued at Week 12 for ACR20 and PASI75 responses and at Week 24 for almost all other outcomes evaluated.[9]
- These results suggest that if there is nonresponse in peripheral musculoskeletal symptoms by 12 weeks (as was measured by the lowest ACR response threshold of ACR20 in the trial), an alternative treatment may be considered. For partial responders by 12 weeks, an additional 12 weeks of therapy (up to 24 weeks) may improve response.

Durability of Response

- In SELECT-PsA 1, ACR20, ACR50, ACR70 responses were maintained with both doses of upadacitinib for up to 56 weeks.[3] From Week 24 to Week 56, other responses were either maintained or improved (Psoriatic Arthritis Response Criteria [PsARC], enthesitis, dactylitis). In patients with presumed psoriatic spondylitis at baseline, Ankylosing Spondylitis Disease Activity Score (ASDAS) and Bath Ankylosing Spondylitis Diseases Activity Index (BASDAI) improved to Week 56.
    - Relative to adalimumab, upadacitinib 15 mg showed higher ACR50 and ACR70 responses (nominal $p \leq 0.05$), and upadacitinib 30 mg showed higher ACR20, ACR50, and ACR70 responses (nominal $p \leq 0.05$) at Week 56.[3]
    - Upadacitinib 15 mg or 30 mg was better than adalimumab in changes from baseline to Week 56 in HAQ-DI, SF-36 PCS, Self-assessment of Psoriasis symptoms, patient global assessment, and patients' assessment of pain (nominal p-values ≤ 0.05); however, these treatment comparisons are inconclusive because no adjustments were made for multiplicity.[3]
    - Upadacitinib 30 mg showed greater improvements (from baseline to Week 56) than adalimumab in C-reactive protein, Disease Activity in Psoriatic Arthritis (DAPSA), and Ankylosing Spondylitis Disease Activity Score (ASDAS) (nominal p-values).[3]
- In SELECT-PsA 2, ACR20, ACR50, ACR70, and minimal disease activity (MDA) responses were maintained with upadacitinib 15 mg and 30 mg for up to 56 weeks.[8] All continuous efficacy outcomes, including Health Assessment Questionnaire–Disability Index (HAQ-DI), Short Form-36 Physical Component Summary (SF-36 PCS), Work Productivity and Activity Impairment showed improvements from baseline to 56 weeks.[8]

Exposure (Dose)-Response Relationships

- The exposure-response analyses showed that the 30-mg dose provided inconsistent, limited, small additional improvements in efficacy over the 15-mg dose for only some outcomes and some time points, mainly at earlier time points (e.g., ACR50 and ACR70 at Week 12 but not Week 24).[9]

Evidence gaps

- Longer-term survival / mortality
- Longer-term disability / morbidity, including those due to radiographic progression beyond 24 weeks.
- Patient satisfaction, especially preference for oral upadacitinib vs injectable adalimumab therapy.

Network Meta-analyses

- In a network meta-analysis indirectly comparing upadacitinib, tofacitinib, and filgotinib in patients with PsA who had csIMM, bDMARD, or TNFI inadequate response or intolerance (K = 5, N = 2539), upadacitinib 30 mg was better than tofacitinib 10 mg in achieving ACR70 response (odds ratio [OR] 8.03; 95% CI 1.14, 64.82).
    - All other upadacitinib comparisons among active treatments (upadacitinib 15 or 30 mg vs tofacitinib 5 mg or 10 mg or filgotinib 200 mg) for ACR20, ACR50, ACR70, and PASI75 responses were not significantly different (95% CIs included the value 1).[10]
    - Tofacitinib 5 mg and 10 mg were less likely than upadacitinib 15 and 30 mg to cause serious adverse events (range of OR: 0.37–0.58); however, none of these indirect comparisons were significantly different by 95% CIs.
    - Upadacitinib 15 mg and 30 mg were consistently more effective than placebo in achieving each of the three ACR outcomes and PASI75.

Safety Considerations

- The safety profile of upadacitinib in patients with PsA was generally consistent with that in patients with rheumatoid arthritis.[1]
- The FDA extrapolated results for tofacitinib from the ORAL Surveillance study to other JAKIs indicated for inflammatory conditions.[11] Thus, like tofacitinib, upadacitinib carries Boxed Warnings for mortality, malignancy, major adverse cardiovascular events, and thrombosis regardless of indication.[1]

Upadacitinib vs Adalimumab: Integrated Safety Analysis of PsA Data Up to 3 Years

Lower Risk With Upadacitinib

- Upadacitinib 15 mg and 30 mg had significantly lower risks (events per 100 patient-years [PY; 95% CI]) of **hepatic disorders** than adalimumab: 13.6 (11.6, 15.8) and 18.8 (16.3, 21.2) vs 26.6 (22.4, 31.2), respectively.[12] Hepatic disorders consisted of mostly transient, nonserious increases in transaminases.
- Upadacitinib 15 mg had a lower risk of **neutropenia** than adalimumab and upadacitinib 30 mg: 1.8 (1.1, 2.7) vs 4.7 (3.1, 6.9) and 5.1 (3.9, 6.5), respectively.[12]

Higher Risk With Upadacitinib

- **Herpes zoster** (HZ; 3.8 [2.8, 5.1] vs 0.5 [0.1, 1.6]), **opportunistic infections** (excluding TB, HZ, oral candidiasis; 0.4 [0.1, 0.9] vs 0), and **lymphopenia** (2.2 [1.4, 3.1] vs 0.2 [0.0, 1.0]) were more frequent with upadacitinib 15 mg than adalimumab, respectively.[8]
- **Acne** occurred only on upadacitinib and not on adalimumab (events per 100 PY; 95% CI not reported): 0.9 for 15 mg and 1.1 for 30 mg vs 0 on adalimumab.[8]
- Upadacitinib 30 mg, relative to upadacitinib 15 mg and adalimumab, had a significantly higher risk of **HZ**, **serious infection**, **anemia**, and **CPK elevations**.[8]

Similar Risks Between Upadacitinib and Adalimumab

- Upadacitinib 15 mg and adalimumab were not significantly different in terms of serious adverse events, withdrawals due to adverse events, serious infection, herpes zoster, venous thromboembolism, major adverse cardiovascular events (MACE), and any adverse events.[12]
- Mortality, malignancy, MACE, and thrombosis occurred at similar rates during the short term between upadacitinib 15 mg and adalimumab.[8]

Safety of Upadacitinib Combination Therapy vs Monotherapy (Subgroup Analyses)

- **Hepatic disorders** (mostly nonserious transaminase increases) were more frequent with upadacitinib in combination with csIMMs, apremilast, or other nonbiologic immunomodulators than with upadacitinib monotherapy.[5,8]

Dose-Response Safety Analyses

- Dose-response analyses of data from the two phase 3 RCTs showed that increases in upadacitinib C_{avg} and C_{max} up to 75% from those for exposures with target doses of 15 mg daily (simulating potential increased exposures due to intrinsic or extrinsic factors) were predicted to produce limited increases in the percentage of patients experiencing certain safety outcomes, while still providing robust efficacy with the 15-mg dose.
- The model-simulated absolute increases in risk were predicted to be 0 percentage points (incidence of 2% for both doses) for serious infections, 1 percentage point (from 3% to 4%) for decreases in hemoglobin > 2 g/dL, and 2 percentage points (from 1% to 3%) for decreases in hemoglobin > 2 g/dL with hemoglobin less than the lower limit of normal.[9]

Gaps in Safety Data

- Long-term safety experience

Other Considerations

- Upadacitinib does not require renal dosage adjustments in psoriatic arthritis (and rheumatoid arthritis).
- In atopic dermatitis and ulcerative colitis, upadacitinib requires dosage reduction in renal impairment (eGFR 15 to < 30 mL/min/1.73 m^2 and use is not recommended for eGFR < 15 mL/min/1.73 m^2.
- Tofacitinib requires dosage reduction in moderate to severe impairment across approved indications.

Other Therapeutic Options

- The approved indication of upadacitinib in PsA places it after TNFIs.
- The most recently published society guidelines for PsA therapy, the 2019 update of the European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacologic therapies, recommends biologic DMARDs in patients with active PsA who have the following characteristics:
    - polyarthritis (> 4 swollen joints) with or without dactylitis, or mono- / oligoarthritis with poor prognostic factors, despite at least one csIMM (3- to 6-month trial), such as methotrexate, leflunomide, or sulfasalazine; or
    - mono- / oligoarthritis without poor prognostic factors despite NSAIDs and at least one csIMM; or
    - enthesitis or predominantly axial disease despite NSAIDs. The treatment alternatives for patients with enthesitis are a TNFI, interleukin-12/23 inhibitor (IL-12/23I, such as ustekinumab), or interleukin-17A inhibitor (IL-17AI). A phosphodiesterase-4 inhibitor (PDE4I) is another alternative if disease is mild and bDMARD and JAKI are inadvisable. For patients with predominantly axial disease, the alternatives are a TNFI (typically preferred) or IL-17AI (can be preferred if there is major skin involvement).

- The typical step-up approach would be a csIMM (for peripheral synovitis only) then biologic DMARD, then either another biologic DMARD or JAKI.[13]
- For patients with arthritis and/or enthesitis who inadequately responded after 3 to 6 months of therapy with the first (or subsequent) biologic DMARDs (or JAKI if biologic DMARD is inadvisable), a switch to an in-class biologic DMARD, out-of-class biologic DMARD, or targeted synthetic immunomodulator (JAKI preferred over PDE4I), should be considered.[13]
- For patients with predominantly axial disease who inadequately respond after 3 to 6 months of therapy with the first and subsequent biologic DMARDs, a switch to an in-class or out-of-class biologic DMARD may be considered.[13]
- Apremilast may be considered for patients with mild disease who inadequately respond to at least one csIMM and for whom neither a biologic DMARD nor JAKI is advisable.[13] Apremilast has not been proven to be effective in preventing radiographic progression of erosive disease. It has been suggested in lieu of nonbiologic or biologic immunomodulators including TNFIs, especially in patients who prefer to avoid injections, infusions, or adverse reactions to the other systemic immunomodulators.[13]
- The alternative treatments for patients with active PsA who inadequately respond or have intolerance to TNFIs and therefore would be at the same level as upadacitinib are summarized in Table 5.

Table 5 Treatment Alternatives for Active Psoriatic Arthritis Inadequately Responding to TNFIs

Drug (Formulary Status)	Place in Therapy for Active PsA in PI and CFU	2019 EULAR Place in Therapy[13]	2018 ACR Place in Therapy[14]	Safety Considerations	Other Considerations
Janus Kinase Inhibitors					
Upadacitinib (NonF, CFU in RA)	PI: Inadequate response or intolerance to ≥ 1 TNFI.	Not specifically reviewed. See tofacitinib.	Not specifically reviewed. See tofacitinib.	Mortality, malignancy, MACE, thrombosis, hematocytopenias, infection, TB, HBV, HZ, hepatotoxicity, increased lipids, bowel perforation. Not recommended in severe (Child-Pugh class C) liver disease.	Also approved for ankylosing spondylitis, ulcerative colitis, rheumatoid arthritis, and atopic dermatitis. Administered orally. Not recommended for co-use with strong CYP3A4 inhibitors or inducers. Hematologic and renal dosage adjustments. E D A R N + + + + ?
Tofacitinib (NonF, CFU)	PI: Inadequate response or intolerance to ≥ 1 TNFI. CFU: After one TNFI, one IL-17AI, and ustekinumab	Consider a JAKI for patients with peripheral arthritis ± enthesitis without predominant axial disease after inadequate response to bDMARD or when a bDMARD is inadvisable (same level as switching to another bDMARD or PDE4I).	For active PsA despite TNFI, IL-17AI, and IL-12/23I (conditionally recommended; same level as abatacept). May consider tofacitinib over TNFI, IL-17AI, or IL-12/23I if patient prefers oral medication.	See upadacitinib. Higher risk of mortality, malignancy, MACE, and thrombosis than TNFIs in patients ≥ 50 yrs with rheumatoid arthritis and ≥ 1 CV risk factor.[15] Not recommended in severe (Child-Pugh class C) liver disease.	Administered orally. Avoid co-use with strong CYP3A4 inducers. Hematologic, renal, and hepatic dosage adjustments. E D A R N + + + + +

Drug (Formulary Status)	Place in Therapy for Active PsA in PI and CFU	2019 EULAR Place in Therapy [13]	2018 ACR Place in Therapy [14]	Safety Considerations	Other Considerations
Interleukin-12/23 Inhibitor					
Ustekinumab (NonF, CFU)	PI: No recommended prior therapies. CFU: After one TNFI and one IL-17AI.	Consider for inadequate responders to TNFI with peripheral arthritis ± enthesitis without predominant axial disease (same level as switching to another TNFI, IL-17AI, abatacept, JAKI, or PDE4I).	Active PsA despite TNFI and IL-17AI (conditionally recommended; same level as abatacept or tofacitinib).	Infections, malignancy, noninfectious pneumonia, posterior reversible encephalopathy syndrome, TB.	For patients with major skin involvement and peripheral arthritis, an IL-12/23I may be preferred over a TNFI. Ineffective for axial spondyloarthritis. [16] Uncertain effects on axial PsA. [17, 18, 19] Patients > 100 kg may require higher doses. E D A R N + + – + +
Interleukin-17A Inhibitors					
Ixekizumab (NonF, CFU)	PI: No recommended prior therapies. CFU: After TNFI.	Consider for TNFI inadequate responders with peripheral arthritis ± enthesitis without predominantly axial disease (same level as switching to another TNFI, IL-12/23I, JAKI, or PDE4I). Consider for TNFI or IL-17AI inadequate responders with predominantly axial disease (same level as switching within or between TNFI or IL-17AI class(es)).	Active PsA despite TNFI (conditionally recommended; same level as IL-12/23I, abatacept, or tofacitinib).	Infections (including mucocutaneous candidiasis), TB, onset or worsening of IBD.	Relative to adalimumab, ixekizumab was similar in ACR50 response and better in PASI100 response at Wk 52. [20] No direct comparisons of secukinumab with TNFI. For patients with major skin involvement (and peripheral or predominantly axial disease), an IL-17AI may be preferred over a TNFI. E D A R N + + + + +
Secukinumab (NonF, CFU)	PI: No recommended prior therapies. CFU: After TNFI.				
Interleukin-23 Inhibitor					
Guselkumab (NonF, CFU)	PI: No recommended prior therapies. CFU: After one TNFI, one IL-17AI, and ustekinumab.	Not included	Not included	Infections, TB Lacks IBD warning of IL-17AIs.	A network meta-analysis showed that secukinumab 300 and 150 mg are nonsignificantly better than guselkumab 100 mg Q4W and Q8W in achieving ACR20. [21] Ineffective for axial spondyloarthritis. Uncertain effects on MRI axial PsA. [17, 22] E D A R N + + – + +
Risankizumab-rzaa (NonF, CFU)	PI: No recommended prior therapies. CFU: TBD	Not included	Not included	Infections, TB Lacks IBD warning of IL-17AIs.	Effective for nail psoriasis in PsA. [23] Ineffective for axial spondyloarthritis. [24] No data for axial PsA.

Drug (Formulary Status)	Place in Therapy for Active PsA in PI and CFU	2019 EULAR Place in Therapy [13]	2018 ACR Place in Therapy [14]	Safety Considerations	Other Considerations
					Ineffective for radiographic progression at Week 24. [25, 26] Later time points not available. E D A R N + + – – +
Phosphodiesterase-4 Inhibitor					
Apremilast (VANF, CFU)	PI: No recommended prior therapies. CFU: After a csIMM and TNFI is medically inadvisable.	Consider for mild, nonerosive, nonaxial disease in csIMM inadequate responders when neither a bDMARD nor JAKI is advisable, or for peripheral arthritis ± enthesitis without predominant axial disease in bDMARD inadequate responders (same level as switching to another bDMARD or JAKI).	Not recommended in TNFI inadequate responders.	Slow up-titration of dosage in first week is recommended to reduce GI adverse effects. Neuropsychiatric effects; weight loss. Renal dosage adjustment.	Generally favorable safety profile. Administered orally. Ineffective in ankylosing spondylitis. E D A R N + + – ? +
T-cell Costimulation Inhibitor					
Abatacept (NonF)	PI: No recommended prior therapies.	Should be limited to inadequate responders to other bDMARDs.	Active PsA despite TNFI, IL-17AI, and IL-12/23I (conditionally recommended; same level as tofacitinib).	Infections, malignancy, COPD exacerbation; TB and HBV screening	Low efficacy. Administered IV or SC. Seems to be ineffective for ankylosing spondylitis. E D A R N – – – ± ?

Sources: 13,14, 27, 28, 29,30,31
CFU, Criteria for use; **NonF**, Nonformulary; **VANF**, VA National Formulary
Key for blue insetted table: **E**, Enthesitis; **D**, Dactylitis; **A**, Axial inflammation (may be extrapolated from efficacy in axial spondyloarthritis); **R**, Radiographic progression (erosions); **N**, Nail psoriasis; **+**, Effective; **–**, Ineffective; **±**, Inconsistent or uncertain effects; **?**, Not studied

Projected Place in Therapy

Potential Place in Therapy in PsA Based on the Evidence

- In accordance with the approved indication, upadacitinib (15 mg once daily) may be used in patients with active PsA who have had an inadequate response or intolerance to TNFI therapy or refuse this treatment because of safety concerns.
- Upadacitinib may be useful for improvement of peripheral synovitis, enthesitis, dactylitis, and axial spondylitis (based on EU approval for ankylosing spondylitis). Upadacitinib was shown to reduce peripheral radiographic progression in patients with inadequate response or intolerance to nbIMMs.
- Based on efficacy for axial PsA or ankylosing spondylitis, upadacitinib may be preferred over ustekinumab, IL-23Is, apremilast, and abatacept.
- For patients with psoriatic nail involvement, upadacitinib may be less preferable than tofacitinib and other agents for PsA except abatacept, based on available evidence to date that the other agents improve nail disease and absence of such evidence for upadacitinib and abatacept.

Potential Place in Therapy in PsA in VHA

- Considering overall risks, benefits, and value, upadacitinib may be used for the treatment of patients with active PsA despite therapy with one **TNFI**. When treatment for axial PsA is needed, a JAKI may be preferable over ustekinumab.
- When a JAKI is indicated, tofacitinib may be preferred over upadacitinib because of cost considerations.
- Upadacitinib was shown to be safe and effective as monotherapy, whereas tofacitinib is labeled for use in combination with a conventional immunomodulator.

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