# Deucravacitinib (SOTYKTU) in Plaque Psoriasis
# National Drug Monograph
# April 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**

- Deucravacitinib is a first-in-class selective, allosteric tyrosine kinase 2 inhibitor (TYK2I or alloTYKinib).[1,2] TYK2 inhibition blocks IL-23, IL-12, and type I interferon-α/β responses with minimal inhibition (≤ 1%) of off-target JAK1/3 and JAK2/2 cytokines affected by other JAK inhibitors (JAKIs).[2]
- The mechanism of TYK2Is in improving moderate to severe plaque psoriasis (PsO) is unknown.
- Deucravacitinib is the fifth small-molecule (after conventional immunomodulators) and second targeted oral small molecule (after apremilast) approved for PsO.

**Indication Under Review in This Document**

- Treatment of moderate to severe PsO in adults who are candidates for systemic therapy or phototherapy.
- Deucravacitinib is not recommended for use in combination with other potent immunosuppressants.

**Pretreatment Evaluation and Tests**

- Tuberculosis (TB) screening. If positive, start treatment for TB before initiating deucravacitinib. Deucravacitinib should not be initiated in patients with latent or active TB infection.
- Update immunizations.
- Consider hepatitis B or C screening (patients positive on screening tests or those with chronic hepatitis B or untreated hepatitis C were excluded from clinical trials). Deucravacitinib is not recommended in patients with active hepatitis B or hepatitis C.
- Consider baseline triglyceride levels.
- Baseline liver enzymes. Not recommended for use in patients with severe hepatic impairment (Child-Pugh C).
- Consider baseline creatine phosphokinase (CPK). A baseline CPK is not recommended in the US prescribing information.

**Monitoring During Therapy**

- Triglyceride levels. Monitor according to clinical guidelines for hyperlipidemia.
- Liver enzymes. Monitor in patients with known or suspected liver disease as per routine patient management.
- Consider checking CPK periodically or in patients with suspected or diagnosed myopathy. Deucravacitinib increases the risk of asymptomatic elevations in CPK and rhabdomyolysis. There are no

recommendations for monitoring of CPK in the US prescribing information. Deucravacitinib should be discontinued if CPK becomes markedly elevated.

### Dosage Regimen and Dosage Form Under Review

- Recommended dose: 6 mg orally once daily with or without food. Do not crush, cut, or chew tablets.
- Tablets, film-coated: 6 mg in bottles of 30.

### Dosage Adjustments in Special Populations

- Renal impairment. No dosage adjustments required.
- Hepatic impairment. No dosage adjustments required for mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Not recommended for use in severe (Child-Pugh C) hepatic impairment.

## Efficacy Considerations

- Two phase 3 active-controlled randomized clinical trials (RCTs), POETYK PSO-1 and POETYK PSO-2, showed the superiority of deucravacitinib over both apremilast and placebo in patients with moderate to severe plaque psoriasis (PsO).[3,4]
- A phase 2, dose- and placebo-controlled RCT provided supportive evidence of efficacy in PsO.[5,6]
- Another phase 2 placebo-controlled RCT showed promising efficacy with deucravacitinib in psoriatic arthritis.[7]

### Phase 3 Randomized Clinical Trials

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

**Table 1 Methods of Phase 3 RCTs**

| Topic | POETYK PSO-1 | POETYK PSO-2 |
|---|---|---|
| **Study Design** | 52-week MN DB DD AC PC RCT with 2:1:1 randomization, including a 16-week AC and PC period, an 8-week AC period, and a 28-week maintenance period.<br>Randomization was stratified by geographic region, previous biologic use, and body weight, except stratification by body weight was not done in Japan or China. | 52-week MN DB DD AC PC RCT with 2:1:1 randomization and including a 16-week AC and PC period, an 8-week AC period, and a 28-week randomized withdrawal and maintenance period.<br>Randomization was stratified by geographic region, previous biologic use, and body weight |
| **Long-term Extension Trial** | POETYK PSO-LTE: 244-week open-label, longer-term safety and efficacy trial | |
| **Major Entry Criteria** | *Inclusion Criteria*<br>≥ 18 years of age, stable moderate to severe plaque psoriasis (sPGA ≥ 3, PASI ≥ 12, BSA ≥ 10%) for ≥ 6 months, deemed to be candidate for phototherapy or systemic therapy<br>*Exclusion Criteria*<br>Active or latent TB or history of opportunistic infections. IGRA-positive patients were eligible to enroll if they had no signs or symptoms of active TB AND had received appropriate treatment for LTBI within the previous 5 years OR had started prophylaxis per local guidelines PLUS was rescreened after 1 month of treatment. To continue in the trial, patients had to have completed a locally-recommended course of treatment for LTBI (except rifampin interacts with apremilast and therefore was not recommended). | |

| Topic | POETYK PSO-1 | POETYK PSO-2 |
|---|---|---|
| **Interventions** | *Week 0 to Week 16:*<br>• Deucravacitinib 6 mg QD<br>• Placebo<br>• Apremilast titrated from 10 mg QD to 30 mg BID over the first 5 days then continued at 30 mg BID (not used in China)<br>*Week 16:* Placebo patients were crossed over to deucravacitinib.<br>*Week 24:* Apremilast nonresponders (< PASI 50) at Week 24 were switched under blinded conditions to deucravacitinib. Apremilast responders continued on apremilast.<br>*Allowed co-medications*: Low-potency TCSs on palms, soles, face, and intertriginous areas | *Week 0 to Week 16:*<br>• Deucravacitinib 6 mg QD<br>• Placebo<br>• Apremilast titrated from 10 mg QD to 30 mg BID over the first 5 days then continued at 30 mg BID<br>*Week 16:* Placebo patients were crossed over to deucravacitinib.<br>*Week 24*: Deucravacitinib PASI-75 responders were rerandomized 1:1 to continue deucravacitinib or switch to placebo.<br>*Allowed co-medications*: Same as for POETYK PSO-1. |
| **Coprimary and Key Efficacy Measures** | PASI-75 response and sPGA-0/1–2 at Week 16 | PASI-75 response and sPGA-0/1–2 at Week 16<br>Median time to relapse, defined as time to ≥ 50% loss of Week-24 PASI percent improvement from baseline after treatment withdrawal at Week 24. |
| **Baseline Patient Characteristics** | N = 666<br>Age, mean: 46.1 y<br>Male: 68.0%<br>Weight, mean: 88.1 kg<br>White / Asian: 80.2% / 18.2%<br>Disease duration, mean: 17.3 y<br>sPGA (0–4), 3 (moderate) / 4 (severe): 78.7% / 21.2%<br>Affected BSA, mean: 26.3%<br>Scalp PsO: 91.4%<br>Nail PsO: 41.7%<br>PsA: 18.2%<br>Prior systemic therapy: 62.8%<br>Prior biologic / nonbiologic: 38.9% / 23.9% | N = 1020<br>Age, mean: 46.9 y<br>Male: 66.1%<br>Weight, mean: 92.4 kg<br>White / Asian: 91.7% / 4.3%<br>Disease duration, mean: 19.5 y<br>sPGA, 3 (moderate / 4 (severe): 80.5% / 19.5%<br>Affected BSA, mean: 26.5%<br>Scalp PsO: 88.2%<br>Nail PsO: 46.2%<br>PsA: 18.6%<br>Prior systemic therapy: 54.2%<br>Prior biologic / nonbiologic: 32.1% / 22.2% |

**AC**, Active-controlled; **BSA**, Body surface area; **DB**, Double-blind; **DD**, Double-dummy; **LTBI**, Laten tuberculosis infection; **MN**, Multinational; **PASI-75**, ≥ 75% improvement on the Psoriasis Area and Severity Index; **PC**, Placebo-controlled; **PsO**, Plaque psoriasis; **sPGA**, Static Physician's Global Assessment

## Results

- Deucravacitinib was significantly better than placebo in all primary and secondary outcome measures in both phase 3 trials. The results here focus on comparisons between deucravacitinib and apremilast.
- Selected efficacy data are summarized in Table 2 and Table 4.

**Table 2 Efficacy results from POETYK PSO-1**

| Outcome | Time (Weeks) | Deucravacitinib | Apremilast | Placebo | Relative Risk,† (95% CI) |
|---|---|---|---|---|---|
| sPGA-0/1–2, n/N (%) | 16 | 178/332 (53.6) | 54/168 (32.1) | 12/166 (7.2) | 1.7 (1.31, 2.12) |
| | 24 | 195/332 (58.7) | 52/168 (31.0) | NA | 1.9 (1.49, 2.42) |
| PASI-75, n/N (%) | 16 | 194/332 (58.4) | 59/168 (35.1) | 21/166 (12.7) | 1.7 (1.33, 2.08) |
| | 24 | 230/332 (69.3) | 64/168 (38.1) | NA | 1.8 (1.48, 2.23) |
| DLQI-0/1, n/N (%) | 16 | 132/322 (41.0) | 46/161 (28.6) | 17/160 (10.6) | 1.5 (1.09, 1.89) |
| | 24 | 155/322 (48.1) | 39/161 (24.2) | NA | 2.0 (1.48, 2.67) |

Sources: [3]; FDA Multi-discipline Review[8]
**DLQI-0/1**, Dermatology Life Quality Index of 0 / Not at All or 1 / A Little on a 4-point scale; **PASI-75**, ≥ 75% improvement on the Psoriasis Area and Severity Index; **sPGA-0/1–2**, Static Physician's Global Assessment score of 0 / Clear or 1 / Almost Clear with ≥ 2-point improvement from baseline
† Relative risk for deucravacitinib vs apremilast

**Table 3 Efficacy results from POETYK PSO-2**

| Outcome | Time (Weeks) | Deucravacitinib | Apremilast | Placebo | Relative Risk,† (95% CI) |
|---|---|---|---|---|---|
| sPGA-0/1–2, n/N (%) | 16 | 253/511 (49.5) | 86/254 (33.9) | 22/255 (8.6) | 1.5 (1.21, 1.77) |
| | 24 | 251/504 (49.8) | 75/254 (29.5) | NA | 1.7 (1.37, 2.08) |
| PASI-75, n/N (%) | 16 | 271/511 (53.0) | 101/254 (39.8) | 24/255 (9.4) | 1.3 (1.12, 1.58) |
| | 24 | 296/504 (58.7) | 96/254 (37.8) | NA | 1.6 (1.31, 1.85) |
| DLQI-0/1, n/N (%) | 16 | 186/495 (37.6) | 57/247 (23.1) | 24/246 (9.8) | 1.6 (1.26, 2.10) |
| | 24 | 205/495 (41.4) | 53/247 (21.5) | NA | 1.9 (1.49, 2.50) |

Sources: 4
**DLQI-0/1**, Dermatology Life Quality Index of 0 / Not at All or 1 / A Little on a 4-point scale; **PASI-75**, ≥ 75% improvement on the Psoriasis Area and Severity Index; **sPGA-0/1–2**, Static Physician's Global Assessment score of 0 / Clear or 1 / Almost Clear with ≥ 2-point improvement from baseline
† Relative risk for deucravacitinib vs apremilast

**Table 4 Absolute Effects for Achieving Selected Outcomes for Deucravacitinib vs Apremilast at Week 24**

| Outcome Measure | Trial | AAE per 1000 pts (95% CI) | NNT (95% CI) | Q |
|---|---|---|---|---|
| sPGA-0/1–2 | PSO-1 | 278 (190, 366) | 4 (3, 6) | H |
| | PSO-2 | 211 (139, 283) | 5 (4, 8) | H |
| PASI-75 | PSO-1 | 312 (223, 400) | 4 (3, 5) | H |
| | PSO-2 | 204 (135, 274) | 5 (4, 8) | H |
| DLQI-0/1 | PSO-1 | 239 (153, 325) | 5 (4, 7) | H |
| | PSO-2 | 200 (133, 267) | 6 (4, 8) | H |

**AAE**, Anticipated absolute effect for achieving the outcome; **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)

**Selected secondary efficacy results:**

- At Week 24, deucravacitinib was better than apremilast in achieving the following outcomes:
  - PASI-90 in POETYK PSO-1 (42.2% [140/332] vs 22.0% [37/168], respectively) and POETYK PSO-2 (32.5% [164/504] vs 19.7% [50/254], respectively); and

  - PASI-100 in POETYK PSO-1 (14.2% [47/332] vs 3.0% [5/168], respectively) and POETYK PSO-2 (13.1% [66/504] vs 6.7% [17/254], respectively; difference 6.5%, 95% CI 2.3, 10.7).
- Deucravacitinib was also superior to apremilast in the percentage of patients who achieved the following outcomes at both Weeks 24 and 52 in POETYK PSO-1:
  - sPGA-0/1 (46% vs 22%, respectively; difference 23%; 95% CI 15, 31)[8]
  - PASI-75 (57% vs 30%, respectively; difference 26%; 17, 34)[8]
  - PASI-90 (31% vs 15%, respectively; difference 15%; 8, 23)[8]

**Subgroup Analyses**

- *Scalp PsO*. In POETYK PSO-1, deucravacitinib was significantly better than apremilast and placebo in the subgroup of patients with moderate to severe scalp psoriasis (scalp-specific–Physician's Global Assessment [ss-PGA] of ≥ 3) who achieved ss-PGA of 0/Clear or 1/Almost Clear (ss-PGA-0/1) at Week 16: 70.3% [146/209] vs 39.1% [43/110] and 17.4% [21/121], respectively.[3] In POETYK PSO-2, deucravacitinib was also superior in ss-PGA-0/1 response at Week 16 (59.7% [182/305) vs 36.7% (61/166) and 17.3% 930/173) for deucravacitinib vs apremilast and placebo, respectively, and at Week 24 (59.0% [180/305] vs 41.6% [69/166] for deucravacitinib vs apremilast, respectively).[4]
- *Fingernail PsO.* In POETYK PSO-1, deucravacitinib was numerically better than placebo in patients with moderate to severe fingernail PsO (Physicians Global Assessment of Fingernails [PGA-F] of ≥ 3) in terms of achieving PGA-F of 0/1 at Week 16: 20.9% (9/43) vs 8.8% (3/34).[3] Results were not reported for apremilast. Deucravacitinib was again numerically better than placebo in PGA-F-0/1 response in POETYK PSO-2 at Week 16: 20.3% vs 7.9%, respectively.[4] The small number of patients with fingernail PsO limited comparisons.
- *Stratified Subgroups.* Patients with lower weight (< 90 kg) had larger treatment effects vs those with baseline body weight ≥ 90 kg for both co-primary endpoints in both phase 3 trials except for PASI-75 in POETYK PSO-1.[8] Patients with more severe disease at baseline (sPGA ≥ 4) in POETYK PSO-1 tended to have a larger treatment effect.[8] There were no remarkable treatment differences by sex, race, age, prior use of systemic therapy, and an FDA exploratory analysis by prior failure or intolerance to prior systemic therapy for PsO or psoriatic arthritis.[8]

**Onset of Treatment Benefit and Duration of an Adequate Therapeutic Trial**

- Onset of effects (earliest significant treatment difference) occurred at Week 8 with deucravacitinib based on sPGA-0/1–2 and PASI-75 response rates in POETYK PSO-1. Apremilast had a similar onset of effects.
- The duration of an adequate therapeutic trial of deucravacitinib seemed to be 24 weeks based on sPGA-0/1–2 and PASI-75 responses in POETYK PSO-1 and 20 weeks for the same outcomes in POETYK PSO-2.[8]

**Maintenance and Durability of Response: POETYK PSO-2**

- In POETYK PSO-2, 80.4% of PASI-75 responders at Week 24 who were rerandomized to continue deucravacitinib maintained response to Week 52.
- In the PASI-75 responders rerandomized to switch to placebo at Week 24, durability of PASI-75 response was seen in 31.3% of patients at Week 52.[4]
- The median time to relapse after rerandomization at Week 24 could not be determined in the continued-deucravacitinib group. The median time to loss of PASI-75 in the switch-to-placebo group was 85 days (95% CI 62, 105) or about 12 weeks (from Week 24 to Week 36).[4]

# Safety Considerations

### Safety Profile from US Prescribing Information

- **Boxed Warnings**: None.

  *PBM Note: Unlike JAKIs, deucravacitinib lacks boxed warnings for serious infections, mortality, major adverse cardiovascular events, malignancy excluding nonmelanoma skin cancer, and thrombosis. However, there is insufficient evidence to determine whether TYK2 inhibition will increase the risk of these JAK inhibitor-related adverse reactions.*[8]

- **Contraindications**: Hypersensitivity
- **Other Warnings / Precautions**: Infections, herpes (e.g., zoster, simplex) viral reactivation, tuberculosis (TB), malignancy including lymphomas, rhabdomyolysis and elevated creatine phosphokinase (CPK), triglyceride elevations (with an unknown effect on cardiovascular morbidity and mortality), liver enzyme elevations (with no increased risk of drug-induced liver injury), update immunizations including prophylactic herpes zoster vaccination (avoid live vaccines during deucravacitinib treatment), potential JAK inhibitor-related adverse reactions.
- **Common Adverse Events (≥ 1%)**: Upper respiratory infections, increased CPK, herpes simplex, mouth ulcers, folliculitis, acne. Most cases of folliculitis or acne occurred in the first 8 weeks of therapy and resolved spontaneously or were manageable with topical or oral antimicrobial agents.[8]
- **Decreased Glomerular Filtration Rate (GFR)**: Among patients with moderate renal impairment (eGFR 30–59 mL/min) at baseline, 4 patients (1.6 per 100 patient-years [PY]) vs 1 patient (0.8 per 100 PY) developed decreased GFR in the deucravacitinib vs placebo groups, respectively.

### Safety Results from Clinical Trials

- **Deaths and Serious Adverse Events (SAEs)**
  - No deaths occurred in patients on deucravacitinib or apremilast vs 1 death (exposure-adjusted incidence rate [EAIR] of 2.1 per 100 patient-years [PY]) occurred on placebo in POETYK PSO-1 (Weeks 0–52).[3] Two deaths (EAIR 0.4 per 100 PY) and one death (EAIR 0.9 per 100 PY) occurred in deucravacitinib and apremilast patients, and none in the placebo group, in POETYK PSO-2. [4]
  - SAEs were less common on deucravacitinib and apremilast than placebo in POETYK PSO-1 from Week 0 to 52 (EAIR per 100 PY: 7.5 and 5.2 vs 19.2, respectively).[3] In POETYK PSO-2, SAEs were somewhat more common on deucravacitinib than apremilast and placebo (EAIR per 100 PY: 4.3 vs 2.8 and 2.5, respectively). SAEs that occurred in the deucravacitinib group included pericarditis and cholecystitis in POETYK PSO-1 and heart failure / sepsis and hepatocellular carcinoma in POETYK PSO-2.
  - Serious infections occurred at similar rates in the deucravacitinib, apremilast, and placebo groups from Weeks 0 to 16 and in the deucravacitinib and apremilast groups from Weeks 0 to 24 and Weeks 0 to 52.[8] No serious opportunistic infections or invasive fungal infections were reported. The most common serious infections were COVID-19 / COVID-19 pneumonia, pneumonia, and diverticulitis.[8] Excluding COVID-19 serious infections, the overall EAIR for serious infections with deucravacitinib was 0.9 per 100 PY.[8] According to the FDA, the non-COVID serious infection rate with deucravacitinib does not seem to exceed rates that were reported with other systemic treatments in a prospective database cohort study[9] (EAIR per 100 PY of 1.63 for biologics and 1.79 for conventional immunomodulators).[8] Based on these data, there is no Boxed Warning for serious infections.

- **Discontinuations Due to Adverse Events (DAEs)**
  - In POETYK PSO-1, DAEs were less common on deucravacitinib than apremilast and placebo during Weeks 0 to 16 (1.8% [6/332] vs 6.0% [10/168; difference 4.2%, 95% CI 0.3, 8.0] and 4.2% [7/165; NSD by 95% CI]), respectively, and from Weeks 0 to 52 (EAIR per 100 PY: 3.3 vs 10.3 and 14.7, respectively).[3] Among patients who remained on the same treatment from Week 0 to Week 52, a lower percentage of patients discontinued due to adverse events in the deucravacitinib group than the apremilast group. The most frequent DAEs involved psychiatric events (EAIR per 100 PY, 1.0 vs 2.1 for deucravacitinib and apremilast, respectively) but only single individuals developed each type of psychiatric DAE.
  - In POETYK PSO-2, DAEs were also less common on deucravacitinib. The corresponding EAIRs per 100 PY were 2.7 vs 4.7 and 3.5 for deucravacitinib, apremilast, and placebo, respectively, from Weeks 0 to 16, and 5.2 vs 13.1 and 8.0, respectively, from Weeks 0 to 52.
- **Mouth Ulcerations**
  - Deucravacitinib had a higher incidence of mouth ulceration than apremilast through Week 52 in POETYK PSO-1 (EAIR per 100 PY, 3.4 vs 0.0, respectively).[8] Most cases were aphthous ulcers.
  - There were no cases of GI ulceration / bleeding (unlike with JAKIs) or mucosal ulcerations suggesting severe immunosuppression.[8]
- **Increased Blood Creatine Phosphokinase (CPK)**
  - Increased CPK was the most common laboratory abnormality in all three treatment groups in POETYK PSO-1. The EAIRs per 100 PY for increased CPK were 3.8, 3.4, and 2.1 for deucravacitinib, apremilast, and placebo, respectively.[3]
  - In POETYK PSO-2, increased CPK was seen at EAIRs per 100 PY of 5.3, 3.7, and 5.0 in the deucravacitinib, apremilast, and placebo groups, respectively.[4]
  - Most cases of increased CPK in both trials were mild or mild to moderate and temporally related to physical exertion, and resolved spontaneously.

**Drug Interactions**

- No relevant drug interactions.
- No pharmacokinetic drug interactions with methotrexate and mycophenolate mofetil.

**Network Meta-analyses**

- A network meta-analysis[10] included only the phase 2 trial of deucravacitinib[5] in patients with PsO and indirectly compared deucravacitinib with JAKIs, none of which have been approved for PsO in the US to date.
- A living Cochrane network meta-analysis[11] included only the phase 2 trial of deucravacitinib.[5]
  - In relative effects tables for PASI-90 and SAEs considered jointly by drug class, IL-17 inhibitors, IL -23 inhibitors, and IL -12/23 inhibitors — but not TNFIs — were significantly better than targeted small molecules.
  - In similar tables by individual agents, deucravacitinib was not significantly different in PASI-90 response or SAEs from each of the evaluated antipsoriatic biologics (TNFIs, IL-12/23I / ustekinumab, IL-17AIs, IL-17RI / brodalumab, and IL-23Is), apremilast, and conventional immunomodulators (acitretin, fumaric acid esters, cyclosporine, and methotrexate). All comparisons were based on moderate-quality evidence except the comparisons with cyclosporine, methotrexate (PASI-90 only), and fumaric acid esters were based on low-quality evidence.
  - Deucravacitinib ranked below most biologics and above most TNFIs and other small molecules. Drugs in descending rank order were as follows with anticipated absolute effects in cases per 1000

(vs placebo) for PASI-90 / SAEs shown in parentheses: infliximab (443 / 19), ixekizumab (422 / 16), risankizumab (415 / 10), secukinumab (360 / 19), brodalumab (329 / 18), guselkumab (388 / 17), ustekinumab (258 / 15), tildrakizumab (256 / 14), **deucravacitinib** (210 / 10), adalimumab (267 / 17), certolizumab (182 / 13), etanercept (146 / 15), cyclosporine (148 / 25), methotrexate (147 / 7), and apremilast (110 / 15).

*PBM Note: The anticipated absolute effect for Week-16 PASI-90 response for deucravacitinib vs placebo based on pooled data from POETYK PSO-1 and POETYK PSO-2 is 270 per 1000 (95% CI 235, 306).[3,4] The corresponding value for SAEs was 11 per 1000 (–7, 29).*

- The results were limited by the absence of the apremilast-controlled phase 3 trials of deucravacitinib in the network meta-analyses.

**Other Considerations**

**Notable Contrasts in Indication and Safety with Deucravacitinib vs JAKIs[8]**

- Not restricted to patients with disease not adequately controlled with other systemic drugs including biologics or when those therapies are inadvisable.
- Lack of hematologic adverse events. Monitoring for cytopenias is not required.
- Elevation of triglycerides vs cholesterol.
- No increased risk of serious and opportunistic infections.
- No evidence of increased risk of mortality, MACE, and thrombosis. No Boxed Warning for mortality, malignancy, MACE, and thrombosis.
- No evidence of liver injury.
- No reports of GI perforation.
- No mean change in serum creatinine.
- Similar observations of increased risk of elevated CPK.

**Evidence Gaps**

- Functional ability / Disability
- Patient satisfaction
- Long-term safety beyond 52 weeks, long-latency and rare adverse events including potential major adverse cardiovascular events (MACE), malignancy, and opportunistic infections. A long-term postmarketing RCT will be required.

**Other Therapeutic Options**

- Systemic treatment options for PsO are summarized in Table 5.

**Table 5 Treatment Alternatives for Moderate to Severe Plaque Psoriasis**

| Drug | On VANF | CFU Place in Therapy | FDA Place in Therapy | AAD-NPF Guideline Place in Therapy | Safety Considerations | Other Considerations |
|---|---|---|---|---|---|---|
| TYK2 Inhibitor | | | | | | |
| Deucravacitinib tab | TBD | TBD | Moderate–severe PsO, candidates for systemic therapy or phototherapy. | NA | Hyper-sensitivity, infections, herpes, malignancy, rhabdomyo-lysis.<br>Not recommended in severe hepatic impairment (Child-Pugh C). | Superior to apremilast, especially for scalp PsO.<br>Limited long-term data.<br>No dosage adjustments required in renal impairment including ESRD. |
| PDE4 Inhibitor | | | | | | |
| Apremilast tab | Yes, PA-F / CFU | After UV and the following:<br>*Mild–moderate PsO* – 3 classes of topicals<br>*Moderate–severe PsO*– 1 cIMM and 2 TIMMs are medically inadvisable (prior trials not required) | PsO, candidates for systemic therapy or phototherapy<br>Also approved for psoriatic arthritis | Recommended for moderate–severe PsO (SOR: A; LOE: I)<br>Especially effective for scalp and PP PsO | Diarrhea, nausea, weight loss, depression, suicidality.<br>DDI with strong CYP450 inducers (e.g., rifampin).<br>No dosage adjustment required in severe hepatic impairment (Child-Pugh C). | Favorable safety profile; no lab monitoring.<br>Apparently lower efficacy than most systemic antipsoriatics.<br>Dosage reduction required in severe renal impairment (CrCl < 30 mL/min). |
| Antimetabolite | | | | | | |
| Methotrexate inj, tab | Yes | NA | Severe PsO (oral soln)<br>After other therapies for severe, recalcitrant, disabling PsO (SC inj) | Recommended for moderate to severe PsO (SOR: A; LOE: I–III) | Multiple Boxed Warnings including for serious infections / invasive fungal and other OI and for lung disease even at low doses.<br>CI in chronic liver disease, alcohol use disorder. | Apparently lower efficacy than most systemic antipsoriatics.<br>Less effective than nb-UVB.<br>Dosage adjustment or discontinua-tion in renal or hepatic impairment. |

| Drug | On VANF | CFU Place in Therapy | FDA Place in Therapy | AAD-NPF Guideline Place in Therapy | Safety Considerations | Other Considerations |
|---|---|---|---|---|---|---|
| | | | | | Hepatotoxicity, pneumonitis, myelosuppression, teratogenicity. | |
| Retinoid | | | | | | |
| Acitretin cap | Yes | NA | When other treatments are inadequate or contraindicated, for severe PsO, nonpregnant patients | Can be recommended as monotherapy for PsO (SOR: B; LOE: II) | Teratogenicity, xerosis, cheilitis, itching / burning skin, brittle nails, hair loss, retinoid dermatitis, hyperlipidemia, hepatitis.<br>Not immunosuppressive. | Useful for hyperkeratotic PP PsO.<br>Apparently lower efficacy than most systemic antipsoriatics. |
| T-cell and IL-2 Inhibitor | | | | | | |
| Cyclosporine Modified, cap, oral soln | Yes | NA | After ≥ 1 other systemic therapy, or other systemic therapies are contraindicated or not tolerated; for severe, recalcitrant PsO in non-immunocompromised patients | Recommended for patients with severe, recalcitrant PsO (SOR: A; LOE: I–III)<br>Rapid-acting; useful for severe, recalcitrant disease, acute flares, and erythroderma. | Immunosuppression, nephrotoxicity, HTN, malignancy / lymphoma.<br>CYP3A4 drug interactions<br>Simultaneous use with NB-UVB is contraindicated. | Apparently lower efficacy than most systemic antipsoriatics.<br>Not used long-term because of toxicity. |
| TNF Inhibitors | | | | | | |
| Adalimumab SC inj | Yes, PA-F | NA | When other systemic therapies are medically less appropriate, for moderate to severe chronic PsO, candidates for systemic therapy or phototherapy<br>Also approved for psoriatic arthritis and IBD. | Recommended for PsO including PP, nail, and scalp lesions (LOE: I–II); monotherapy (LOE: I–II) or combination therapy (LOE: I–III) | Boxed Warning for serious infections including invasive fungal and other OIs. | Apparently less effective than infliximab (high QE). |

| Drug | On VANF | CFU Place in Therapy | FDA Place in Therapy | AAD-NPF Guideline Place in Therapy | Safety Considerations | Other Considerations |
|---|---|---|---|---|---|---|
| Certolizumab SC inj<br><br>Etanercept SC inj | Yes, PA-F | NA | Moderate to severe PsO, candidates for systemic therapy or phototherapy<br>Also approved for psoriatic arthritis.<br>Certolizumab lacks indication for inducing remission of Crohn's disease.<br>Etanercept is ineffective for IBD. | No specific recommendation | TB, HBV, HCV, HIV, skin cancer, demyelinating disorders, lupus, CHF, cytopenia.<br>TNFIs used as monotherapy for PsO are not associated with risk of solid tumor or lymphoreticular malignancy. | Certolizumab may be the preferred TNFI in pregnancy.<br>Apparently less effective than infliximab (moderate QE). |
| Infliximab-abda IV inj | Yes, PA-F | NA | When other systemic therapies are medically less appropriate, for chronic severe (i.e., extensive and/or disabling) PsO, candidates for systemic therapy<br>Also effective for psoriatic arthritis and IBD. | No specific recommendation<br>TNFI biosimilars "should be considered similar to the reference … drug and therefore interchangeable…." | | Infliximab is ranked the most effective antipsoriatic biologic in NMA and seems to be more effective than other TNFIs.<br>Requires in-clinic IV infusions. |
| IL-12/23I | | | | | | |
| Ustekinumab SC inj | No, CFU | After MTX, UV, 1 TNFI, and 1 IL-17AI therapy | Moderate to severe PsO, candidates for systemic therapy or phototherapy<br>Also approved for psoriatic arthritis and IBD. | Recommended as monotherapy treatment option for moderate to severe PsO (SOR: A; LOE: I, III), including PP, nail, and scalp (SOR: B–C; LOE: I–III). May be used in combination therapy (SOR: B–C; LOE: I–III) | Might be considered for patients with history of or currently active HBV or HCV.<br>No definitive evidence of increased risk of solid tumor or lympho-reticular malignancy. | Weight-based dosing and costs; 90-mg dosage may be the highest in cost among antipsoriatic treatments. |
| IL-17AIs | | | | | | |
| Ixekizumab SC inj<br><br>Secukinumab SC inj | No, CFU | After MTX, UV, and TNFI | Moderate to severe PsO, candidates for systemic therapy or phototherapy | Recommended as monotherapy for moderate to severe PsO (SOR: A; LOE: I–II), including scalp (SOR: B; LOE: II); nails (SOR: B), PP (secukinumab only, SOR: A; LOE: I) | Candida infections.<br>May cause or worsen IBD.<br>No definitive evidence of increased risk of solid tumor or lymphoreticular malignancy. | Ixekizumab is the preferred IL-17AI in VHA.<br>Both IL-17AIs are better in efficacy than either etanercept or ustekinumab. |

| Drug | On VANF | CFU Place in Therapy | FDA Place in Therapy | AAD-NPF Guideline Place in Therapy | Safety Considerations | Other Considerations |
|---|---|---|---|---|---|---|
| | | | | | May be used in patients with history of or currently active HCV or HBV (consult expert). | |
| IL-17RI | | | | | | |
| Brodalumab SC inj | No, CFU | After MTX, UV, TNFI, IL-17AI, IL-23I, and ustekinumab | After failing other systemic therapies, moderate to severe PsO, candidates for systemic therapy or phototherapy | Recommended as monotherapy for moderate to severe PsO (SOR: A; LOE: I–II). | As for IL-17AIs.<br>Associated with depression and suicidality (REMS program). | Considered comparable in efficacy to IL-17AIs.<br>Better in efficacy than ustekinumab. |
| IL-23Is | | | | | | |
| Guselkumab SC inj<br><br>Risankizumab-rzaa SC inj<br><br>Tildrakizumab-asmn SC inj | No, CFU | After MTX, UV, TNFI, and one of either IL-17AI or ustekinumab | Moderate to severe PsO, candidates for systemic therapy or phototherapy<br>Guselkumab and risankizumab are also approved for psoriatic arthritis.<br>Risankizumab is also approved for Crohn's disease. | No specific recommendations. | Well tolerated and no reports of systemic fungal infections in studies up to 3–5 years. | Guselkumab is more effective than adalimumab and secukinumab, and somewhat less effective than ixekizumab.<br>Risankizumab is more effective than adalimumab, ustekinumab, and secukinumab.<br>Tildrakizumab is somewhat more effective than etanercept. |

Sources: 8,11– 24

**CFU**, Criteria for Use; **cIMM**, Conventional immunomodulators; **MMMT**, Mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis; **MTX**, Methotrexate; **NMA**, Network meta-analysis; **OI**, Opportunistic infection; **TIMM**, Targeted immunomodulator; **UV**, Ultraviolet therapy

## Projected Place in Therapy

- **Epidemiology and Prevalence of Plaque Psoriasis**. Plaque psoriasis is a common, immune-mediated, chronic inflammatory disease of the skin. Its prevalence varies from 0.5 to 11.4 percent across the world, being higher in locations farther from the equator than those closer.[25]
- **Potential Place in Therapy Based on the Evidence**. High-quality evidence from two apremilast- and placebo-controlled trials supports the use of deucravacitinib in adults with moderate to severe chronic plaque psoriasis who are candidates for phototherapy or systemic therapy. Compared with apremilast, lesion clearance benefits are small to moderate and clinically meaningful. Deucravacitinib was significantly superior to apremilast for scalp psoriasis, numerically better for fingernail psoriasis, and

better tolerated. Deucravacitinib may require monitoring of triglyceride levels, liver enzymes, and CPK, whereas apremilast requires no laboratory monitoring except checking for potential age-related reduction in renal function, which may necessitate dosage reduction. A network meta-analysis of biologic and small molecule antipsoriatic agents including only phase 2 data for deucravacitinib showed that, in general, tumor necrosis factor (TNF) inhibitors, interleukin-17 inhibitors, interleukin-23 inhibitors, and interleukin-12/23 inhibitors probably have better ranking joint PASI-90 / serious adverse event profiles than targeted small molecules (deucravacitinib and apremilast). Relative to JAKIs, deucravacitinib may have potential safety advantages; however, JAKIs have not been approved for psoriasis in the US, and no head-to-head trials have been performed.

- **Potential Place in Therapy in VHA**. Deucravacitinib may be used as an alternative to apremilast for moderate to severe plaque psoriasis based on better efficacy and tolerability, although issues to consider are an uncertain comparative risk of serious adverse events and its lack of long-term safety experience relative to the better characterized, favorable safety profile of apremilast. The efficacy of deucravacitinib relative to biologics and other small-molecule immunomodulators is uncertain; however, it seems likely that interleukin-17 inhibitors and interleukin-23 inhibitors priced lower than deucravacitinib can provide a more favorable efficacy–cost profile. In the shorter-term trials, deucravacitinib seemed to lack an increased risk of invasive fungal and other opportunistic infections, which may be a potential advantage over TNFIs. Longer term comparative studies are needed to further evaluate the risks of serious or invasive infection, malignancy, and other long-latency or rare adverse effects with deucravacitinib. Deucravacitinib lacks the issues of weight-based costs seen with ustekinumab. Similar to other small molecules, deucravacitinib offers the potential convenience of oral administration.

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