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TIMs for Ulcerative Colitis and Crohn's Disease (April 2023)
TIMs for Plaque Psoriasis, Psoriatic Arthritis, and Generalized Pustular Psoriasis (February 2024)
OHSU Drug Effectiveness Review Project Summary Reports

Date of Review: August 2024

Dates of Last Reviews: October 2021 – UC and CD
October 2022 – PsO and PsA
Literature Search: DERP: 01/01/2019-07/14/2022
DURM: 01/01/2022-01/09/2024

Current Status of PDL Class:
See **Appendix 1**.

Purpose: Summarize new comparative evidence for targeted immune modulators (TIMS) used to treat specific autoimmune conditions as presented in two separate Drug Effectiveness Review Project (DERP) systematic reviews for 1) Crohn's disease (CD) and ulcerative colitis (UC) and 2) plaque psoriasis (PsO), psoriatic arthritis (PsA), and generalized pustular psoriasis (GPP). Evaluate new guidelines and expanded indications for TIMs in CD, UC, PsO, PsA, and GPP.

Plain Language Summary:
Crohn's Disease and Ulcerative Colitis

- Crohn's disease and ulcerative colitis are conditions that cause diarrhea, abdominal discomfort, and bloody bowel movements.
- Targeted immune modulators are medicines that treat these conditions. The Food and Drug Administration (FDA) has approved 13 targeted immune modulators to manage symptoms of ulcerative colitis or Crohn's disease.
- This review identified new evidence for the following targeted immune modulators which shows that:
    - Adalimumab and ustekinumab are equally effective symptoms of Crohn's disease. Both medicines had similar side effects.
    - Vedolizumab and a type of targeted immune modulator called tumor necrosis factor inhibitors (e.g., adalimumab, certolizumab, infliximab, or golimumab) have similar side effects in people with Crohn's Disease.
    - Tofacitinib or vedolizumab may have fewer side effects in people with ulcerative colitis compared to tumor necrosis factor inhibitors.
    - Etrasimod and mirikizumab are effective for moderate to severe symptoms of ulcerative colitis in adults compared to placebo. Studies have not compared these medicines to other targeted immune modulators. People who take etrasimod may be at increased risk for infections, liver problems, and high blood pressure. People who take mirikizumab may have itching, swelling, or trouble breathing, burning and stinging where the medicine was injected, and have increased risk for infections or liver problems.

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Plaque Psoriasis, Psoriatic Arthritis and Generalized Pustular Psoriasis

- Plaque psoriasis is a skin condition with raised, irritated, and scaly patches of skin that may be itchy and painful. The most common type of psoriasis is plaque psoriasis. Generalized pustular psoriasis is a type of psoriasis that occurs less often. People with generalized pustular psoriasis can have pus-filled blisters on the skin. The blisters can crack, which causes painful breaks in the skin and makes it difficult to walk or complete daily activities using the hands.
- Psoriatic arthritis is a condition that affects some people with psoriasis. In addition to skin symptoms, psoriatic arthritis causes pain and swelling in the joints.
- Targeted immune modulators can treat these conditions for people who have moderate to severe symptoms. In total, the FDA has approved 20 different targeted immune modulators for plaque psoriasis, psoriatic arthritis, and generalized pustular psoriasis.
- One new study compared risankizumab with apremilast in people with plaque psoriasis. More people who received risankizumab had better symptom improvement than those who received apremilast. No new studies were published that compared treatments for psoriatic arthritis.
- Since this class was last reviewed, the FDA has approved 3 new targeted immune modulators for these conditions. New evidence shows that:
    - Deucravacitinib improves skin symptoms in people with plaque psoriasis compared to a tablet that did not contain any medicine (placebo). Side effects that can happen with deucravacitinib include an increased risk of infections and blood clots.
    - Spesolimab improves blisters and skin irritation in people with generalized pustular psoriasis compared to an injection that did not contain medicine. Side effects with spesolimab include increased risk for infections and serious allergic reactions.
    - Bimekizumab improves skin symptoms in people with plaque psoriasis compared to an injection that did not contain medicine. Side effects with bimekizumab include increased risk for infections and headache.
- For all targeted immune modulators, the provider must explain to the Oregon Health Authority why their patient needs the medicine. This is process is called prior authorization. We recommend new targeted immune modulators (e.g., etrasimod, mirikizumab, deucravacitinib and spesolimab) be included in the prior authorization criteria.

Research Questions:

April 2023 DERP Report – Crohn's Disease and Ulcerative Colitis

1. What is the comparative efficacy of TIMs to treat CD or UC?
2. What are the comparative harms of TIMs to treat CD or UC?
3. Do the included drugs differ in their effectiveness or harms for managing CD or UC based on age, race, ethnicity, gender, patients with comorbidities, patients taking other commonly prescribed drugs, or in patients with early versus established disease?

February 2024 DERP Report – Psoriasis, Psoriatic Arthritis, and Generalized Pustular Psoriasis

1. What is the comparative efficacy of TIMs to treat PsO, PsA, or GPP?
2. What are the comparative harms of TIMs to treat PsO, PsA, or GPP?
3. Do the included drugs differ in their effectiveness or harms for managing PsO, PsA, or GPP based on age, race, ethnicity, gender, patients with comorbidities, patients taking other commonly prescribed drugs, or in patients with early versus established disease?

Conclusions:

DERP Report for TIMs in Crohn's Disease and Ulcerative Colitis

- Nineteen new studies met inclusion criteria for the 2023 DERP report focused on TIMs for treatment of adults with CD or UC.[1] Seven studies were conducted in people with CD, 9 studies were in people with UC and 3 cohort studies were conducted in mixed populations of people with CD and UC.

Crohn's Disease

- One randomized controlled trial (RCT) provided an efficacy and safety comparison of adalimumab and ustekinumab in people with CD.[1] In this double-blind RCT, a similar percentage of patients achieved clinical remission at 52 weeks with adalimumab and ustekinumab (65% vs. 61%; p=0.42; 95% confidence interval [CI] not reported [NR]); moderate certainty of evidence [CoE]).[1] At 52 weeks, a lower incidence of injection-site reactions was reported with ustekinumab versus adalimumab (1% vs. 10%; low CoE) at 52 weeks.[1] No statistically significant differences were observed between these 2 medications in overall adverse effects [AEs] (high CoE), serious adverse effects [SAEs] (moderate CoE), withdrawal due to AEs (low CoE), or serious infections (very low CoE).[1]
- Vedolizumab was compared to tumor necrosis factor (TNF)-inhibitors in 5 cohort studies to assess the rate of serious infections. No statistically significant difference in incidence of serious and opportunistic infections was observed in any of these reports (moderate CoE).[1] Another cohort study assessed the risk of malignancies with vedolizumab compared with TNF-inhibitors and found no differences between vedolizumab and TNF-inhibitors (moderate CoE).[1]

Ulcerative Colitis

- No new RCTs were identified to evaluate comparative effectiveness of TIMs in UC.[1] Six new cohort studies met inclusion criteria to provide head-to-head safety comparisons of TIMs in UC.[1] Harms associated with TNF-inhibitors were compared to tofacitinib or vedolizumab.[1]
    - In one cohort study with high risk of bias, a statistically significant lower incidence of serious (incidence rate [IR] 1.75 vs. 3.33) and opportunistic (IR 0.16 vs. 1.45) infections and non-melanoma skin cancer (IR 0.78 vs. 1.69) was observed with tofacitinib compared with TNF-inhibitors (very low CoE).[1] Tofacitinib-treated patients had a statistically significant higher rate of herpes zoster infections compared with the TNF-inhibitor-treated group (IR 3.57 vs. 1.77; very low CoE).[1] There was no statistically significant difference between groups for major adverse cardiovascular events (myocardial infarction, stroke, or heart failure death in hospital; very low CoE).[1]
    - Four cohort studies compared the risk of serious infections for vedolizumab with TNF-inhibitors.[1] A statistically significant lower incidence of SAEs (hazard ratio [HR] 0.37; 95% CI, 0.21 to 0.63 and serious infections (HR 0.68; 95% CI, 0.50 to 0.93) were observed with vedolizumab compared to TNF-inhibitors (very low CoE for both outcomes).[1] Another cohort study reported no statistically significant differences in the risk of incident malignancy when vedolizumab was compared to TNF-inhibitors (incidence rate ratio [IRR] 1.26; 95% CI 0.50 to 2.81; moderate CoE).[1]
- Two new placebo controlled RCTs were identified that assessed the safety and efficacy of 2 TIMS, etrasimod and mirikizumab, which were recently approved by the FDA to treat UC.
    - Oral etrasimod 1 mg and 2 mg once daily were compared to placebo in a moderate risk of bias RCT that enrolled 156 adults with moderately to severely active UC.[1] A statistically significant improvement in the modified Mayo Clinic Score was reported with etrasimod 2 mg versus placebo at 12 weeks (least square mean [LSM] 2.49 vs. 1.50; p<0.05; 95% CI NR; low CoE).[1] Refer to **Appendix 2** for a description of outcomes used in UC trials. No statistically significant differences were observed between treatment groups in incidence of overall AEs (low CoE), SAEs, withdrawals due to AEs (very low CoE), or serious infections (very low CoE).[1]
    - Intravenous (IV) mirikizumab 50 mg, 200 mg, and 600 mg administered every 4 weeks was compared to placebo in one moderate risk of bias RCT which randomized 249 adults with moderately to severely active UC to placebo or mirikiziumab.[1] A statistically significant higher incidence of clinical remission as assessed by the Mayo Clinic Score was reported with IV mirikizumab versus placebo for the 50 mg (41% vs. 21%; p=0.01), 200 mg (60% vs. 21%; p<0.001), and 600 mg (49% vs. 21%; p=0.001) doses at 12 weeks (low CoE).[1] No statistically significant differences in overall AEs (low CoE), SAEs (very low CoE), or withdrawal due to AEs (very low CoE) were reported between placebo and mirilkizuamb.[1]

Mixed Populations (Crohn's Disease and Ulcerative Colitis)

- No new RCTs were identified that focused on comparative efficacy of TIMs in mixed populations of patients with CD or UC.[1]
- Three new cohort studies met inclusion criteria to evaluate the comparative harms of TIMs in mixed populations of CD and UC.[1] Two cohort studies that compared ustekinumab with TNF-inhibitors had conflicting results regarding the risk of serious infections.[1] The larger cohort study (n=21,821) reported no statistically significant difference between the 2 groups (HR 0.84; 95% CI 0.66 to 1.03; moderate CoE).[1] While the smaller study (n=1,575) reported a lower

risk of serious infections with ustekinumab versus TNF-inhibitors (HR 1.58; 95% CI 1.07 to 2.34; moderate CoE).[1] A third cohort study compared adalimumab, infliximab, and vedolizumab with each other and ustekinumab.[1] Patients treated with vedolizumab had a lower risk of serious infection compared with infliximab (HR 1.61; 95% CI 1.06 to 2.45; very low CoE).[1] No other significant differences were identified between treatments (very low CoE).[1]

- The DERP report did not evaluate differences amongst TIMs for their effectiveness or harms in managing CD or UC based on age, race, ethnicity, or gender.[1]

DERP Report for TIMs in Plaque Psoriasis, Psoriatic Arthritis, and Generalized Pustular Psoriasis

- The February 2024 DERP report focused on evidence for TIMs to manage PsO, PsA, and GPP to update a previous 2022 DERP report on TIMs for PsO and PsA.[2] Four new RCTs were included.[2]

Plaque Psoriasis

- Two new RCTs with moderate risk of bias compared deucravacitinib 6 mg orally once a day with apremilast 30 mg orally twice a day in adults with moderate-to-severe PsO.[2] All primary endpoints compared deucravacitinib with placebo (see **Appendix 2** for a description of outcomes used in psoriasis trials). For secondary endpoints, response rates were higher with deucravacitinib versus apremilast for Psoriasis Area and Symptom Score (PASI) 75 at week 24 (58.4% vs. 35.1%; RR, 1.2; 95% CI 1.3 to 2.1; high CoE) in the first RCT (n=500).[2] In the second RCT (n=765), more patients in the deucravacitinib group achieved PASI 75 than patients in the apremilast group at week 24 (53.0% vs. 39.8%; RR 1.3; 95% CI 1.1 to 1.6; high CoE).[2]
- One small, open-label, RCT with high risk of bias enrolled 40 patients with a PASI score less than 10 who had at least 1 plaque refractory to ustekinumab.[2] Patients were assigned to either guselkumab or secukinumab. The primary endpoint was improvement in the treatment-refractory plaque as measured by an endpoint called total clinical score, which is not an endpoint typically used in clinical trials.[2] No difference in clinical improvement was observed between guselkumab and secukinumab at 16 weeks (60% vs. 40%; p=0.17; very low CoE).[2]
- One RCT with moderate risk of bias compared risankizumab to apremilast.[2] In this trial, 352 patients with moderate chronic PsO with or without PsA were randomized to subcutaneous (SC) risankizumab 150 mg at weeks 0 and 4 or oral apremilast 30 mg twice daily for 16 weeks.[2] At 16 weeks, more participants in the risankizumab arm experienced PASI 90 compared with the apremilast arm (55.9% vs. 5.1%; RR 10.9; 95% CI 6.1 to 19.4; moderate CoE).[2] More patients also experienced PASI 75 on risankizumab at 16 weeks (66% vs. 49%; RR 4.5; 95% CI 3.4 to 5.9; moderate CoE).[2]
- All the new RCTs that evaluated efficacy also reported on harms of TIM agents.[2] Few differences in harms for TIMs were reported in head-to-head comparisons.[2] Of note, fewer AEs were reported with risankizumab compared with apremilast at 16 weeks (RR 0.68; 95% CI 0.54 to 0.86; moderate CoE).[2]

Psoriatic Arthritis

- No new evidence was identified for comparative efficacy or harms of TIMs in PsA for the 2024 DERP update.[2]

Generalized Pustular Psoriasis

- No comparative RCTs evaluated TIMs for GPP, although a new interleukin (IL)-36 antagonist, spesolimab, received approval for treatment of GPP in September 2022.[3] The evidence supporting approval of spesolimab was provided in a placebo-controlled trial.[4]
- No new evidence was identified for the 2024 DERP report to evaluate differences amongst TIMs for their effectiveness or harms in managing PsO or PsA based on age, race, ethnicity, or gender.[2]

High-Quality Guidelines

- In 2021 the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) updated 2015 guidance for management of PsA as follows:
    - For patients with peripheral arthritis related to PsA and an inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), high-quality evidence supports the use of TNF inhibitors, interleukin (IL)-17 inhibitors, IL-23 inhibitors, and janus kinase (JAK) inhibitors;

and moderate-quality evidence supports IL-12/23 inhibitors or phosphodiesterase 4 (PDE4) inhibitors being superior to placebo.[5] Based on the evidence, including head-to-head studies, TNF inhibitors, IL-17 inhibitors and JAK inhibitors are equally recommended in this population.[5]
    - For patients with peripheral arthritis and previous experience with biologic DMARDs (bDMARDs), TNF inhibitors, IL-17 inhibitors, IL-23 inhibitors, and JAK inhibitors are strongly recommended based on moderate-to high-quality evidence. PDE4 inhibition is conditionally recommended.[5]
    - TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors, IL-23 inhibitors, JAK inhibitors and PDE4 inhibitors are effective and strongly recommended as treatment options for active enthesitis in patients with PsA.[5] None of the drug classes have shown consistent superiority over the other classes.[5]
    - For patients with more widespread psoriasis or psoriasis unresponsive to alternative treatments (e.g., topicals, phototherapy, and oral therapies like methotrexate, cyclosporine, PDE4 inhibitors and JAK inhibitors), bDMARDs are strongly recommended (e.g., TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors, and IL-23 inhibitors).[5]
- National Institute for Health and Care Excellence (NICE) recommendations of TIMs for CD or UC were updated in 2022 and 2023:
    - May 2023: Risankizumab is recommended for moderate or severe active CD in people 16 years of age or older if CD has not responded to a previous biological treatment, or if previous biological treatment was not tolerated, or if TNF-inhibitors are not suitable.[6]
    - June 2023: Upadacitinib is recommended for moderate or severe active CD in adults if the disease has not responded to a previous biological treatment, or if previous biological treatment was not tolerated, or if TNF-inhibitors are contraindicated.[7]
    - October 2023: Mirikizumab is recommended for moderate or severe active UC in adults if conventional treatment and TNF-inhibitor treatment are not tolerated, or the condition has not responded to previous conventional treatment and TNF-inhibitor treatment.[8]
    - October 2022: Ozanimod is recommended for moderate or severe active UC in adults if conventional treatment is not tolerated or does not sufficiently treat the condition, and if infliximab was not tolerable or did not sufficiently treat the condition.[9]
    - January 2023: Upadacitinib is recommended for moderate or severe active UC in adults when conventional or other biological treatment are not tolerated, or if the condition has not responded to these treatments.[10]
- NICE recommendations for bimekizumab and deucravacitinib as second-line treatment options for PsO were updated in 2021 and 2023:
    - Bimekizumab is an alternative to other biological treatments already recommended by NICE for treating severe plaque PsO in adults.[11] Bimekizumab (September 2021) is recommended for severe plaque psoriasis in adults if the PASI score is 10 or higher and the Dermatology Quality of Life (DLQI) score is greater than 10, and the condition has not responded to other systemic treatments, including cyclosporine, methotrexate and phototherapy, or these treatments are contraindicated or not tolerated.[11] Deucravacitinib (June 2023) is recommended as an option for treating moderate-to-severe PsO n adults only if the PASI score is 10 or more and the DLQI score is more than 10, and the condition has not responded to other systemic treatments, including cyclosporine, methotrexate and phototherapy, or these options are contraindicated or not tolerated.[12]
- NICE recommendations for guselkumab, risankizumab and upadacitinib in adults with PsA who have not responded to DMARD treatment were updated in 2022:
    - Guselkumab,[13] risankizumab[14] or upadacitinib[15] are recommended as monotherapy or with methotrexate for active PsA in adults whose disease has not responded to DMARDs or who cannot tolerate DMARDs. They are recommended only if adults have tried 2 conventional DMARDs and have had at least one TNF-inhibitor, or TNF-inhibitors are contraindicated.

New Formulations and Expanded Indications

- Since the last time this class was reviewed by the Pharmacy and Therapeutics committee, the Food and Drug Administration (FDA) has approved the following treatments:
    - Upadacitinib for adults with moderate or severe active UC who have had an inadequate response to one or more TNF-inhibitors (October 2022). [16]
    - Upadacitinib for adults with moderate or severe active CD who have had an inadequate response to one or more TNF-inhibitors (May 2023).[16]

- Etrasimod for moderate or severe UC in adults (October 2023).[17]
- Mirikizumab-mrkz for moderate or severe UC in adults (October 2023).[18]
- Bimekizumab-bkzx for adults with moderate or severe PsO who are candidates for systemic therapy or phototherapy (October 2023).[19]
- Deucravacitinib for moderate or severe PsO in adults who are candidates for systemic therapy or phototherapy (September 2022).[20]
- Spesolimab-sbzo for GPP flares in adults (September 2022) via intravenous infusion.[3] The indication was expanded to include adults and pediatric patients aged 12 years and older in March 2024.[3] A new SC formulation was also approved in March 2024 for use in patients with GPP after the flare was resolved.[3]
- Apremilast for treatment of moderate-to-severe PsO in pediatric patients 6 to 17 years of age weighing ≥ 20 kg who are candidates for phototherapy or systemic therapy. (April 2024).[21]
- A new SC formulation of vedolizumab for treatment of adults with moderately to severely active CD and UC. (April 2024).[22]
- Sarilumab for patients who weigh 63 kg or greater with active polyarticular juvenile idiopathic arthritis (pJIA) (June 2024).[23]
- Risankizumab for adults with moderately to severely active UC (June 2024).[24]

Recommendations:

- Update TIMs prior authorization (PA) criteria as outlined in **Appendix 4** including implementation of tiered step therapy for common diagnoses.
- Update clinical PA criteria for TIMs to include coverage for new drugs and indications.
- Maintain etrasimod, mirikizumab, bimekizumab, deucravacitinib, and spesolimab as non-preferred products on the Preferred Drug List (PDL).
- Review costs in the executive session.

Summary of Prior Reviews and Current Policy

- Targeted immune modulators for CD and UC were last reviewed by the Pharmacy and Therapeutics (P&T) Committee in October 2021. A DERP report provided the basis for the review.[25] At that time, PA criteria were revised to include a pathway to treat for adalimumab in children 5 years and older with moderate or severe UC and ozanimod for the treatment of adults with moderate or severe UC.
- Guidance from the American Gastroenterological Association (2020) recommended the use of adalimumab, golimumab, infliximab, tofacitinib, ustekinumab, or vedolizumab in adult outpatients with moderate-to-severe UC, over no treatment (strong recommendation; moderate quality of evidence).[26]
- Janus kinase inhibitor therapies (tofacitinib, upadacitinib, and baricitinib) are effective treatment options for immune-mediated inflammatory diseases, but their use has been limited by adverse event warnings from licensing authorities.[27] In September 2021, the FDA issued a drug safety communication warning providers and patients about the increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors used to treat rheumatoid arthritis, PsA, and UC.[28] Interim analysis of the data results from long term extension trials resulted in an FDA advisory warning regarding the use of tofacitinib at a higher dose (10 mg twice daily) due to an increased risk of venous thromboembolism events.[29]
- Targeted immune modulators for PsO and PsA were last reviewed by the P&T Committee in October 2022. A DERP report provided the basis for the review.[30] At that time, PA criteria were revised to include ustekinumab in children aged 6 years and older with active PsA. In addition, risankizumab was added to the PA criteria to provide a pathway for treatment in adults with CD.
- The 2022 DERP report reviewed head-to-head RCTs for certolizumab pegol, etanercept, ixekizumab, guselkumab, secukinumab and risankizumab in the treatment of moderate-to-severe PsO.[30] No differences were found between ixekizumab and secukinumab for disease remission of PsO at 24 weeks (moderate CoE).[30] The following head-to-head comparisons found statistically significant results:

- The PASI 75 response rate was higher for certolizumab pegol 400 mg versus etanercept at 12 weeks (calculated RR 1.2; 95% CI, 0.04 to 1.5; moderate certainty of evidence [CoE]).[30]
- At 12 weeks, ixekizumab achieved higher PASI 100 remission versus guselkumab (41% vs. 25%, respectively; calculated RR 1.7; 95% CI 1.4 to 2.0; high CoE).[30] However, no differences were noted between ixekizumab and guselkumab for disease remission at 24 weeks (PASI 100: 50% vs. 52%, respectively; calculated RR 0.96; 95% CI, 0.85 to 1.1; high CoE).[30]
- No difference in disease remission was observed between risankizumab and secukinumab at 16 weeks (PASI 90: 73.8% vs. 65.6%, respectively; absolute risk difference [ARD] 8.2%; 95% CI, -2.2 to 18.6). However at 52 weeks, risankizumab achieved higher PASI 90 remission than secukinumab (PASI 90: 86.6% vs. 57.1%, respectively; ARD 29.8; 95% CI, 20.8 to 38.8; moderate CoE).[30]
- Few differences in harms were found between certolizumab pegol, etanercept, ixekizumab, guselkumab, secukinumab, and risankizumab when used to treat PsO based on low and moderate certainty of evidence.[30]

- The 2022 DERP report concluded that in patients with PsA, the efficacy of ixekizumab, secukinumab, and upadacitinib were all superior to adalimumab for improving skin disease based on moderate certainty of evidence, but only higher doses of upadacitinib (30 mg) were superior for improving arthritis symptoms.[30]
- The European League against Rheumatism (EULAR) guidance for the management of PsA with TIMs was updated in 2019.[31] In patients with polyarthritis, a conventional synthetic DMARD (i.e., MTX, sulfasalazine, leflunomide) should be initiated rapidly, with MTX preferred in those with relevant skin involvement.[31] In patients with peripheral arthritis and an inadequate response to at least one conventional synthetic DMARD, therapy with a biologic DMARD should be commenced.[10] When there is relevant skin involvement, an IL-17 inhibitor or IL-12/23 inhibitor may be preferred.[31] In patients with peripheral arthritis and an inadequate response to at least one conventional synthetic DMARD and at least one biologic DMARD, or when a biologic DMARD is not appropriate, a JAK inhibitor may be considered.[31] In patients with mild disease and an inadequate response to at least one conventional synthetic DMARD, in whom neither a biologic DMARD nor a JAK inhibitor is appropriate, a phosphodiesterase (PDE) 4 inhibitor may be considered.[31]
- Adalimumab, etanercept, and secukinumab are preferred medications on the PDL. **Appendix 1** provides a summary of PDL status for all TIMs. All preferred and nonpreferred TIMs require PA to ensure appropriate utilization. A 3-month trial and failure of adalimumab, secukinumab or etanercept is required for management of PsO or PsA before advancing to another TIM. A 3-month trial of adalimumab is required for management of CD or UC before advancing to another TIM. Current clinical PA criteria are outlined in **Appendix 4.**
- In the first quarter of 2024, there were 96 pharmacy claims for biologic agents in the fee-for-service (FFS) population. Seventy-two percent of claims were for the preferred TIMs adalimumab, etanercept, and secukinumab. For the non-preferred TIMs, 10% of claims were for upadacitinib, 5% of claims were for risankizumab, and 3% of claims were for tofacitinib. In the fourth quarter of 2023, the most common claims for physician administered TIMs were infliximab, canakinumab, abatacept, tocilizumab, golimumab, and ustekinumab.

Methods:

The April 2023 drug class report on TIMS for CD and UC[32] and the February 2024 report on TIMs for PsO, PsA, and GPP[2] by the DERP at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) were used to inform recommendations for this drug class. The original reports are available to P&T Committee members upon request.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

Background:

Targeted Immune Modulators

Targeted immune modulators include bDMARDs and targeted synthetic DMARDs. Biologic DMARDs are large, complex, proteins that must be administered parentally. The biologic DMARDs include TNF-inhibitors (e.g., adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab), integrin inhibitors (e.g., natalizumab, vedolizumab), IL-antagonists (e.g., bimekizumab, brodalumab, ixekizumab, guselkumab, mirikizumab, risankizumab, secukinumab, tildrakizumab, and ustekinumab), and lymphocyte antagonists (e.g., rituximab and abatacept). The FDA has approved biosimilars for adalimumab, etanercept, infliximab, natalizumab, rituximab, and ustekinumab.[32] Targeted synthetic DMARDs are small chemical molecules that can be taken orally. The JAK inhibitors (e.g., tofacitinib, upadacitinib), sphingosine 1-phosphate (S1P) receptor modulators (e.g., ozanimod, etrasimod), tyrosine kinase inhibitor (deucravacitinib) and PDE-4 inhibitor (apremilast) are classified as targeted synthetic DMARDs.

Crohn's Disease and Ulcerative Colitis

Crohn's disease and UC are classified as inflammatory bowel diseases. Crohn's disease is characterized by chronic, relapsing inflammation involving the full thickness of the gastrointestinal wall at any point from mouth to rectum, whereas UC is characterized by mucosal ulceration limited to the colon and rectum. Persistent inflammation can lead to bowel scarring and further complications requiring surgery.[1] Clinical diagnosis of both conditions is most accurately made with colonoscopy or sigmoidscopy.[1] Symptoms of both conditions include blood and/or mucus in the stool, urgency, tenesmus, incontinence, increased frequency of bowel movements, and abdominal discomfort. Systemic symptoms include fatigue, weight loss, loss of appetite, anemia, inflammatory eye disease, sclerosing cholangitis, and arthritis.

Two scoring tools are used to assess disease activity in CD and UC. The Crohn's Disease Activity Score (CDAI) is an evaluation of 8 clinical factors involved in CD assessment, including number of soft stools per day, abdominal pain, general well-being, use of medications for diarrhea, presence of abdominal mass, hematocrit, and percentage deviation from standard weight. A total score of 450 or greater indicates extremely severe disease, a score of 150 or greater indicates active disease, and a score less than 150 indicates minimal disease.[33] The Mayo Clinic Score is used to evaluate UC symptoms.[1] Four subscores evaluate rectal bleeding, stool frequency, patient-reported outcomes, and endoscopy results. Each domain is scored from 0 to 3 points, with a higher score indicating more severe disease.[1] The total score can range from 0-12 with higher scores indicating worse severity. A critical component of this score are the endoscopic findings. Patients with lower scores but with an endoscopic score of 2 or greater are considered more severe regardless of the final score.[1] The domains for the CDAI and Mayo Clinic Score are presented in more depth in **Appendix 2**.

Clinical practice guidelines for CD recommend taking into account the disease location, severity, complications, and extra intestinal manifestations when choosing a treatment strategy.[33,34] Treatment is largely directed at symptom relief rather than cure, and active treatment of acute disease (inducing remission) should be distinguished from preventing relapse (maintaining remission).[33] The 2019 NICE guidance recommends TNF-inhibitors (adalimumab, infliximab), ustekinumab, or vedolizumab for management of severe CD, but only after failure of conventional therapy with corticosteroids, aminosalicylates (i.e., sulfasalazine, mesalamine), or thiopurines (i.e., azathioprine, mercaptopurine).[34] The 2018 American College of Gastroenterology (ACG) guidance strongly recommends induction with a TNF-inhibitor to maintain remission in patients who have moderate-to-severe CD despite standard therapies.[33] Cyclosporine, mycophenolate mofetil, and tacrolimus should not be used to treat CD due to insufficient evidence demonstrating efficacy.[33]

The choice of therapy for UC considers the level of disease activity (mild, moderate, or severe), the extent of the disease (proctitis, left-sided disease, extensive disease, or pancolitis), and patient preferences.[35] The 2019 ACG[36] and the NICE[37] guidelines recommend the use of TIMs for treating moderately to severely active UC in adults whose disease has responded inadequately to conventional therapy including aminosalicylates, corticosteroids, azathioprine or

mercaptopurine. Continuation of these agents is only recommended if there is clear evidence of response.[36,37] The TIMs that are FDA-approved to treat CD and UC are presented in **Table 1.**

Table 1. FDA-Approved Targeted Immune Modulators for Crohn's Disease and Ulcerative Colitis[38,39]

Drug – Route of Administration	Molecular Target	Approved Indication(s)
Adalimumab (HUMIRA) - SC	TNF	CD and UC
Infliximab (REMICADE) - IV		CD and UC
Certolizumab Pegol (CIMZIA) - SC		CD
Golimumab (SIMPONI) - SC		UC
Ustekinumab (STELARA) - IV (initial dose) followed by SC	IL-12 and IL-23	CD and UC
Risankizumab (SKYRIZI) - SC	IL-23	CD
Mirikizumab (OMVOH) – IV (initial dose) followed by SC		UC
Vedolizumab (ENTYVIO) – IV, SC	Integrin receptor	CD and UC
Natalizumab (TYSABRI) – IV		CD
Tofacitinib (XELJANZ) - PO	JAK	UC
Upadacitinib (RINVOQ)- PO		CD and UC
Ozanimod (ZEPOSIA)- PO	S1P Receptor	UC
Etrasimod (VELSIPITY)– PO		UC
Abbreviations: CD=Crohn's Disease; FDA=Food and Drug Administration; IL=interleukin; IV=intravenous; JAK=Janus Kinase; PO=oral; SC=subcutaneous; S1P=sphingosine-1-phosphate; TNF=tumor necrosis factor; UC=Ulcerative Colitis		

Plaque Psoriasis, Psoriatic Arthritis, and Generalized Pustular Psoriasis

Plaque psoriasis is a chronic, immune-mediated inflammatory disorder of the skin and nails which affects about 3% of the United States (U.S.) adult population.[40] Psoriasis occurs equally in men and women, with a mean age of onset of 33 years.[41] Approximately 1% of children are affected by psoriasis, typically with onset during adolescence.[42] A 2020 population-based cross-sectional study sampled the U.S. civilian population and estimated psoriasis prevalence as highest in White individuals at 3.6%, followed by other racial/ethnic groups (non-Hispanic, including multiracial) at 3.1%, Asian individuals at 2.5%, Hispanic individuals (including Mexican American and other Hispanic individuals) at 1.9%, and Black individuals at 1.5%.[40]

The development of psoriasis is complex and appears to be influenced by many factors, including genetic changes, local trauma, infections, certain drugs (such as beta-blockers, lithium, chloroquine, and non-steroidal anti-inflammatory drugs), the duration of antipsoriatic treatments, endocrine factors, sunlight, alcohol, smoking, and stress.[43] Psoriasis is driven by multiple pathways of immune mediators including TNF, IL-17, IL-23, and IL-36 cytokines.[41] Plaque psoriasis is the most common type of psoriasis and is characterized by symmetrically distributed, erythematous plaques with sharply defined margins with overlying coarse scale.[41] The plaques may be asymptomatic, but itching is common. Typically, PsO is classified as mild, moderate, or severe. An estimated 20% of patients with PsO have moderate-to-severe disease, defined as greater than 10% of body surface area (BSA).[40] Mild disease involves less than 5% of BSA and has little to no impact on quality of life or function.[44] Mild PsO is not a funded condition per the HERC Guideline Note 21.[45]

Other subtypes of psoriasis include guttae, erythrodermic, and pustular psoriasis.[41] Generalized pustular psoriasis is an uncommon subtype that manifests as widespread pustular skin eruptions or erythematous plaques.[41] In generalized pustular psoriasis, small pustules may join into larger pustules to form pus-filled blisters on the skin, feet, and hands. The blisters can crack, which causes painful breaks in the skin and makes it difficult to walk or complete daily activities using the hands. Other symptoms of this condition include red, irritated, or burning skin, itching, fatigue, achy joints, headache and fever. Laboratory abnormalities, including leukocytosis, an elevated erythrocyte sedimentation rate, hypocalcemia and other electrolyte abnormalities, hypoalbuminemia, and elevated liver enzymes, are common [41] In addition, serious complications, including sepsis and hepatic, respiratory, or renal dysfunction, can occur.[46] Serious complications including sepsis, hepatic, respiratory, or renal dysfunction can occur with acute onset of GPP.[41] Generalized pustular psoriasis can be triggered by rapid tapering of systemic and potent topical corticosteroids, exposure to sunlight, hypocalcemia, pregnancy, and infection.[41] It epidemiologically distinct from chronic plaque psoriasis and more common in women than in men.[41]

Data on treatment of generalized pustular psoriasis primarily consist of retrospective studies, case reports, and expert opinion, with most studies originating from Japan.[46] The data are extremely limited for this type of psoriasis.[47] Interpretation of the available data is difficult due to the lack of a validated grading system for the severity of generalized pustular psoriasis, and the absence of a standardized method of assessing the response to treatment.[46] First line treatments for adults include acitretin, methotrexate, and cyclosporine. [46] Infliximab and ustekinumab have the most evidence of efficacy and safety for the treatment of pustular psoriasis with biologic agents.[48] Several medications targeting IL-17 or IL-23 have also recently been studied with ixekizumab, secukinumab, brodalumab, and guselkumab having shown some efficacy.[49] None of these medications are FDA-approved to treat generalized pustular psoriasis. Guidance from the National Psoriasis Foundation Medical Board (2012) recommends acitretin, cyclosporine, methotrexate as first-line immunomodulating therapies for those with generalized pustular psoriasis.[47] Treatment of patients with pustular psoriasis depends on the severity of presentation and patient's underlying risk factors.[47]

Per the 2020 American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) guidance, first-line topical agents to treat mild-to-moderate PsO include: corticosteroids, vitamin D analogues (e.g., calcipotriene), retinoids (e.g., tazarotene) or salicylic acid.[50] Phototherapy is an option for patients with moderate-to-severe PsO who have not responded to topical therapy.[51] Systemic non-biologic treatments are recommended for patients with moderate-to-severe PsO unresponsive to topical treatment or phototherapy and include methotrexate, cyclosporine, mycophenolate or azathioprine.[52] Targeted immune modulators may be added for patients with moderate-to-severe PsO not controlled by other therapies.[53]

Psoriatic arthritis is a chronic inflammatory disease with heterogeneous manifestations in patients who have psoriasis.[31] Psoriatic arthritis is reported in less than 1% of the general population, but in about 20% to 30% of patients with psoriasis.[54] Symptoms of PsA include pain and stiffness in the affected joints and associated tendons and ligaments, swelling, and loss of range of motion.[30] Psoriatic arthritis comprises both musculoskeletal as well as non-musculoskeletal manifestations including the gastrointestinal tract (inflammatory bowel disease) or the eyes (uveitis).[31] First-line treatment for PsA includes NSAIDs, although in most cases conventional synthetic DMARDs (methotrexate, sulfasalazine or leflunomide) are necessary.[31] In patients with active PsA despite conventional DMARD therapy, switching to a TNF-inhibitor, IL-17 antagonist, or IL-12/23 antagonist is recommended by the American College of Rheumatology/National Psoriasis Foundation.[55] Targeted immune modulators approved for use in PsO, PsA, and GPP are presented in **Table 2**.

Table 2. FDA-Approved Targeted Immune Modulators for Plaque Psoriasis, Psoriatic Arthritis, Generalized Pustular Psoriasis[38,39]

Drug – Route of Administration	Molecular Target	Approved Indication(s)
Adalimumab (HUMIRA) - SC	TNF	PsA, PsO
Certolizumab Pegol (CIMZIA) - SC		PsA, PsO,
Etanercept (ENBREL) - SC		PsA, PsO
Golimumab - (SIMPONI and SIMPONI ARIA) – SC or IV		PsA
Infliximab (REMICADE) - IV		PsA, PsO
Ustekinumab (STELARA) – IV or SC	IL-12 and IL-23	PsA, PsO
Bimekizumab (BIMZELX) - SC	IL-17	PsO
Brodalumab (SILIQ) - SC		PsO
Ixekizumab (TALTZ) - SC		PsA, PsO
Secukinumab (COSYNTEX) - SC		PsA, PsO
Guselkumab (TREMFYA) - SC	IL-23	PsA, PsO
Risankizumab (SKYRIZI) - SC		PsA, PsO
Tildrakizumab (ILUMYA) - SC		PsO
Spesolimab (SPEVIGO) - IV	IL-36	GPP
Abatacept (ORENCIA) - IV or SC	T-lymphocyte	PsA
Tofacitinib (XELJANZ)- PO	JAK 1,2,3	PsA
Upadacitinib (RINVOQ) - PO	JAK 1	PsA
Apremilast (OTEZLA) - PO	PDE4	PsA, PsO
Roflumilast (ZORYVE) – Topical Cream		PsO
Deucravacitinib (SOTYKU) – PO	TYK2	PsO

Abbreviations: FDA=Food and Drug Administration; GPP=generalized pustular psoriasis; IL=interleukin; IV=intravenous; JAK=Janus Kinase; PDE=phosphodiesterase; PO=oral; PsA=psoriatic arthritis; PsO=plaque psoriasis; SC=subcutaneous; TNF=tumor necrosis factor; TYK2=tyrosine kinase 2

Several tools have been developed to evaluate symptom improvement and quality of life in patients with PsO and PsA. In PsO clinical trials, symptom improvement is often evaluated using the PASI, the static Physician's Global Assessment (sPGA), or the Psoriasis Symptom Inventory (PSI). There is no consensus on the most reliable scale, but the PASI is used most often in clinical trials and is considered the most validated scale.[56] The PASI ranges from 0 to 72 points and evaluates body surface area involvement, induration, scaling, and erythema. Because the PASI only evaluates skin involvement on the trunk, head, arms and legs, the PASI has limited sensitivity in patients with mild to moderate disease or limited BSA involvement.[56,57] It does not consider symptoms affecting hands, feet, face or genitals. Because the PASI scale is not linear, small changes in BSA involvement can result in a significant improvement of the overall score without change in other symptoms.[56] The most commonly reported outcome in clinical trials is improvement of greater than 75% in the PASI score. However, an improvement of 100%, indicating complete disease clearance, is considered more clinically significant.[57] This tool is rarely used in clinical practice to assess psoriasis severity due to the substantial amount of time required to complete the scoring.[50] The PGA is a scoring system that assesses degree of erythema, induration, and scaling.[50] There are several different versions of the PGA, with most severity scores ranging from 0 to 4 or 0 to 5.[50] Higher scores indicate more severe disease. The PGA is also used in research, but not frequently used in clinical practice.[50] The Investigators Global Assessment (IGA) has also been used to

measure the severity of PsO based on skin thickening and hyperpigmentation in clinical trials.[58] Similar to the PGA, the IGA is a 5-point scale ranging from 0 (clear), 1 (almost clear), 2 (mild symptoms), 3 (moderate symptoms) to 4 (severe symptoms).[58] Response to therapy is indicated by a score of 0 or 1.[58] The most common outcome used to assess clinical improvement and disease remission in patients with PsA is the American College of Rheumatology (ACR) score.[2] The ACR score is a composite measure of disease activity that considers the number of tender and swollen joints, functional ability, pain, and inflammatory markers (i.e., erythrocyte sedimentation rate and C-reactive protein).[2] Additional information about the outcomes used to assess PsO and PsA in clinical trials is summarized in **Appendix 2.**

Summary Findings

1. DERP Report for Crohn's Disease and Ulcerative Colitis

The April 2023 DERP report focused on use of TIMs in adults with CD or UC.[1] Literature was searched from January 1, 2019 through July 14, 2022 for RCTs that evaluated comparative efficacy and safety of TIMs and cohort studies that evaluated comparative harms.[1] Outcomes of interest included measures of clinical improvement and disease remission, quality of life, AEs, and SAEs. Nineteen new studies met inclusion criteria.[1] Seven studies evaluated TIMs in people with CD and 9 studies included people with UC.[1] Three studies enrolled mixed populations with UC or CD and did not distinguish the results by condition.[1]

A. Crohn's Disease - Comparative Effectiveness of TIMs: One new RCT provided a head-to-head efficacy comparison for 2 TIMs in people with CD.[1]

- *Ustekinumab vs. Adalimumab (1 RCT):* Ustekinumab was compared to adalimumab in one new, double-blind RCT with moderate risk of bias.[1] In this trial, 386 biologic-naïve patients with moderate-to-severe CD who had not responded or were intolerant to conventional therapy were randomized to adalimumab 40 mg SC every 2 weeks or ustekinumab 90 mg SC every 8 weeks (after an IV loading dose).[1] The primary outcome was clinical remission (CDAI score < 150 points) at 52 weeks. The percentage of patients who achieved clinical remission was similar between adalimumab and ustekinumab (65% vs. 61%; p=0.42; 95% CI NR; moderate CoE).[1] For secondary outcomes, clinical response (CDAI score decreased by ≥100 points from baseline or CDAI score < 150 points) was 72% for adalimumab compared with 66% for ustekinumab (p=0.18) at 52 weeks.[1] No statistically significant difference was observed for corticosteroid-free remission (57% vs. 55%; p=0.49) or remission based upon patient-reported outcomes (57% vs. 55%; p=0.79) at 52 weeks.[1]

B. Crohn's Disease - Comparative Harms of TIMs: One new RCT at moderate risk of bias and 6 new cohort studies provided evidence for head-to-head safety TIM comparisons in people with CD.[1] The cohort studies had moderate risk of bias.[1] The main concerns for risk of bias were manufacturer involvement, no intention-to-treat analysis, and analysis not adjusted for confounders.[1]

- *Ustekinumab vs. Adalimumab (1 RCT):* Ustekinumab administered as an IV loading dose followed by SC administration every 8 weeks was compared with SC adalimumab administered every 2 weeks in one new, moderate risk of bias, double-blind RCT (n=386).[1] A lower incidence of injection-site reactions was reported with ustekinumab versus adalimumab (1% vs. 10%; low CoE) at 52 weeks.[1] No statistically significant differences were observed between these 2 medications in overall AEs (high CoE), SAEs (moderate CoE), withdrawal due to AEs (low CoE), or serious infections (very low CoE) at 52 weeks.[1]
- *Vedolizumab vs. TNF-Inhibitors (6 Cohort Studies):* Vedolizumab was compared to TNF-inhibitors in 5 cohort studies to assess the rate of serious infections.[1] In one large cohort study (n=21,366), the risk of serious infections was not statistically significantly different between vedolizumab and TNF-inhibitors (HR 1.10; 95%; 0.87 to 1.38; moderate CoE).[1] Four other cohort studies reported no statistically significant difference in incidence of serious and opportunistic (moderate CoE).[1] A separate cohort study assessed the risk of malignancies and found no differences between vedolizumab and TNF-inhibitors (moderate CoE).[1]

C. Ulcerative Colitis - Comparative Effectiveness of TIMs: No new RCTs were identified to evaluate comparative effectiveness of TIMs in UC.[1]

D. Ulcerative Colitis - Comparative Harms of TIMs: Six new cohort studies met inclusion criteria to evaluate comparative safety of TIMS in UC.[1]

- *Tofacitinib vs. TNF-inhibitors (1 Cohort Study)*: In one high-risk of bias cohort study, a statistically significant lower incidence of serious (IR, 1.75 vs. 3.33) and opportunistic (IR, 0.16 vs. 1.45) infections and non-melanoma skin cancer (IR, 0.78 vs. 1.69) were observed with tofacitinib compared with TNF-inhibitors (very low CoE).[1] The tofacitinib group had a statistically significant higher rate of herpes zoster infections compared with the TNF-inhibitor group (IR, 3.57 vs. 1.77).[1] There was no statistically significant difference reported between groups for major adverse cardiovascular events (myocardial infarction, stroke or heart failure death in hospital).[1]
- *Vedolizumab vs. TNF-Inhibitors (5 Cohort Studies):* Four cohort studies compared the risk of serious infections for vedolizumab with TNF-inhibitors.[1] A statistically significant lower incidence of SAEs (HR 0.37; 95% CI, 0.21 to 0.63 and serious infections (HR 0.68; 95% CI, 0.50 to 0.93) were observed with vedolizumab compared to TNF-inhibitors (very low CoE for both outcomes).[1] Another cohort study reported no statistically significant differences in the risk of incident malignancy (incidence rate ratio [IRR], 1.26; 95% CI 0.50 to 2.81; moderate CoE).[1]

E. Comparative Effectiveness and Harms of New Agents: Two new RCTs were identified to assess the safety and efficacy of 2 new TIMS, etrasimod (VELSIPITY) and mirikizumab (OMVOH) recently FDA-approved to treat UC.

- *Etrasimod vs. Placebo (1 RCT):* Etrasimod 1 mg and 2 mg orally once daily were compared to placebo in one moderate risk of bias RCT that enrolled 156 adults.[1] A statistically significant higher improvement in the total Mayo Clinic Score was reported with etrasimod 2 mg versus placebo at 12 weeks (LSM 2.49 vs. 1.50, $p<0.05$, 95% CI not reported; low CoE).[1] No statistically significant differences in incidence of overall AEs (low CoE), SAEs, withdrawals to AEs, or serious infections (very low CoE) were observed.[1]
- *Mirikizumab vs. Placebo (1 RCT):* Mirikizumab 50 mg, 200 mg, and 600 mg were compared to placebo in one moderate risk of bias RCT which randomized 249 adults to placebo or mirkiziumab.[1] A statistically significant higher incidence of clinical response was reported with IV mirikizumab versus placebo for the 50 mg (41% vs. 21%; p=0.01), 200 mg (60% vs. 21%; $p<0.001$), and 600 mg (49% vs. 21%; p=0.001) doses at 12 weeks (low CoE). No statistically significant differences in overall AEs (low CoE), SAEs, or withdrawal due to AEs (very low CoE) were noted between placebo and mirilkizuamb.[1]

F. Comparative Effectiveness and Harms of TIMs in Mixed Populations

No new RCTs were identified that focused on comparative efficacy of TIMs in mixed populations of patients with CD or UC.[1] Three new cohort studies with moderate risk of bias met inclusion criteria to evaluate the comparative harms of TIMs in mixed populations. The results were not stratified by disease.[1] Comparative harms data were reported for TNF-inhibitors (adalimumab, infliximab, certolizumab, or golimumab), tofacitinib, ustekinumab, and vedolizumab.[1] Two cohort studies compared ustekinumab with TNF-inhibitors with conflicting results regarding the risk of serious infections.[1] The larger cohort study (n=21,821) reported no statistically significant difference between the 2 groups (HR 0.84; 95% CI, 0.66 to 1.03).[1] The smaller study (n=1,575) reported a lower risk of serious infections with ustekinumab versus TNF-inhibitors (HR, 1.58; 95% CI 1.07 to 2.34).[1] Both studies reported no statistically significant difference between the groups regarding the risk of herpes zoster infections.[1] A third cohort study with moderate risk of bias compared adalimumab, infliximab, and vedolizumab with each other as well as ustekinumab.[1] Patients treated with vedolizumab had a lower risk of serious infection compared with infliximab (HR 1.61; 95% CI, 1.06 to 2.45).[1] No other statistically significant differences were identified between treatments.[1]

Conclusions

In summary, no statistically significant difference in efficacy observed between ustekinumab and adalimumab in patients with CD (moderate CoE).[1] In the safety evaluation, no statistically significant differences were observed between these ustekinumab and adalimumab in overall AEs (high CoE), SAEs (moderate CoE), withdrawal due to AEs (low CoE), or serious infections (very low CoE) at 52 weeks.[1] Vedolizumab was compared to TNF-inhibitors in 5 cohort studies to assess the rate of serious infections in people with CD.[1] No statistically significant difference in incidence of serious and opportunistic infections was observed in any of

these reports (moderate CoE). Another cohort study assessed the risk of malignancies and found no differences between vedolizumab and TNF-inhibitors (moderate CoE).[1]

No new evidence was identified to evaluate the comparative efficacy of TIMs in UC. New evidence regarding the comparative harms in UC is limited to comparisons between TNF-inhibitors versus tofacitinib or vedolizumab.[1] A lower incidence of serious infections, opportunistic infections and non-melanoma skin cancer were observed with tofacitinib compared with TNF-inhibitors (very low CoE) in one cohort study.[1] However, the tofacitinib group had a statistically significant higher rate of herpes zoster infections compared with the TNF-inhibitor group.[1] Data from 5 cohort studies showed a lower incidence of SAEs and serious infections with vedolizumab compared to TNF-inhibitors (very low CoE for both outcomes).[1] Two new medications, etrasimod and mirikizumab, were recently FDA-approved to treat UC based on evidence from one placebo-controlled RCT for each medication.[17,18] Very low CoE showed etrasimod and mirikizumab improved symptoms of UC compared with placebo.[1] No differences from placebo in overall AEs or SAEs were observed with either medication.[1]

2. DERP Report for Plaque Psoriasis and Psoriatic Arthritis

The February 2024 DERP report focused on new evidence for TIMs to manage PsO, PsA, and GPP to update the previous 2022 DERP report.[2] Literature was searched for relevant RCTs evaluating comparative effectiveness and harms of FDA-approved TIMs from August 1, 2021 through August 1, 2023.[2] Outcomes of interest included disease remission, clinical improvement, quality of life (QoL), AEs and SAEs.

A. Plaque Psoriasis - Comparative Effectiveness of TIMs: Four RCTs are new for the 2024 DERP report.[2] The RCTs enrolled patients with a 6-month history of moderate-to-severe PsO and were conducted over 12 weeks or longer.[2] The primary endpoints were the PASI 90 or PASI 75 (indicating a reduction in PASI score 90% and 75%, respectively).

- *Deucravacitinib vs. Apremilast (2 RCTs*): Two new RCTs with moderate risk of bias were identified that compared deucravacitinib 6 mg orally once a day with apremilast 30 mg orally twice a day in adults with moderate-to-severe PsO.[2] All primary endpoints were compared between deucravacitinib and placebo. For secondary outcome, response rates were higher with deucravacitinib versus apremilast for PASI 75 at week 24 (58.4% vs. 35.1%; RR 1.2; 95% CI, 1.3 to 2.1; high CoE) in the first trial (n=500).[2] In the second trial (n=765), more deucravacitinib-treated patients versus apremilast-treated patients achieved PASI 75 at week 24 (53.0% vs. 39.8%; RR 1.3; 95% CI 1.1, to 1.6; high CoE).[2] In both trials, deucravacitinib was more effective than apremilast for achieving DLQI 0 or 1 at 24 weeks (RR 1.4; 95% CI, 1.1 to 1.9 and RR 1.6; 95% CI, 1.3 to 2.1).[2]
- *Guselkumab vs. Secukinumab (1 RCT):* In this small, open-label, RCT with high risk of bias, 40 patients with a PASI score less than 10 at baseline, but with at least 1 plaque refractory to treatment with ustekinumab were assigned to either guselkumab or secukinumab.[2] The primary endpoint was designated as improvement in the treatment-refractory plaque as measured by an outcome called total clinical score, which is not an outcome used by any other included studies.[2] No difference in clinical improvement in at least one plaque refractory to ustekinumab treatment was observed between guselkumab and secukinumab at 16 weeks (60% vs. 40%; p=0.17; very low CoE).[2]
- *Risankizumab vs. Apremilast (1 RCT):* One new RCT with moderate risk of bias compared risankizumab to apremilast.[2] In this RCT, 352 patients with moderate chronic PsO with or without PsA were randomized to risankizumab 150 mg SC at weeks 0 and 4 or oral apremilast 30 mg twice daily for 16 weeks.[2] At 16 weeks, more participants in the risankizumab arm experienced PASI 90 response compared with the apremilast arm (55.9% vs. 5.1%; RR 10.9; 95% CI, 6.1 to 19.4; moderate CoE).[2] Similar results were observed clinical improvement at 16 weeks (PASI 75:66% vs. 49%; RR 4.5; 95% CI, 3.4 to 5.9; moderate CoE).[2]

B. Plaque Psoriasis - Comparative Harms of TIMs: All the RCTs that evaluated efficacy also reported on harms of TIM agents.[2] Few differences in harms for TIMs were reported in head-to-head comparisons.[2] One RCT reported statistically significant differences in AEs.[2]

- *Risankizumab vs. Apremilast (1 RCT):* Fewer AEs with risankizumab compared with apremilast at 16 weeks (RR 0.68; 95% CI, 0.54 to 0.86; moderate CoE).[2]

C. Psoriatic Arthritis - Comparative Effectiveness and Harms of TIMs: No new evidence was identified for comparative efficacy or harms of TIMs in PsA for the 2024 DERP update.[2]

D. Generalized Pustular Psoriasis - Comparative Efficacy and Harms of TIMs: No eligible RCTs evaluating comparative evidence for TIMs in GPP were identified.[2] A new IL-36 antagonist, spesolimab, received FDA approval for treatment of GPP flares in September 2022.[3] The evidence supporting FDA-approval of spesolimab was provided in a placebo controlled trial.[4]

E. Differences in Effectiveness or Harms by Subgroup Analysis: No new evidence to analyze safety or effectives by subgroups was identified for the 2024 DERP report.[2]

High-Quality Guidelines:

Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

In 2021, GRAPPA updated their 2015 treatment recommendations for PsA as therapeutic options for PsA.[5] The guidance is provided based on specific symptoms of PsA as follows:

Peripheral Arthritis

- NSAIDs and intra-articular and oral glucocorticoids are conditionally recommended for relieving symptoms of peripheral arthritis.[5]
- For treatment-naive patients, there remains a low level of evidence to support the use of conventional synthetic DMARDs (csDMARDs) for the treatment of peripheral arthritis. However, in view of supportive observational and universal accessibility, the use of csDMARDs (methotrexate, sulfasalazine or leflunomide) is strongly recommended.[5]
- In many circumstances, csDMARDs can be used as first-line therapy, with regular assessment of clinical response (every 12–24 weeks) and early escalation of therapy (between 12 and 24 weeks) advised as necessary.[5]
- It is important to acknowledge that new, high-quality data support the superiority of TNF inhibitors over csDMARDs as first-line therapy, particularly in patients with early disease.[5]
- For all RCTs reviewed for PDE4 inhibitors, TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors, IL-23 inhibitors and JAK inhibitors, there were no differences in efficacy for these treatment options in subgroups of patients with or without concurrent csDMARDs.[5]
- For patients with an inadequate response to csDMARDs, high-quality evidence supports the use of TNF inhibitors, IL-17 inhibitors, IL-23 inhibitors, and JAK inhibitors; and moderate-quality evidence supports IL-12/23 inhibitors or PDE4 inhibitors being superior to placebo. Based on the evidence, including head-to-head studies, TNF inhibitors, IL-17 inhibitors and JAK inhibitors are equally recommended.[5]
- For patients with previous experience with biologic DMARDs (bDMARDs), TNF inhibitors, IL-17 inhibitors, IL-23 inhibitors, and JAK inhibitors are strongly recommended based on moderate-to-high quality evidence. PDE4 inhibition is conditionally recommended.[5]

Axial Disease

- For patients with axial symptoms who have not responded to treatment with NSAIDs, physiotherapy and/or sacroiliac joint glucocorticoid injections (when appropriate), initiation of a targeted therapy is strongly recommended. TNF inhibition and IL-17 inhibition have demonstrated efficacy in both radiographic and non-radiographic axial ankylosing spondylitis (axSpA) and are recommended for axial PsA.[5]

- Several RCTs have demonstrated the efficacy of the JAK inhibitors tofacitinib and upadacitinib in ankylosing spondylitis. Extrapolating from the evidence in axSpA, these agents are recommended for axial PsA as well.[5]

Enthesitis

- The use of NSAIDs, local glucocorticoid injections and physiotherapy was conditionally recommended, despite the lack of high-quality studies that investigated their efficacy for enthesitis in PsA or SpA.[5]
- Classes of advanced therapies found to be effective and thus strongly recommended as treatment options for active enthesitis in patients with PsA include TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors, IL-23 inhibitors, JAK inhibitors and PDE4 inhibitors.[5] Despite novel information about the comparative efficacy of different classes of medications emerging from head-to-head studies, including comparisons of IL-17 inhibitors with TNF inhibitors, methotrexate with TNF inhibitors, and IL-12/23 inhibitors with TNF inhibitors, none of the evaluated classes of medications was found to have clear and consistent superiority over the other.[5]
- Methotrexate received a conditional recommendation for the treatment of active enthesitis.[5]

Dactylitis

- The IL-17 inhibitors secukinumab, ixekizumab, and brodalumab, demonstrated superior efficacy compared with placebo for improving dactylitis signs and symptoms in RCTs; another IL-17 inhibitor, bimekizumab, is being studied. In RCTs the IL-23 inhibitors guselkumab and risankizumab were found to be effective for dactylitis as assessed by the proportion of patients with total resolution of dactylitis at week 24.[5]
    - Considering the evidence, the group made a conditional recommendation for the use of methotrexate and against the use of other csDMARDs in the treatment of dactylitis. The use of NSAIDs and local glucocorticoid injections was also conditionally recommended for the treatment of dactylitis. A strong recommendation was established for the use of TNF inhibitors, IL-12/23 inhibitors, IL-23 inhibitors, IL-17 inhibitors, JAK inhibitors and PDE4 inhibitors, in the treatment of dactylitis in PsA.[5]

Skin

- Topical agents are strongly recommended as first-line treatment for patients with limited body surface area involvement. For patients with more widespread psoriasis or psoriasis unresponsive to topicals, phototherapy, and oral therapies (methotrexate, cyclosporin, PDE4 inhibitors and JAK inhibitors), bDMARDs (TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors, and IL-23 inhibitors) are strongly recommended.[5]

National Institute for Health and Care Excellence Guidelines for TIMs in Autoimmune Conditions

Specific medication-related recommendations from NICE for 4 auto-immune conditions (CD, UC, PsO, and PsA) are summarized below.

Crohn's Disease: Treatments for moderately to severely active CD include conventional therapy such as glucocorticoids and immunomodulators (azathioprine, mercaptopurine, methotrexate).[6,7] This is followed by biological treatments if there is inadequate response, intolerance or contraindication to conventional therapy.[6,7] Biological treatments for moderately to severely active CD include TNF-inhibitors (adalimumab and infliximab), ustekinumab and vedolizumab.[6]

- *Risankizumab – May 2023*

Clinical trial evidence suggests that risankizumab reduces symptoms and increases the likelihood of disease remission compared with placebo.[6] Risankizumab is recommended as an option for treating moderately to severely active CD in people 16 years and over, only if the disease has not responded well enough or lost response to a previous biological treatment, or a previous biological treatment was not tolerated, or TNF-inhibitors are not suitable.[6]

- *Upadacitinib – June 2023*

Clinical trial evidence shows that upadacitinib increases the likelihood of disease remission compared with placebo.[7] Upadacitinib is recommended as an option for treating moderately to severely active CD in adults, only if the disease has not responded well enough, or lost response, to a previous biological treatment, or a previous biological treatment was not tolerated or TNF-inhibitors are contraindicated.[7]

***Ulcerative Colitis**:* At initial diagnosis, UC is managed with conventional treatments such as corticosteroids, mesalamine and thiopurines (azathioprine and mercaptopurine).[9] If the condition does not respond well enough or stops responding to conventional treatment, a biological treatment, usually a TNF-inhibitor, commonly infliximab, is most often offered.[9] TNF-inhibitors should be used with thiopurines to be most effective.[9] In about 30% of people, UC does not respond to a TNF-inhibitor and about 40% of people with UC will lose response over 12 months.[9] For a minority of people, another TNF-inhibitor such as adalimumab or golimumab may be offered, but other options include vedolizumab, ustekinumab, and tofacitinib.[9]

- *Mirikizumab – October 2023*

Clinical trial evidence shows that mirikizumab is more effective than placebo for treating moderately to severely active UC.[8] There are no clinical trials directly comparing mirikizumab with vedolizumab or ustekinumab.[8] Mirikizumab is recommended as an option for treating moderately to severely active UC in adults when conventional or biological treatment cannot be tolerated, or the condition has not responded well enough or lost response to treatment, only if a TNF-inhibitor has not worked (the condition has not responded well enough or has lost response to treatment) or a TNF-inhibitor cannot be tolerated or is not suitable.[8]

- *Ozanimod – October 2022*

Clinical trial evidence shows that ozanimod is more effective than placebo for treating moderately to severely active UC.[9] There is no direct evidence comparing ozanimod with standard treatments that are offered after conventional treatment.[9] Ozanimod is recommended as an option for treating moderately to severely active UC in adults, only if conventional treatment cannot be tolerated or is not working well enough and infliximab is not suitable, or biological treatment cannot be tolerated or is not working well enough.[9]

- *Upadacitinib – January 2023*

Clinical trial evidence shows that upadacitinib is more effective than placebo for treating moderately to severely active ulcerative colitis.[10] There is no direct evidence comparing upadacitinib with treatments that are offered after conventional treatment.[10] Upadacitinib is recommended as an option for treating moderately to severely active UC in adults when conventional or biological treatment cannot be tolerated, or if the condition has not responded well enough or stopped responding to these treatments.[10]

***Plaque Psoriasis**:* People with PsO may have topical treatments (such as corticosteroids, vitamin D analogues or dithranol) as first-line treatments, followed by phototherapy as second-line treatments.[12] If this does not control the psoriasis, people may have conventional systemic non-biological treatments as third-line options (such as methotrexate, cyclosporine or acitretin).[12] If the psoriasis does not respond adequately to these treatments, people may move onto a fourth-line treatment option, which includes apremilast or systemic biological treatments.[12] Biological treatments include TNF-inhibitors (adalimumab, certolizumab pegol, etanercept, infliximab), IL-17 inhibitors (bimekizumab, brodalumab, ixekizumab, secukinumab) and IL-23 inhibitors (risankizumab, tildrakizumab, guselkumab, ustekinumab).[12]

- *Bimekizumab – September 2021*

Bimekizumab is an alternative to other biological treatments already recommended by NICE for treating severe plaque PsO in adults.[11] Evidence from clinical trials shows that bimekizumab is more effective than adalimumab, secukinumab and ustekinumab.[11]

  - Bimekizumab is recommended as an option for treating PsO in adults, only if the disease is severe, as defined by a total PASI of 10 or more and a DLQI of more than 10 and the disease has not responded to other systemic treatments, including cyclosporine, methotrexate and phototherapy, or these options are contraindicated or not tolerated.[11]
  - Stop bimekizumab treatment at 16 weeks if the psoriasis has not responded adequately. An adequate response is defined as:
    - 75% reduction in the PASI score (PASI 75) from when treatment started, or
    - 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started.[11]

- *Deucravacitinib – June 2023*

Clinical trial evidence shows that deucravacitinib improves symptoms of PsO compared with placebo and apremilast.[12]

  - Deucravacitinib is recommended as an option for treating moderate-to-severe PsO n adults only if the PASI score is 10 or more and the DLQI score is more than 10, and the condition has not responded to other systemic treatments, including cyclosporine, methotrexate and phototherapy, or these options are contraindicated or not tolerated.[12]
  - Consider stopping deucravacitinib between 16 weeks and 24 weeks if there has not been at least a 50% reduction in the PASI score (PASI 50) from when treatment started.[12]
  - Consider stopping deucravacitinib at 24 weeks if the psoriasis has not responded adequately. An adequate response is defined as:
    - 75% reduction in the PASI score (PASI 75) from when treatment started, or
    - 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started.[12]

***Psoriatic Arthritis**:* The main aim of treatment for active PsA is to control joint and connective tissue inflammation.[15] This prevents joint damage progressing and the associated pain and disability.[15] People will usually have treatment with NSAIDs, corticosteroids and conventional DMARDs, such as methotrexate.[15] In line with NICE's technology appraisal guidance on etanercept, infliximab and adalimumab, people are eligible for biological or small-molecule treatments if their disease is poorly controlled after 2 conventional DMARDs.[15] Biological or small-molecule treatments include TNF-inhibitor treatments such as etanercept and adalimumab, secukinumab and ixekizumab (IL-17A inhibitors) and ustekinumab (an IL-12 and IL-23 inhibitor), tofacitinib, and apremilast.[15] Stop biological treatment at 24 weeks if the PsA has not responded adequately using the Psoriatic Arthritis Response Criteria (PsARC; an adequate response is an improvement in at least 2 of the 4 criteria, 1 of which must be joint tenderness or swelling score, with no worsening in any of the 4 criteria).[13] If the PsARC response is not adequate but there is a PASI 75 response, a dermatologist should decide whether continuing treatment is appropriate based on skin response.[13]

- *Guselkumab – August 2022*

Clinical evidence shows that guselkumab is effective compared with placebo, but it has not been compared directly with other bDMARDs for treating PsA.[13]

  - Guselkumab, alone or with methotrexate, is recommended as an option for treating active PsA in adults whose disease has not responded well enough to DMARDs or who cannot tolerate them.[13] It is recommended only if they have had 2 conventional DMARDs and have had at least 1 biologic DMARD (bDMARD), or TNF inhibitors are contraindicated.
  - Active psoriatic arthritis is defined as peripheral arthritis with 3 or more tender joints and 3 or more swollen joints.[13]

- *Risankizumab – July 2022*

Clinical evidence shows that risankizumab is effective for active psoriatic arthritis compared with placebo.[14] Risankizumab has not been compared directly with other bDMARDs for PsA.[14]

  - Risankizumab, alone or with methotrexate, is recommended as an option for treating active PsA in adults whose disease has not responded well enough to DMARDs or who cannot tolerate them.[14] It is recommended only if they have peripheral arthritis with 3 or more tender joints and 3 or more swollen joints, moderate-to-severe psoriasis (body surface area at least 3% affected by PsO and a PASI score >10, and had 2 conventional DMARDs and ≥1 bDMARD.[14]

- *Upadacitinib – February 2022*

Clinical evidence shows that upadacitinib is more effective than placebo for treating active PsA and may be similarly as effective as adalimumab.[15] Upadacitinib has not been directly compared with any other bDMARD for this condition.[15]

  - Upadacitinib, alone or with methotrexate, is recommended as an option for treating active PsA in adults whose disease has not responded well enough to DMARDs or who cannot tolerate them. It is recommended only if they have peripheral arthritis with 3 or more tender joints and 3 or more swollen joints and they have had 2 conventional DMARDs and at least 1 bDMARD or TNF-inhibitors are contraindicated.[15]

New Formulations and Indications:

- The FDA recently approved expanded indications for the use of upadacitinib (RINVOQ) in irritable bowel diseases. The approval for upadacitinib treatment for adults with moderately to severely active UC who have had an inadequate response to one or more TNF-inhibitors occurred October 2022.[16] Two phase 3 RCTs (n=988) provided data to support the efficacy of upadacitinib induction in adults with UC.[16] In these trials, adults with moderate-to-severe UC who had an inadequate response, loss of response, or intolerance to oral aminosalicylates, corticosteroids, immunosuppressants, and/or biologic therapy were randomized to upadacitinib 45 mg orally once daily or placebo for 8 weeks.[16] In the first RCT, 5% of placebo-treated patients achieved clinical remission at 8 weeks versus 26% of upadacitinib patients (mean difference 22%; 95% CI, 16 to 27; p<0.001).[16] Similar results were observed in the second RCT which compared placebo to upadacitinib (4% vs. 33%; mean difference 29%; 95% CI, 23 to 35; p<0.001).[16] A third study evaluated maintenance upadacitinib 15 or 30 mg once daily treatment versus placebo over 52 weeks. More adults treated with upadacitinib 15 and 30 mg doses achieved clinical remission compared with placebo at 52 weeks.[16] The safety profile observed in patients with UC treated with upadacitinib was similar to the safety profile observed in patients with rheumatoid arthritis and atopic dermatitis.[16] Serious infections and elevated hepatic transaminase enzymes were reported more frequently with upadacitinib compared with placebo.[16]

  In May 2023, upadacitinib received an FDA-approved indication for adults with moderately to severely active CD who have had an inadequate response to one or more TNF-inhibitors.[16] Two phase 3 RCTs (n=857) provided data to support the efficacy of upadacitinib induction.[16] In both trials, adults with moderate-to-severe CD who had an inadequate response, or were intolerant, to treatment with one or more biologic therapies were randomized to upadacitinib 45 mg or placebo over 12 weeks.[16] In the first study, 18% of placebo treated-patients achieved clinical remission at 12 weeks versus 36% of upadacitinib treated-patients (mean difference 17%; 95% CI 9 to 25; p<0.001) and 3% of patients in the placebo group achieved endoscopic response compared with 35% of patients in the upadacitinib group (mean difference 30%; 95% CI, 24 to 36; p<0.001).[16] Similar results were reported in the second RCT. A third study evaluated maintenance upadacitinib 15 or 30 mg once daily treatment versus placebo over 52 weeks. More adults treated with upadacitinib 15 and 30 mg doses achieved clinical and endoscopic remission compared with placebo at 52 weeks.[16] The safety profile observed in patients with CD treated with upadacitinib was similar to the safety profile observed in patients with other indications.[16]

- The FDA approved a new oral S1P receptor modulator, etrasimod (VELSIPITY), for the treatment of moderate-to-severe UC in adults in October 2023.[17] The recommended etrasimod dose is 2 mg orally once a day.[17] Two phase 3 RCTs provided data to support the efficacy of etrasimod in adults with UC who had an inadequate response, loss of response, or intolerance to one or more treatment options including oral aminosalicylates, corticosteroids, thiopurines, JAK inhibitors, TNF-inhibitors, anti-integrins, or IL-12/23 inhibitors.[17] Disease activity was assessed using the modified Mayo Clinic score, which only used 3 components of the original Mayo Clinic score (stool frequency, rectal bleeding, and endoscopy findings).[17] In the first RCT, remission at 12 weeks was achieved by 7% of placebo-treated patients versus 27% of etrasimod-treated patients (mean difference 20%; 95% CI, 13 to 27%; p<0.001).[17] Similar results were observed at 52 weeks with 7% of placebo-treated patients achieving clinical remission versus 32% of etrasimod-treated patients (mean difference 26%; 95% CI, 19 to 33; p<0.001).[17] In the second RCT, the proportion of placebo-treated patients with remission was reported in 15% of participants versus 26% of etrasimod-treated patients (mean difference 11%; 95% CI 3 to 20%; p<0.05).[17] The most common adverse effects reported with etrasimod included headache, elevated liver function testes, and dizziness.[17] Contraindications to etrasimod therapy include patients who experienced myocardial infarction, unstable angina pectoris, stroke, transient ischemic attack, or decompensated heart failure requiring hospitalization in the previous 6 months.[17] In addition, unless the patient has a functioning pacemaker, people with a history of second-degree or third-degree atrioventricular block, sick sinus syndrome, or sino-atrial block should not receive etrasimod.[17]

- A new IL-23 antagonist, mirikizumab (OMVOH), received FDA approval in October 2023 for the treatment of moderate-to-severe UC in adults.[18] Mirikizumab is initiated with a 300 mg IV infusion loading dose every 4 weeks for 3 doses followed by 200 mg SC every 4 weeks.[18] After proper training, patients may self-administer mirikizumab using 2 prefilled pens for each dose. The safety and efficacy of mirikizumab were studied in 2 double-blind, placebo-controlled RCTs in adults with UC who had an inadequate response, loss of response, or failed to tolerate any of the following: azathioprine, TNF-inhibitor, vedolizumab, or tofacitinib.[18] In the first RCT, 24% of mirikizumab-treated patients achieved clinical remission at week 12 compared with 15% of placebo-treated patients (mean difference 10%; 95% CI 5 to 15; p<0.001).[18] In the second study, 51% of mirikizumab-treated patients achieved clinical remission at week 40 compared with 27% of placebo-treated patients (mean difference 22%; 95% CI 15 to 31; p<0.001).[18] The most frequently reported AEs with mirikizumab were respiratory tract infections and arthralgia.[18]

- In October 2023, a new IL-17 inhibitor, bimekizumab (BIMZELX) received FDA approval for treatment of moderate-to-severe PsO in adults who are candidates for systematic therapy or phototherapy.[19] Two RCTs provided data for FDA approval. In the first RCT, 567 adults were randomized to receive either bimekizumab 320 mg SC every 4 weeks, ustekinumab (if ≤100 kg, 45 mg initially and 4 weeks later, then every 12 weeks; if >100 kg, 90 mg initially and 4 weeks later, then every 12 weeks), or placebo for 16 weeks.[19] In the second RCT, 435 adults were randomized to either bimekizumab 320 mg SC every 4 weeks or placebo through week 16.[19] The co-primary endpoints for both RCTs were the proportion of patients who achieved IGA 0 or 1 and PASI 90 compared with placebo.[19] In the first RCT, more people in the bimekizumab group achieved PASI 90 at week 16 compared to placebo (85% vs. 5%; mean difference = 80%; 95% CI, 74 to 86) and achieved an Investigator's Global Assessment (IGA) score of 0 or 1 (84% vs. 5%; mean difference = 79%; 95% CI, 73 to 85).[19] In the second RCT, more people in the bimekizumab group achieved PASI 90 at week 16 compared to placebo (91% vs. 1%; mean difference 90%; 95% CI, 86 to 93)[19] and an IGA score of 0 or 1 (93% vs. 1%; difference = 91%; 95% CI 88 to 95).[19] Adverse reactions that occurred in the bimekizumab group and at a higher rate than in the placebo group through week 16 were upper respiratory tract infections, oral candidiasis, headache, injection site reactions, and tinea infections.[19]

- In September 2022, the FDA approved a new oral tyrosine kinase 2 inhibitor, deucravacitinib (SOTYKTU), for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.[20] Two RCTs contributed data for the FDA approval. In the first RCT, adults were randomized 2:1:1 to deucravacitinib 6 mg daily (n=332), placebo (n=166), or apremilast 30 mg twice a day (n=168) in a 52-week, double-blinded, phase 3 trial.[59] Co-primary end points included achievement of PASI 75 and static Physician's Global Assessment (sPGA) score of 0 or 1 with deucravacitinib versus placebo at week 16.[59] At week 16, response rates were higher with deucravacitinib versus placebo for PASI 75 (58% vs. 13%; mean difference 46%; 95% CI, 39 to 53) and sPGA 0/1 (54% vs. 7%; mean difference 47%; 95% CI 40 to 53).[59] The second RCT was a 52-week, double-blinded, phase 3 trial which randomized patients 2:1:1 to deucravacitinib 6 mg daily (n 511), placebo (n=255), or apremilast 30 mg twice a day (n=254).[60] At week 16, more patients in the deucravacitinib achieved ≥75% reduction from baseline in PSAI versus placebo (53% vs. 9%; mean difference 44%; 95% CI, 38 to 49) and sPGA score of 0 or 1 (50% vs. 9%; mean difference 41%; 95% CI, 35 to 46). In the first RCT, AE rates with deucravacitinib were similar to those with placebo.[59] In the second RCT, the most frequent AE with deucravacitinib was nasopharyngitis.[60] Serious adverse events and discontinuations due to AEs were infrequent.[60] No clinically meaningful changes were observed in laboratory parameters.[60]

- Spesolimab (SPEVIGO), a new IL-36 antagonist, received FDA-approval September 2022 for treatment of GPP flares in adults.[3] A 12-week, phase 2 trial conducted in 53 adults with a moderate to severe GPP flare provided data for the FDA approval.[4] In this RCT, adults were randomly assigned in a 2:1 ratio to receive a single 900 mg IV dose of spesolimab or placebo on day 1, with options for open-label spesolimab on day 8 based upon response and subsequent open-label spesolimab as a rescue treatment.[4] At day 8, 19 of 35 patients (54%) in the spesolimab group achieved a GPP Physician Global Assessment score of 0 (no visible pustules) compared with only 1 of 18 (6%) in the placebo group (difference 49%; 95% CI 21 to 67).[4] Infections occurred in 17% of patients in

the spesolimab group and 6% in the placebo group in week 1.[4] Over 12 weeks, SAEs occurred in 6 of 51 patients (12%) who received at least one dose of spesolimab, including 2 patients with drug reaction with eosinophilia and systemic symptoms (DRESS).[4]

In March 2024, spesolimab received an expanded indication for SC administration every month to treat GPP in adults and pediatric patients aged 12 years and older and weighing at least 40 kg not experiencing a GPP flare.[3] If required, a loading dose of spesolimab 600 mg may be administered by a health care professional. For subsequent dosing, 300 mg SC may be self-injected every 4 weeks in patients who have demonstrated the ability to self-inject.[3] The safety and efficacy of SC spesolimab was evaluated in 123 patients in a placebo controlled RCT.[3] Adults and pediatric patients aged 12 years and older with a history of at least 2 GPP flares of moderate to severe intensity were eligible for enrollment. The study population was 38% male and 62% female with a mean age of 40 years.[3] Eight patients (7%) were children.[3] Most of the patients were Asian (64%) and 36% were White.[3] The occurrence of least one GPP flare up to week 48 was observed in 3 (10%) of spesolimab-treated patients compared with 16 (52%) placebo-treated patients (risk difference, -39%; 95% CI, -62 to -16).[3] Injection site reactions (erythema, pain, swelling, induration, urticaria, and warmth at the injection site) were the most frequently reported AEs with spesolimab in this RCT.[3]

- In April 2024, apremilast received an expanded indication for treatment of pediatric patients 6 to 17 years of age weighing ≥ 20 kg for treatment of moderate-to-severe PsO who are candidates for phototherapy or systemic therapy.[21] Use of apremilast in pediatrics is supported by evidence from a 52-week multi-center, placebo-controlled RCT (PSOR-6) in 245 pediatric subjects 6 to 17 years of age with moderate-to-severe PsO.[21] Patients received apremilast 20 mg or 30mg twice daily, based on body weight.[21] The primary endpoint was the proportion of subjects who achieved an sPGA response (defined as a score of clear [0] or almost clear [1] with at least a 2-point reduction from baseline) at Week 16.[21] Eleven percent of placebo-treated patients achieved sPGA response compared with 33% of apremilast-treated patients (difference: 22%; 95% CI 12 to 32).[21] The key secondary endpoint was the proportion of subjects who achieved a PASI-75 response score from baseline at Week 16.[21] Sixteen percent of placebo-treated patients achieved PASI-75 response compared with 46% of apremilast-treated patients (difference: 30%; 95% CI 18 to 42).[21] Overall, the safety profile observed in pediatric patients treated with apremilast was consistent with the safety profile established in adults with moderate-to-severe PsO.[21] Most frequently reported AEs included diarrhea, nausea, and upper respiratory tract infections.[24]

- In April 2024, a new SC formulation of vedolizumab for treatment of adults with moderately to severely active CD and UC received FDA-approval.[22] Vedolizumab was administered as a SC injection in adult patients with UC and CD in 2 double-blind, placebo-controlled clinical trials (one RCT for each diagnosis). Patients who achieved clinical response following 2 doses of vedolizumab administered as an intravenous infusion at Week 0 and Week 2 were randomized 2:1 at Week 6 vedolizumab as a subcutaneous injection (N=106) or placebo (N=56) (SC UC Trial) and as a subcutaneous injection (N=275) or placebo (N=134) (SC CD Trial).[22] The primary endpoint in the UC trial was the proportion of patients in clinical remission defined as a Mayo score of ≤2 points and no individual subscore >1 point at week 52.[22] Fourteen percent of placebo-treated patients achieved clinical remission at week 52 compared with 46% of vedolizumab-treated patients for a treatment difference of 32% (95% CI 20 to 45).[22] The primary endpoint for the CD trials was the proportion of patients with clinical remission (CDAI score ≤150) at Week 52. At week 52, 34% of placebo-treated patients achieved clinical remission compared with 48% of vedolizumab-treated patients for a treatment difference of 14% (95% CI 4 to 24).[22] The safety profile for up to 52 weeks of total treatment was similar between patients who were switched to vedolizumab SC injection compared to patients in UC and CD clinical trials who received vedolizumab as an intravenous infusion in both clinical trials, except for injection site reactions, which were reported with subcutaneous vedolizumab.[22]

- Sarilumab received an expanded indication for patients who weigh 63 kg or greater with active polyarticular juvenile idiopathic arthritis (pJIA) in June of 2024.[23] Use of sarilumab in pediatric patients with pJIA is supported by evidence from adequate and well-controlled studies of sarilumab in adults with rheumatoid arthritis.[23]

- In June 2024, risankizumab received an expanded indication for adults with moderately to severely active UC.[24] Risankizumab was studied up to 12 weeks in subjects with moderately to severely active ulcerative colitis in a randomized, double-blind, placebo-controlled induction study (UC-1).[24] The primary endpoint was clinical remission defined using the Mayo score at Week 12 (see **Appendix 2**). At week 12, 8% of placebo-treated patients were in clinical remission compared with 24% of risankizumab-treated patients (difference: 16%; 95% CI 12 to 20).[24] Long-term safety up to 52 weeks was evaluated in subjects who responded to induction therapy in a randomized, double-blind, placebo-controlled maintenance study (UC-2).[24] The most frequently reported AEs included arthralgia, fever, injection site reactions, and rash. The rates of infections, serious infections, and lipid elevations in subjects with UC who received risankizumab compared in the UC induction studies and maintenance study were similar to the rates in subjects with CD who received risankizumab the CD induction studies and maintenance study.[24]

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
etanercept	ENBREL MINI	SUBCUT	CARTRIDGE	Y
adalimumab	HUMIRA PEN	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA PEN CROHN'S-UC-HS	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA PEN PSOR-UVEITS-ADOL HS	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA(CF) PEN	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA(CF) PEN CROHN'S-UC-HS	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA(CF) PEN PEDIATRIC UC	SUBCUT	PEN IJ KIT	Y
adalimumab	HUMIRA(CF) PEN PSOR-UV-ADOL HS	SUBCUT	PEN IJ KIT	Y
secukinumab	COSENTYX SENSOREADY (2 PENS)	SUBCUT	PEN INJCTR	Y
secukinumab	COSENTYX SENSOREADY PEN	SUBCUT	PEN INJCTR	Y
secukinumab	COSENTYX UNOREADY PEN	SUBCUT	PEN INJCTR	Y
etanercept	ENBREL SURECLICK	SUBCUT	PEN INJCTR	Y
secukinumab	COSENTYX (2 SYRINGES)	SUBCUT	SYRINGE	Y
secukinumab	COSENTYX SYRINGE	SUBCUT	SYRINGE	Y
etanercept	ENBREL	SUBCUT	SYRINGE	Y
adalimumab	HUMIRA	SUBCUT	SYRINGEKIT	Y
adalimumab	HUMIRA(CF)	SUBCUT	SYRINGEKIT	Y
adalimumab	HUMIRA(CF) PEDIATRIC CROHN'S	SUBCUT	SYRINGEKIT	Y
etanercept	ENBREL	SUBCUT	VIAL	Y
tocilizumab	ACTEMRA	INTRAVEN	VIAL	N
infliximab-axxq	AVSOLA	INTRAVEN	VIAL	N
vedolizumab	ENTYVIO	INTRAVEN	VIAL	N
infliximab-dyyb	INFLECTRA	INTRAVEN	VIAL	N
infliximab	INFLIXIMAB	INTRAVEN	VIAL	N
abatacept/maltose	ORENCIA	INTRAVEN	VIAL	N
infliximab	REMICADE	INTRAVEN	VIAL	N
infliximab-abda	RENFLEXIS	INTRAVEN	VIAL	N
rituximab-arrx	RIABNI	INTRAVEN	VIAL	N
rituximab	RITUXAN	INTRAVEN	VIAL	N
rituximab-pvvr	RUXIENCE	INTRAVEN	VIAL	N
golimumab	SIMPONI ARIA	INTRAVEN	VIAL	N
risankizumab-rzaa	SKYRIZI	INTRAVEN	VIAL	N
spesolimab-sbzo	SPEVIGO	INTRAVEN	VIAL	N
ustekinumab	STELARA	INTRAVEN	VIAL	N
rituximab-abbs	TRUXIMA	INTRAVEN	VIAL	N
natalizumab	TYSABRI	INTRAVEN	VIAL	N
tofacitinib citrate	XELJANZ	ORAL	SOLUTION	N

apremilast	OTEZLA	ORAL	TAB DS PK	N
upadacitinib	RINVOQ	ORAL	TAB ER 24H	N
tofacitinib citrate	XELJANZ XR	ORAL	TAB ER 24H	N
baricitinib	OLUMIANT	ORAL	TABLET	N
apremilast	OTEZLA	ORAL	TABLET	N
deucravacitinib	SOTYKTU	ORAL	TABLET	N
tofacitinib citrate	XELJANZ	ORAL	TABLET	N
adalimumab-atto	AMJEVITA(CF) AUTOINJECTOR	SUBCUT	AUTO INJCT	N
adalimumab-bwwd	HADLIMA PUSHTOUCH	SUBCUT	AUTO INJCT	N
adalimumab-bwwd	HADLIMA(CF) PUSHTOUCH	SUBCUT	AUTO INJCT	N
abatacept	ORENCIA CLICKJECT	SUBCUT	AUTO INJCT	N
ixekizumab	TALTZ AUTOINJECTOR	SUBCUT	AUTO INJCT	N
ixekizumab	TALTZ AUTOINJECTOR (2 PACK)	SUBCUT	AUTO INJCT	N
ixekizumab	TALTZ AUTOINJECTOR (3 PACK)	SUBCUT	AUTO INJCT	N
guselkumab	TREMFYA	SUBCUT	AUTO INJCT	N
adalimumab-aaty	YUFLYMA(CF) AUTOINJECTOR	SUBCUT	AUTOINJKIT	N
certolizumab pegol	CIMZIA	SUBCUT	KIT	N
adalimumab-afzb	ABRILADA(CF) PEN	SUBCUT	PEN IJ KIT	N
adalimumab-aacf	ADALIMUMAB-AACF(CF) PEN	SUBCUT	PEN IJ KIT	N
adalimumab-adbm	ADALIMUMAB-ADBM(CF) PEN CROHNS	SUBCUT	PEN IJ KIT	N
adalimumab-adbm	ADALIMUMAB-ADBM(CF) PEN PS-UV	SUBCUT	PEN IJ KIT	N
adalimumab-adbm	ADALIMUMAB-ADBM(CF)PEN	SUBCUT	PEN IJ KIT	N
adalimumab-fkjp	ADALIMUMAB-FKJP(CF) PEN	SUBCUT	PEN IJ KIT	N
adalimumab-adbm	CYLTEZO(CF) PEN	SUBCUT	PEN IJ KIT	N
adalimumab-adbm	CYLTEZO(CF) PEN CROHN'S-UC-HS	SUBCUT	PEN IJ KIT	N
adalimumab-adbm	CYLTEZO(CF) PEN PSORIASIS-UV	SUBCUT	PEN IJ KIT	N
adalimumab-fkjp	HULIO(CF) PEN	SUBCUT	PEN IJ KIT	N
adalimumab-aacf	IDACIO(CF) PEN	SUBCUT	PEN IJ KIT	N
adalimumab-aacf	IDACIO(CF) PEN CROHN'S-UC	SUBCUT	PEN IJ KIT	N
adalimumab-aacf	IDACIO(CF) PEN PSORIASIS	SUBCUT	PEN IJ KIT	N
tocilizumab	ACTEMRA ACTPEN	SUBCUT	PEN INJCTR	N
adalimumab-adaz	ADALIMUMAB-ADAZ(CF) PEN	SUBCUT	PEN INJCTR	N
vedolizumab	ENTYVIO PEN	SUBCUT	PEN INJCTR	N
adalimumab-adaz	HYRIMOZ(CF) PEN	SUBCUT	PEN INJCTR	N
adalimumab-adaz	HYRIMOZ(CF) PEN CROHN-UC START	SUBCUT	PEN INJCTR	N
adalimumab-adaz	HYRIMOZ(CF) PEN PSORIASIS	SUBCUT	PEN INJCTR	N
sarilumab	KEVZARA	SUBCUT	PEN INJCTR	N
golimumab	SIMPONI	SUBCUT	PEN INJCTR	N
risankizumab-rzaa	SKYRIZI PEN	SUBCUT	PEN INJCTR	N
adalimumab-aqvh	YUSIMRY(CF) PEN	SUBCUT	PEN INJCTR	N

tocilizumab	ACTEMRA	SUBCUT	SYRINGE	N
adalimumab-adaz	ADALIMUMAB-ADAZ(CF)	SUBCUT	SYRINGE	N
adalimumab-atto	AMJEVITA(CF)	SUBCUT	SYRINGE	N
adalimumab-bwwd	HADLIMA	SUBCUT	SYRINGE	N
adalimumab-bwwd	HADLIMA(CF)	SUBCUT	SYRINGE	N
adalimumab-adaz	HYRIMOZ(CF)	SUBCUT	SYRINGE	N
adalimumab-adaz	HYRIMOZ(CF) PEDIATRIC CROHN'S	SUBCUT	SYRINGE	N
tildrakizumab-asmn	ILUMYA	SUBCUT	SYRINGE	N
sarilumab	KEVZARA	SUBCUT	SYRINGE	N
anakinra	KINERET	SUBCUT	SYRINGE	N
abatacept	ORENCIA	SUBCUT	SYRINGE	N
brodalumab	SILIQ	SUBCUT	SYRINGE	N
golimumab	SIMPONI	SUBCUT	SYRINGE	N
risankizumab-rzaa	SKYRIZI	SUBCUT	SYRINGE	N
ustekinumab	STELARA	SUBCUT	SYRINGE	N
ixekizumab	TALTZ SYRINGE	SUBCUT	SYRINGE	N
guselkumab	TREMFYA	SUBCUT	SYRINGE	N
adalimumab-afzb	ABRILADA(CF)	SUBCUT	SYRINGEKIT	N
adalimumab-adbm	ADALIMUMAB-ADBM(CF)	SUBCUT	SYRINGEKIT	N
adalimumab-fkjp	ADALIMUMAB-FKJP(CF)	SUBCUT	SYRINGEKIT	N
certolizumab pegol	CIMZIA	SUBCUT	SYRINGEKIT	N
adalimumab-adbm	CYLTEZO(CF)	SUBCUT	SYRINGEKIT	N
adalimumab-fkjp	HULIO(CF)	SUBCUT	SYRINGEKIT	N
adalimumab-aacf	IDACIO(CF)	SUBCUT	SYRINGEKIT	N
adalimumab-aaty	YUFLYMA(CF)	SUBCUT	SYRINGEKIT	N
canakinumab/PF	ILARIS	SUBCUT	VIAL	N
ustekinumab	STELARA	SUBCUT	VIAL	N
risankizumab-rzaa	SKYRIZI ON-BODY	SUBCUT	WEAR INJCT	N
secukinumab	COSENTYX	INTRAVEN	VIAL	N
mirikizumab-mrkz	OMVOH	INTRAVEN	VIAL	N
bimekizumab-bkzx	BIMZELX AUTOINJECTOR	SUBCUT	AUTO INJCT	N
adalimumab-aaty	YUFLYMA(CF) AI CROHN'S-UC-HS	SUBCUT	AUTOINJKIT	N
adalimumab-aaty	YUFLYMA(CF) AUTOINJECTOR	SUBCUT	AUTOINJKIT	N
mirikizumab-mrkz	OMVOH PEN	SUBCUT	PEN INJCTR	N
bimekizumab-bkzx	BIMZELX	SUBCUT	SYRINGE	N
ozanimod hydrochloride	ZEPSOIA	ORAL	CAPSULE	N
etrasimod	VELSIPITY	ORAL	TABLET	N

Appendix 2: Selected Outcomes Used for Assessment of Disease Progression in Clinical Trials[25,61,62]

Crohn's Disease and Ulcerative Colitis		
Outcome Measure	**Domains**	**Scale and Scoring**
Inflammatory Bowel Disease Questionnaire (IBDQ) for assessing Crohn's Disease and Ulcerative Colitis	32 questions grouped into 4 domains: bowel symptoms, systemic symptoms, emotional functioning, and social functioning.	• Each domain is rated on a score of 0 to 7 points, higher scores represent better quality of life. • Total score ranges from 32 to 224. • Scores of patients in remission usually range from 170 to 190. • Scores $\leq$ 130 are associated with severely active disease. • A difference of 16 points is considered clinically significant.
Crohn's Disease Activity Score (CDAI)	Evaluation of 8 clinical factors (each weighted and summed to reach a total score) 1. Number of liquid or soft stools each day for 1 week (weight x 2) 2. Abdominal pain (graded on a severity scale of 0-3) for 1 week (weight x 5) 3. General Well-being (subjective score of 0-4) for 1 week (weight x 7) 4. Presence of complications (weight x 20) 5. Use of diphenoxylate/atropine or opiates for diarrhea (weight x 30) 6. Presence of abdominal mass (graded as 0 [none], 2 [questionable] or 5 [definite]) (weight x 10) 7. Absolute deviation of Hematocrit from 47% (men) or 42% (women) (weight x 6) 8. Percentage deviation from standard weight (weight x 1)	Each factor is weighted and summed to achieve a total score. • Scores ≤150 indicate minimal disease. • Scores >150 indicate active disease. • Scores >450 indicate extremely severe disease.

Mayo Clinic Score for Grading Activity of Ulcerative Colitis	Assessment Points **1.Stool Frequency** -Patient reporting a normal number of daily stools -3-4 more stools than normal -≥ 5 more stools than normal **2. Rectal Bleeding** -None -Blood streaks seen with stool less than half the time -Blood with most stools -Pure blood passed **3.Endoscopic Findings** -Normal or inactive colitis -Mild friability, erythema, decreased vascularity -Friability, marked erythema, absent vascular pattern, erosions -Ulcerations and spontaneous bleeding **4. Physician Global Assessment** -Normal -Mild colitis -Moderate colitis -Severe colitis	The score can range from 0-12 with higher scores indicating worse severity. A critical component of this score are the endoscopic findings. Patients with lower scores but with an endoscopic score of 2 or greater are considered more severe regardless of the final score.
Plaque Psoriasis and Psoriatic Arthritis		
Outcome Measure	**Domains**	**Scale and Scoring**
Static Physician's Global Assessment Scale (sPGA)	The static PGA is a 0-5 ordinal rating ranging from "clear" to "very severe psoriasis" as evaluated by the provider	Scale of 0 – 5: 0 = clear; scores 1–5 = increasing severity Response to therapy indicated by a score of 0 or 1
Psoriasis Symptom Inventory (PSI)	Patient reported outcome in 8 areas: 1. Itch 2. Redness 3. Scaling 4. Burning 5. Cracking 6. Stinging 7. Flaking 8. Pain of Lesions	Scale of 0-4: 0 = not at all severe, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe Score ranges from 0 – 32 Response to therapy indicated by scores < 8 with no single item rated higher than 1

Psoriasis Area and Severity Index (PASI) PASI 75 PASI 90	Measure of overall psoriasis severity and coverage on head, upper extremities, trunk, and lower extremities • Erythema • Induration • Scaling 75% Improvement in PASI score 90% Improvement in PASI score – clear or almost clear skin	Scale of 0-4: 0 is clear, 1-4 increasing severity PASI score: 1. Sum rows 1, 2, and 3 for each area of the body using 0-4 scale 2. Add an area score based on percentage involvement from 0 (clear) to 6 (≥90% coverage) 3. Multiply score as rated for each body area (0.1, 0.2, 0.3, 0.4 for head, arms, trunk, and legs, respectively) 4. Add all the scores together Composite score ranges from 0 -72: 0 = normal 72 = maximal disease
PsA Response Criteria (PsARC)	Used by the National Institute of Health Care Excellence (NICE) to continue TNF inhibitor therapy with an assessment at baseline and 12 weeks 1. 66 swollen joint score 2. 68 tender joint score 3. Patient global assessment 4. Physician global assessment	**Response** = improvement in ≥ 2 of the 4 tests: -One of which must be the joint tenderness or swelling score -No worsening in any of the four measures • **Improvement** is defined as a decrease ≥ 30% in the swollen or tender joint score and ≥1 in either of the global assessments
American College of Rheumatology (ACR) ACR 20 ACR 50	Definition of improvement in Rheumatoid Arthritis symptoms • 20% improvement in tender and swollen joint counts • 20% improvement in 3 of 5 remaining ACR core set measures ○ patient global assessment (VAS score) ○ physician global assessment (VAS score) ○ self-reported physical disability (HAQ score) ○ an acute phase reactant (ESR or CRP) ○ patient pain assessment (VAS score) • 50% improvement in tender and swollen joint counts • 50% improvement in 3 of 5 remaining ACR core set measures	20% improvement 50% improvement

ACR 70	• 70% improvement in tender and swollen joint counts 70% improvement in 3 of 5 remaining ACR core set measures	70% improvement
Dermatology Quality of Life (DQLI)	10 question patient self-reported assessment 1. How itchy has your skin been? 2. How embarrassed are because of your skin? 3. Has your skin interfered with activities? 4. Has your skin influenced the clothes you wear/ 5. Has your skin affected social activities? 6. How your skin impacted your ability to participate in a sport? 7. Has your skin prevented you from working? 8. Has your skin caused any problems with friends? 9. Has your skin impacted sexual activities? 10. How much has the treatment for your skin affected your daily activities?	Scale of 0-3: 0 not at all, 1 a little, 2 a lot, and 3 very much Interpretation of DQLI score: 0 – 1 no effect at all on patient's life 2 – 5 small effects on patient's life 6 – 10 moderate effects on patient's life 11 – 20 very large effect on patient's life 21 – 30 extremely large effect on patient's life
Abbreviations: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; HAQ = health assessment questionnaire; VAS = visual analog scale		

Appendix 3: Medline Search

Medline Search from 01/01/2022 to 01/09/2024 for UC and CD
Ovid MEDLINE(R) 1996 to December Week 5 2023; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to January 09, 2024

1	Crohn Disease/dt [Drug Therapy]	8636
2	Colitis, Ulcerative/dt [Drug Therapy]	8706
3	Adalimumab/	7077
4	Infliximab/	12182
5	Certolizumab Pegol/	742
6	Colitis, Ulcerative/ or golimumab.mp. or Tumor Necrosis Factor-alpha/	151361
7	Ustekinumab/	1862
8	Crohn Disease/ or risankizumab.mp. or Biological Products/	62094
9	Inflammatory Bowel Diseases/ or Crohn Disease/ or mirikizumab.mp.	57934
10	Protein Kinase Inhibitors/ or Janus Kinase Inhibitors/ or Colitis, Ulcerative/ or tofacitinib.mp.	86770
11	Janus Kinase Inhibitors/ or upadacitinib.mp. or Crohn Disease/	33776
12	Colitis, Ulcerative/ or Sphingosine-1-Phosphate Receptors/ or Inflammatory Bowel Diseases/ or ozanimod.mp. or Immunosuppressive Agents/	140613
13	estrasimod.mp. or Crohn Disease/ or Colitis, Ulcerative/ or Janus Kinase Inhibitors/ or Inflammatory Bowel Diseases/	76072
14	Colitis, Ulcerative/ or vedolizumab.mp. or Inflammatory Bowel Diseases/ or Crohn Disease/	74720
15	Natalizumab/	1978
16	1 or 2	15315
17	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	371979
18	16 and 17	15315
19	limit 18 to yr="2022 -Current"	2367
20	limit 19 to (guideline or meta-analysis or practice guideline or "systematic review")	134

Targeted Immune Modulators for Autoimmune Conditions

Goal(s):

- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Restrict use of targeted immune modulators to OHP-funded diagnoses in adults.
- Allow case-by-case review for members covered under the EPSDT program.
- Promote use of cost-effective products.

Length of Authorization:

- Up to 12 months

Requires PA:

- All targeted immune modulators for autoimmune conditions (both pharmacy and physician-administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Targeted Immune Modulators FDA-Approved for Ankylosing Spondylitis, Juvenile Idiopathic Arthritis, Rheumatoid Arthritis, and Non-Radiographic Axial Spondyloarthritis

Generic Name (BRAND NAME)	Ankylosing Spondylitis (AS)	Juvenile Idiopathic Arthritis (JIA)	Rheumatoid Arthritis (RA)	Non-Radiographic Axial Spondyloarthritis (NR-axSpA)
Tier 1				
Adalimumab (HUMIRA)	≥18 y	≥2 yo	≥18 yo	
Etanercept (ENBREL)	≥18 yo	≥2 yo	≥18 yo	
Tier 2				
Secukinumab (COSENTYX)	≥18 yo			≥18 yo
Tier 3				
Abatacept (ORENCIA)		≥2 yo	≥18 yo	
Anakinra (KINERET)			≥18 yo	
Baricitinib (OLUMIANT)			≥18 yo	
Canakinumab (ILARIS)		≥2 yo		
Certolizumab (CIMZIA)	≥18 yo		≥18 yo	≥18 yo
Golimumab (SIMPONI and SIMPONI ARIA)	≥18 yo	≥2 yo (SIMPONI ARIA)	≥18 yo	
Infliximab (REMICADE)	≥18 yo		≥18 yo	
Ixekizumab (TALTZ)	≥ 18 yo			≥18 yo

Generic Name (BRAND NAME)	Ankylosing Spondylitis (AS)	Juvenile Idiopathic Arthritis (JIA)	Rheumatoid Arthritis (RA)	Non-Radiographic Axial Spondyloarthritis (NR-axSpA)
Rituximab (RITUXAN)			≥18 yo	
Sarilumab (KEVZARA)		≥63 kg	≥18 yo	
Tocilizumab (ACTEMRA)		≥2 yo	≥18 yo	
Tofacitinib (XELJANZ)	≥18 yo	≥2 yo	≥18 yo	
Upadacitinib (RINVOQ)	≥18 yo	≥2 yo	≥18 yo	≥18 yo
Abbreviations: FDA = Food and Drug Administration; yo = years old				

Note: Biosimilar products are Tier 3 unless specifically mentioned

Table 2. Targeted Immune Modulators FDA-Approved for Plaque Psoriasis, Psoriatic Arthritis, and Hidradenitis Suppurativa

Generic Name (BRAND NAME)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Hidradenitis Suppurativa (HS)
Tier 1			
Adalimumab (HUMIRA)	≥18 yo	≥18 yo	≥ 12 yo
Etanercept (ENBREL)	≥4 yo	≥2 yo	
Tier 2			
Secukinumab (COSENTYX)	≥6 yo	≥2 yo	≥18 yo
Tier 3			
Abatacept (ORENCIA)		≥2 yo	
Apremilast (OTEZLA)	≥ 6 yo and ≥ 20 kg	≥18 yo	
Bimekizumab (BIMZELX)	≥18 yo		
Brodalumab (SILIQ)	≥18 yo		
Certolizumab (CIMZIA)	≥18 yo	≥18 yo	
Deucravacitinib (SOTYKU)	≥18 yo		
Golimumab (SIMPONI and SIMPONI ARIA)		≥2 yo (SIMPONI ARIA) ≥18 yo (SIMPONI)	
Guselkumab (TREMFYA)	≥18 yo	≥18 yo	
Infliximab (REMICADE)	≥18 yo	≥18 yo	
Ixekizumab (TALTZ)	≥6 yo	≥18 yo	
Risankizumab (SKYRIZI)	≥18 yo	≥18 yo	
Tildrakizumab (ILUMYA)	≥18 yo		
Tofacitinib (XELJANZ)		≥18 yo	
Upadacitinib (RINVOQ)		≥2 yo	
Ustekinumab (STELARA)	≥6 yo	≥6 yo	
Abbreviations: FDA = Food and Drug Administration; yo = years old			

Note: Biosimilar products are Tier 3 unless specifically mentioned

Table 3. Targeted Immune Modulators FDA-Approved for Crohn's Disease and Ulcerative Colitis

Generic Drug Name (BRAND NAME)	Crohn's Disease	Ulcerative Colitis
Tier 1		
Adalimumab (HUMIRA)	≥6 yo	≥5 yo (HUMIRA)
Tier 3		
Certolizumab (CIMZIA)	≥18 yo	
Etrasimod (VELSIPITY)		≥18
Golimumab (SIMPONI and SIMPONI ARIA)		≥18 yo (SIMPONI)
Infliximab (REMICADE)	≥6 yo	≥6 yo
Mirikizumab (OMVOH)		≥18 yo
Risankizumab (SKYRIZI)	≥18 yo	
Ozanimod (ZEPOSIA)		≥18 yo
Tofacitinib (XELJANZ)		≥18 yo
Upadacitinib (RINVOQ)	≥ 18 yo	≥18 yo
Ustekinumab (STELARA)	≥ 18 yo	≥18 yo
Vedolizumab (ENTYVIO)	≥18 yo	≥18 yo
Abbreviations: FDA = Food and Drug Administration; yo = years old		

Note: Biosimilar products are Tier 3 unless specifically mentioned

Table 4. Targeted Immune Modulators FDA-Approved for Other Indications not Listed in Table 1, 2 or 3

Generic Drug Name (BRAND NAME)	Other Indications
Adalimumab (HUMIRA) and biosimilars	• Uveitis (non-infectious) ≥2 yo (HUMIRA only)
Abatacept (ORENCIA)	• Acute Graft Versus Host Disease (aGVHD) ≥ 2 yo
Anakinra (KINERET)	• DIRA • COVID ≥ 18 yo (hospitalized) • NOMID
Apremilast (OTEZLA)	• Oral Ulcers associated with Behcet's Disease ≥ 18 yo
Baricitinib (OLUMIANT)	• COVID ≥ 18 yo (hospitalized)
Canakinumab (ILARIS)	• FCAS ≥4 yo • FMF ≥ 4 yo • Gout flares unresponsive to NSAIDs and colchicine ≥18 yo • HIDS ≥ 4 yo • MKD ≥ 4 yo • MWS ≥ 4 yo • Stills Disease ≥ 2 yo • TRAPS ≥ 4 yo

Generic Drug Name (BRAND NAME)	Other Indications
Rituximab (RITUXAN) and biosimilars	• BL ≥ 6 mo • BLL ≥ 6 mo • B-AL ≥ 6 mo • CLL ≥ 18 yo • DLBCL ≥ 6 mo • GPA ≥ 2yo • MPA ≥ 2 yo • NHL ≥18 yo • Pemphigus Vulgaris ≥ 18 yo (RITUXAN only)
Sarilumab (KEVZARA)	• Polymyalgia Rheumatica (PMR) ≥ 18 yo
Secukinumab (COSENTYX)	• Enthesitis-Related Arthritis (ERA) ≥ 4 yo
Spesolimab (Spevigo)	• Generalized Pustular Psoriasis Flares > 12 yo and weighing > 40 kg • Generalized Pustular Psoriasis after Flares > 12 yo and weighing > 40 kg
Tocilizumab (ACTEMRA)	• CRS ≥2 yo • COVID ≥ 18 yo (hospitalized) • GCA ≥18 yo • SSc-ILD ≥ 18 yo
Upadacitinib (RINVOQ)	• Atopic Dermatitis ≥ 12 yo
Abbreviations: BL = Burkitt Lymphoma; BLL = Burkitt-like Lymphoma; B-AL = mature B-cell acute leukemia; CLL = Chronic Lymphocytic Leukemia; COVID = Covid-19 infection; CRS = Cytokine Release Syndrome; DIRA = Deficiency of Interleukin-1 Receptor Antagonist; DLBCL = Diffuse Large B-Cell Lymphoma; FCAS = Familial Cold Autoinflammatory Syndrome; FMF = Familial Mediterranean Fever; GCA = Giant Cell Arteritis; GPA = Granulomatosis with Polyangiitis (Wegener's Granulomatosis); HIDS: Hyperimmunoglobulin D Syndrome; MKD = Mevalonate Kinase Deficiency; mo = months old; MPA = Microscopic Polyangiitis; MWS = Muckle-Wells Syndrome; NHL = Non-Hodgkin's Lymphoma; NOMID = Neonatal Onset Multi-Systemic Inflammatory Disease; NSAIDs = non-steroidal anti-inflammatory drugs; SSc-ILD = Systemic Sclerosis-Associated Interstitial Lung Disease; TRAPS = Tumor Necrosis Factor Receptor Associated Periodic Syndrome; yo = years old	

Table 5. First-Line Conventional Therapy Recommended for Select Conditions

Conditions	Recommended Conventional Therapy Prior To A Targeted Immune Modulator
Arthritis (Juvenile Idiopathic, Psoriatic, Rheumatoid)	• DMARD therapy: Methotrexate, leflunomide, sulfasalazine or hydroxychloroquine for ≥ 6 months; AND • Concurrent DMARD therapy with plans to continue concomitant use. Biologic therapy is recommended in combination with DMARDs (e.g. methotrexate) for those who have had inadequate response with DMARDs.
Atopic Dermatitis	• Moderate to high potency topical corticosteroid (e.g., clobetasol, desoximetasone, desonide, mometasone, betamethasone, halobetasol, fluticasone, or fluocinonide), in combination with a topical calcineurin inhibitor (e.g., tacrolimus) for at least 4 weeks OR • Oral immunomodulator therapy (e.g., cyclosporine, methotrexate, or azathioprine) for at least 8 weeks
Crohn's Disease	• Mercaptopurine, methotrexate, or azathioprine for ≥6 months
Generalized Pustular Psoriasis	• Acitretin, methotrexate, or cyclosporine for ≥ 3 months
Hidradenitis Suppurativa (HS)	• 90-day trial of conventional HS therapy (e.g. oral antibiotics)

Conditions	Recommended Conventional Therapy Prior To A Targeted Immune Modulator
Plaque Psoriasis	• Topical high potency corticosteroid (e.g., betamethasone dipropionate 0.05%, clobetasol propionate 0.05%, fluocinonide 0.05%, halcinonide 0.1%, halobetasol propionate 0.05%; triamcinolone 0.5%) for a minimum of 4 weeks; AND • At least one other topical agent: calcipotriene, tazarotene, anthralin for a minimum of 8 weeks; AND • Phototherapy for at least 8 weeks; AND • At least one other systemic therapy: acitretin, cyclosporine, or methotrexate for at least 16 weeks
Ulcerative Colitis	• 5-aminosalicylate products, mercaptopurine, or azathioprine for ≥ 6 months
Abbreviations: DMARD=Disease Modifying Anti-Rheumatic Drug; HS=Hidradenitis Suppurativa	

Table 6. FDA-recommended Baseline Safety Assessments for Sphingosine 1-Phosphate Receptor Modulators

	Negative Pregnancy Test	LFTs	CBC with lymphocyte count	Ophthalmic Exam	Baseline ECG (see notes)	Skin Exam for Malignancy	Varicella Zoster Antibodies
Etrasimod (VELSIPITY)	X	X	X	X	X	X	X
Ozanimod (ZEPOSIA)	X	X	X	X	X		X
Abbreviations: CBC=complete blood count; ECG=electrocardiogram; FDA =Food and Drug Administration; LFTs = liver function tests							

Sphingosine 1-Phosphate Receptor Modulators Clinical Notes:

- Patients on antiarrhythmics, beta-blockers or calcium channel blockers or with risk factors for bradycardia (h/o MI, age >70 yrs., electrolyte disorder, hypothyroidism) may be more prone to development of symptomatic bradycardia and should be initiated on etrasimod or ozanimod with caution. A cardiology evaluation should be performed before considering treatment in patients with significant QT prolongation, heart disease, heart failure, history of cardiac arrest or myocardial infarction, cerebrovascular disease, and uncontrolled hypertension, a history of with second-degree Mobitz type II or higher AV block, sick-sinus syndrome, or sinoatrial heart block.
- An ophthalmology evaluation should be repeated 3-4 months after etrasimod or ozanimod initiation with subsequent evaluations based on clinical symptoms.

Approval Criteria	
1. What diagnosis is being treated?	Record ICD-10 code.

Approval Criteria		
2. Is the diagnosis funded by OHP? Notes: A. Mild-to-moderate psoriasis, plaque psoriasis, and atopic dermatitis are unfunded, severe forms are funded. B. Mild Hidradenitis Suppurativa (HS) is unfunded, moderate-to-severe HS (e.g., Hurley Stage II or III) is funded. C. Alopecia areata is unfunded. Psoriasis and atopic dermatitis are severe in nature when resulting in functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's DLQI ≥ 13 (or severe score on other validated tool) AND one or more of the following: • At least 10% body surface area involvement; OR • Hand, foot, face, or mucous membrane involvement?	**Yes:** Go to # 4	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP. For current age < 21 years: Go to #3.
3. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny, medical necessity.
4. Is the request for a drug FDA-approved for this condition and age as defined in Table 1,2,3 or 4 above?	**Yes:** Go to #6~~5~~	**No:** Go to #5~~Deny; medical appropriateness~~
5. Is there documentation of 1) inadequate response, contraindication or intolerance to FDA-approved targeted immune modulators AND 2) prescribing by, or in consultation with, a relevant specialist for the condition?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Has the patient been annually screened for latent or active tuberculosis and if positive, started tuberculosis treatment? *(Note: this requirement does not apply to requests for apremilast.)	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness. If patient meets all other criteria, may approve once for up to 3 months to allow time for screening for ongoing therapy to avoid interruptions in care.
7. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #8
8. Is there documentation of one of the following: • Treatment failure or inadequate response to conventional treatment in outlined Table 5 OR • contraindication or intolerance to first-line conventional treatments outlined in Table 5 OR • request is for a condition not outlined in Table 5?	**Yes:** Go to #9 Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No**: Pass to RPh. Deny; medical appropriateness
9. Is the request for a preferred Tier 1 product in Table 1, 2 or 3?	**Yes:** Go to #11	**No:** Go to #10

Approval Criteria		
10. Is there documentation that therapy with an agent from each of the lower tiers would be inappropriate? Note: documentation could include inadequate response after ≥3 months with at least one product from each lower tier, contraindication or intolerance to products from each lower tier, or lack of products FDA-approved for the requested indication in lower tiers. Message: Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Go to #11	**No**: Pass to RPh. Deny; medical appropriateness
11. Is the request for upadacitinib for severe atopic dermatitis?	**Yes:** Go to #12	**No:** Go to #13
12. Has the provider submitted baseline assessment for the severity of atopic dermatitis: Eczema Area and Severity Index score (EASI 50) OR Dermatology Life Quality Index (DLQI) OR Investigators Global Assessment (IGA) score?	**Yes:** Document date of baseline assessment and results here_____	**No:** Pass to RPh. Deny; medical appropriateness
13. Is the request for a JAK inhibitor (e.g., tofacitinib, baricitinib, or upadacitinib)?	**Yes:** Go to #14	**No:** Go to #15

Approval Criteria		
14. Is the patient currently on other biologic therapy or on a potent immunosuppressant like azathioprine, tacrolimus OR cyclosporine? Note: Tofacitinib, baricitinib, and upadacitinib may be used concurrently with methotrexate or other nonbiologic DMARD drugs. Tofacitinib, baricitinib, or upadacitinib are not recommended to be used in combination with other JAK inhibitors, biologic DMARDs, azathioprine, or cyclosporine.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve baricitinib or upadacitinib for up to 6 months. Approve tofacitinib for up to 6 months at a maximum dose of 10 or 11 mg daily for Rheumatoid Arthritis OR 10 mg twice daily for 8 weeks then 5 or 10 mg twice daily for Ulcerative Colitis
15. Is the prescription for a sphingosine 1-phosphate receptor modulator (etrasimod or ozanimod)?	**Yes:** Go to #16	**No:** Go to #18
16. Have baseline safety assessments been completed as outlined in **Table 6**?	**Yes:** Go to #17	**No:** Pass to RPh. Deny; medical appropriateness.
17. Does the patient have preexisting cardiac disease, risk factors for bradycardia, or is on an anti-arrhythmic, beta-blocker, or calcium channel blocker?	**Yes:** Go to #17	**No:** Go to #18
18. Has the patient had a cardiology consultation before initiation (see clinical notes attached to **Table 6**)?	**Yes:** Go to #19	**No:** Pass to RPh. Deny; medical appropriateness.
19. Duration of initial approval based on indication	AS, Plaque psoriasis, RA, AD: 6 months HS: 12 weeks UC/Crohn's: 12 months Other: length of treatment or 1 year, whichever is longer	

Renewal Criteria		
1. Is the request to renew therapy for atopic dermatitis?	**Yes:** Go to #2	**No:** Go to #3
2. Have the patient's symptoms improved with upadacitinib therapy? • at least a 50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started, OR • at least a 4-point reduction in the Dermatology Life Quality Index (DLQI) from when treatment started, OR • at least a 2-point improvement on the Investigators Global Assessment (IGA) score?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the request for continuation of adalimumab or secukinumab to treat moderate-to-severe Hidradenitis Suppurativa in an adult?	**Yes:** Go to #4	**No:** Go to #5
4. Has the patient had clear evidence of response to adalimumab therapy as evidenced by: • a reduction of 25% or more in the total abscess and inflammatory nodule count, AND • no increase in abscesses and draining fistulas.	**Yes:** Approve for an additional 12 weeks of therapy	**No:** Pass to RPh. Deny; medical appropriateness.
5. Has the patient been adherent to both biologic and DMARD therapy (if DMARD therapy has been prescribed in conjunction with the biologic therapy)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient's condition improved as assessed by the prescribing provider and provider attests to patient's improvement?	**Yes:** Approve for 12 months. Document baseline assessment and provider attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

Natalizumab (Tysabri®)

Goal(s):

- Approve therapy for covered diagnosis which are supported by the medical literature.

Length of Authorization:

- Up to 12 months

Requires PA:

- Natalizumab (Tysabri®)

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Has the patient been screened for John Cunningham (JC) Virus?	**Yes:** Go to #3	**No:** Pass to RPH; Deny for medical appropriateness
3. Does the patient have a diagnosis of relapsing multiple sclerosis (CIS, RRMS, or SPMS)?	**Yes:** Go to #4	**No:** Go to #6
4. Has the patient failed trials for at least 2 drugs indicated for the treatment of RRMS?	**Yes:** Document drug and dates trialed: 1._____(dates) 2._____(dates) Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
5. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Approve for 12 months	**No:** Pass to RPH; Deny for medical appropriateness.
6. Does the patient have Crohn's Disease?	**Yes:** Go to #7	No: Pass to RPH; Deny for medical appropriateness.
7. Has the patient been screened for latent or active tuberculosis and if positive, started tuberculosis treatment?	**Yes:** Go to #8	**No:** Pass to RPH; Deny for medical appropriateness**.**
8. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication to conventional therapy? • AND • Has the patient tried and failed a 3-month trial of Humira?	**Yes:** Approve for up to 12 months. Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness.

P&T / DUR Action: *8/24 (DM); 10/21 (DM);10/20; 11/17*
Implementation: *TBD; 1/1/18*