Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCOTH021.1224	**MISCELLANEOUS PRODUCTS** **MEDICALLY INFUSED THERAPEUTIC IMMUNOMODULATORS (TIMs)** See Table 1 for Applicable Medications
Effective Date: 2/1/2025	**Review/Revised Date**: 01/17, 02/17, 03/17, 09/17, 01/17, 03/18, 05/18, 11/18, 01/19, 03/19, 09/19, 12/19, 01/20, 09/20, 05/21, 09/21, 11/21, 03/22, 08/22, 09/22, 09/23, 02/24, 05/24, 08/24, 11/24 (snm)
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Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Commercial

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-approved indications not otherwise excluded from the benefit. Drug Compendia supported indications may be covered.

REQUIRED MEDICAL INFORMATION:
1. For **all requests**, the patient must have an FDA labeled indication for the requested agent or use to treat the indication is supported in drug compendia (such as the American Hospital Formulary Service-Drug Information (AHFS-DI) or Truven Health Analytics’ DRUGDEX® System). Exception: biosimilar products may be covered for all FDA-approved indications that the innovator product has been granted.

AND

2. The requested agent will not be given concurrently with another therapeutic immunomodulator (TIMs) agent or apremilast (Otezla®)

AND

3. One of the following:
    a. For patients already established on the requested TIMs agent:
        i. Documentation of response to therapy (such as slowing of disease progression or decrease in symptom severity and/or frequency)
        ii. Requests for infliximab products Remicade® and Avsola® will require documentation of failure, intolerance, or contraindication to the preferred infliximab products Inflectra® AND Renflexis® in addition the indication-specific criteria below. Accepted contraindications include: contraindications listed in the package

insert or a documented allergic reaction to an ingredient found only in the preferred biosimilar product(s).

iii. Note: Medications obtained as samples, coupons, or any other method of obtaining medications outside of an established health plan benefit are NOT considered established on therapy.

b. Patients not established on the requested TIMs agent must meet ALL of the following criteria (note: if indication is not listed below, the requested drug may be covered if it is a FDA approved indication for the requested drug):

i. Requests for infliximab products Remicade® and Avsola® will require documentation of failure, intolerance, or contraindication to the preferred infliximab products Inflectra® AND Renflexis® in addition the indication-specific criteria below. Accepted contraindications include: contraindications listed in the package insert or a documented allergic reaction to an ingredient found only in the preferred biosimilar product(s).

ii. For moderate to severe **ulcerative colitis:**

1) Preferred infliximab products (Inflectra® and Renflexis®) or vedolizumab (Entyvio®) may be covered
2) For non-preferred agents: documentation of trial, failure, intolerance, or contraindication to a preferred infliximab product (Inflectra® or Renflexis®) or vedolizumab (Entyvio®)

iii. For moderate to severe **Crohn's disease**:

1) Preferred infliximab products (Inflectra® and Renflexis®) or vedolizumab (Entyvio®) may be covered
2) For non-preferred agents: documentation of trial, failure, intolerance, or contraindication to a preferred infliximab product (Inflectra® or Renflexis®) or vedolizumab (Entyvio®)

iv. For **rheumatoid arthritis**:

1) For all agents: Documentation of trial and failure, intolerance, or contraindication to at least one oral disease modifying anti-rheumatic agent (DMARD) (such as methotrexate, leflunomide, hydroxychloroquine, sulfasalazine)
2) Preferred infliximab products (Inflectra® and Renflexis®) may be covered
3) For non-preferred agents: documentation of trial, failure, intolerance, or contraindication to a preferred infliximab product (Inflectra® or Renflexis®)

v. For moderate to severe **plaque psoriasis:**

1) For all agents: Documentation of trial and failure, intolerance, or contraindication to at least one conventional therapy (such as methotrexate, tazarotene, topical corticosteroids, calcitriol)
2) Preferred infliximab products (Inflectra® and Renflexis®) may be covered
3) For non-preferred agents: documentation of trial, failure, intolerance, or contraindication to a preferred infliximab product (Inflectra® or Renflexis®)

vi. For **psoriatic arthritis**:
1) For all agents: Documentation of trial and failure, intolerance, or contraindication to at least one conventional therapy (such as methotrexate, leflunomide, sulfasalazine)
2) Preferred infliximab products (Inflectra® and Renflexis®) may be covered
3) For non-preferred agents: documentation of trial, failure, intolerance, or contraindication to a preferred infliximab product (Inflectra® or Renflexis®)

vii. For **ankylosing spondylitis**:
1) Preferred infliximab products (Inflectra® and Renflexis®) may be covered
2) For non-preferred agents: documentation of trial, failure, intolerance, or contraindication to a preferred infliximab product (Inflectra® or Renflexis®)

viii. For **juvenile idiopathic arthritis**:
1) For all agents: A one-month trial (unless contraindicated or intolerant) of previous therapy with either oral non-steroidal anti-inflammatory drugs (NSAIDs) OR an oral disease-modifying anti-rheumatic agent (DMARD) (such as methotrexate, leflunomide, sulfasalazine)
2) Preferred tocilizumab products (Actemra® or Tyenne®) may be covered
3) For non-preferred agents: documentation of trial, failure, intolerance, or contraindication to a preferred tocilizumab product (Actemra® or Tyenne®)

ix. For **non-radiographic axial spondyloarthritis**:
1) For all agents: Patient has objective signs of inflammation noted by an elevation of C-reactive protein (CRP) above the upper limit of normal and/or sacroiliitis on magnetic resonance imaging (MRI)

x. For **giant cell arteritis**:

1) For all agents: Documentation of trial and failure, intolerance, or contraindication to at least one conventional therapy (such as systemic corticosteroid therapy)
2) Preferred tocilizumab products (Actemra® or Tyenne®) may be covered
3) For non-preferred agents: documentation of trial, failure, intolerance, or contraindication to a preferred tocilizumab product (Actemra® or Tyenne®)

xi. For **immune checkpoint inhibitor related toxicities**:
1) Preferred infliximab products (Inflectra® and Renflexis®) may be covered when one of the following is met:
   i. Mild diarrhea or colitis if persistent or progressive symptoms and positive lactoferrin/calprotectin
   ii. Moderate to severe diarrhea or colitis unresponsive to high-dose systemic corticosteroids
   iii. Moderate to severe pneumonitis if no improvement after 48 hours of high-dose systemic corticosteroids
   iv. Severe (stage 3) kidney injury or elevated serum creatinine if toxicity remains greater than stage 2 after 4-6 weeks of corticosteroids
   v. Myocarditis if unresponsive to high-dose systemic corticosteroids
   vi. Moderate, severe, or life-threatening inflammatory arthritis unresponsive to corticosteroids or anti-inflammatory agents
   vii. Grade 1-4 uveitis that is refractory to high-dose systemic corticosteroids

xii. For **sarcoidosis**:
1) Preferred infliximab products (Inflectra® or Renflexis®) may be covered when one of the following is met:
   i. Trial and failure, contraindication, or intolerance to corticosteroids (such as prednisone, methylprednisolone)
   ii. Trial and failure, contraindication, or intolerance to one immunosuppressant (such as methotrexate, cyclophosphamide, azathioprine)

Note:
- Conventional therapy requirements may be waived if the patient has previously used another therapeutic immunomodulator agent OR apremilast (Otezla®) for the same indication.

- Conventional therapy and preferred agent requirements may be waived with clinically appropriate medical rationale.

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
Age must be appropriate based on FDA-approved indication

PRESCRIBER RESTRICTIONS:
- Rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, non-radiographic axial spondyloarthritis: must be prescribed by, or in consultation with, a rheumatologist
- Psoriasis: must be prescribed by, or in consultation with, a dermatologist
- Psoriatic arthritis: must be prescribed by, or in consultation with, a dermatologist or rheumatologist
- Inflammatory Bowel Disease: must be prescribed by, or in consultation with, a gastroenterologist
- Systemic sclerosis-associated interstitial lung disease: must be prescribed by, or in consultation with, a pulmonologist or rheumatologist
- Giant cell arteritis: must be prescribed by, or in consultation with, a rheumatologist or neurologist
- Immune checkpoint inhibitor related toxicity: must be prescribed by, or in consultation with, an oncologist, gastroenterologist, pulmonologist, ophthalmologist or rheumatologist
- Sarcoidosis: must be prescribed by, or in consultation with a pulmonologist, ophthalmologist, neurologist, cardiologist, rheumatologist or dermatologist

COVERAGE DURATION:
- For immune checkpoint inhibitor related toxicity: Authorization will be approved for three months
- For all other indications: Authorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes

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Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale,

formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

Table 1. Therapeutic Immunomodulators (TIMs) covered by this policy

BILLING GUIDELINES AND CODING:

CODES◊		
Preferred Agents		
Q5103	Injection, infliximab-dyyb, biosimilar, (Inflectra), 10 mg	Inflectra®
Q5104	Injection, infliximab-abda, biosimilar, (Renflexis), 10 mg	Renflexis®
J3380	Injection, vedolizumab, intravenous, 1 mg	Entyvio®
Secondary Preferred Agents		
J3262†	Injection, tocilizumab, 1 mg	Actemra® IV
Q5135†	Injection, tocilizumab-aazg (Tyenne), biosimilar, 1 mg	Tyenne®
*Non-Preferred Agents*ŧ		
J1745	Injection, infliximab, excludes biosimilar, 10 mg	Remicade®
Q5121	Injection, infliximab-axxq, biosimilar, (Avsola), 10 mg	Avsola®
J3247	Injection, secukinumab, intravenous, 1 mg	Cosentyx® IV
J0129†	Injection, abatacept, 10 mg (code may be used for medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)	Orencia® IV
J3245	Injection, tildrakizumab, 1 mg	Ilumya®
J1602	Injection, golimumab, 1 mg, for intravenous use	Simponi Aria®
J0717	Injection, certolizumab pegol, 1 mg (code may be used for medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)	Cimzia® lyophilized powder vial
Q5133	Injection, tocilizumab-bavi (Tofidence), biosimilar, 1 mg	Tofidence®
Agents Indicated for Induction Dosing Only		
J1628†	Injection, guselkumab, 1 mg	Tremfya® Vial*
J2267†	Injection, mirikizumab-mrkz, 1 mg	Omvoh® Vial*
J2327†	Injection, risankizumab-rzaa, intravenous, 1 mg	Skyrizi® Vial**

J3358	Ustekinumab, for intravenous injection, 1 mg	Stelara® Vial***
ADMINISTRATION◊		
96365	Ther/proph/diag iv inf init	
96366	Ther/proph/diag iv inf addon	
96372	Ther/proph/diag inj sc/im	
96374	Ther/proph/diag inj iv push	
96413	Chemo iv infusion 1 hr	
96415	Chemo iv infusion addl hr	
MODIFIERS†		
-JA	Administered Intravenously	
-JB	Administered Subcutaneously	
-JW	Drug Amount Discarded/Not Administered to Any Patient	

*intravenous mirikizumab-mrkz and intravenous guselkumab are indicated for three induction doses for ulcerative colitis. Subcutaneous guselkumab is eligible for coverage and is considered a preferred product under the pharmacy benefit. Subcutaneous mirikizumab-mrkz is eligible for coverage and is considered a non-preferred product under the pharmacy benefit. Medical benefit induction doses will be covered upon approval of a pharmacy benefit prior authorization.
**intravenous risankizumab-rzaa is indicated for three induction doses for Crohn's disease and ulcerative colitis. Subcutaneous risankizumab-rzaa is eligible for coverage and is considered a preferred product under the pharmacy benefit. Medical benefit induction doses will be covered upon approval of a pharmacy benefit prior authorization.
***intravenous ustekinumab is indicated for a one-time induction dose for Crohn's disease and ulcerative colitis. Subcutaneous ustekinumab is eligible for coverage and is considered a preferred self-administered product under the pharmacy benefit. Medical benefit induction doses will be covered upon approval of a pharmacy benefit prior authorization.
ŧAny self-administered TIMs agent that is requested for coverage through the medical benefit will be subject to requirements outlined in this policy.
† Must be billed with the JA modifier for the intravenous infusion of the drug or billed with the JB modifier for the subcutaneous injection form of administration
◊ Coding/Administration Notes:
• The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
• HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

INTRODUCTION:

Therapeutic Immunomodulators (TIMs) have become standard of care in patients with moderate to severe, chronic inflammatory diseases where conventional

therapies have not been adequate. These agents work by targeting specific steps in the inflammatory and immune cascade.

FDA APPROVED INDICATIONS:

Table 2. Infusible therapeutic immunomodulators (TIMs) and their respective FDA-approved Indications. FDA approvals listed below are for adult patients, unless otherwise indicated.

Drug	MOA	RA	CD	UC	Ps	PsA	AS	Other
abatacept (Orencia®)	T-cell inhibitor	X				X[1]		PJIA (age 6+) aGVHD (age 2+)
certolizumab (Cimzia®)	Anti-TNF	X	X		X	X	X	NRAS PJIA (age 2+)
guselkumab (Tremfya®)	IL-23 inhibitor			X[2]				
golimumab IV (Simponi Aria®)	Anti-TNF	X				X (age 2+)	X	PJIA (age 2+)
infliximab (Remicade®)	Anti-TNF	X	X (age 6+)	X (age 6+)	X	X	X	
infliximab-dyyb (Inflectra®)	Anti-TNF	X	X (age 6+)	X (age 6+)	X	X	X	
infliximab-abda (Renflexis®)	Anti-TNF	X	X (age 6+)	X (age 6+)	X	X	X	
infliximab-axxq (Avsola®)	Anti-TNF	X	X (age 6+)	X (age 6+)	X	X	X	
mirikizumab-mrkz (Omvoh®)	IL-23 inhibitor			X[2]				
risankizumab-rzaa (Skyrizi® IV)	IL-23 inhibitor		X[3]	X[3]				
secukinumab (Cosentyx® IV)	IL-17A inhibitor					X	X	NRAS
tildrakizumab-asmn (Ilumya®)	IL-23 inhibitor				X			
tocilizumab (Actemra®)	IL-6 inhibitor	X						GCA PJIA/SJIA (age 2+) CRS (age 2+)
tocilizumab-aazg (Tyenne®)	IL-6 inhibitor	X						GCA PJIA/SJIA (age 2+)
tocilizumab-bavi (Tofidence®)	IL-6 Inhibitor	X						GCA, PJIA/SJIA (age 2+)

Drug	MOA	RA	CD	UC	Ps	PsA	AS	Other
ustekinumab (Stelara® IV)	IL-12/23 inhibitor		X[4]	X[4]				
vedolizumab (Entyvio®)	α4β7 inhibitor		X	X				

[1] Intravenous abatacept is only indicated for use in adults with psoriatic arthritis. The subcutaneous injection is approved for use in pediatric patients aged 2 years and above.
[2] Intravenous mirikizumab-mrkz and intravenous guselkumab are indicated for three induction doses for ulcerative colitis
[3] Intravenous risankizumab-rzaa is indicated for three induction doses for Crohn's disease and ulcerative colitis
[4]Intravenous ustekinumab is indicated for a one-time induction dose for Crohn's disease and ulcerative colitis
Abbreviations: MOA = mechanism of action; RA = rheumatoid arthritis; SJIA = Systemic juvenile idiopathic arthritis; CD = Crohn's disease; UC = ulcerative colitis; Ps = psoriasis; PsA = psoriatic arthritis; AS = ankylosing spondylitis; GCA = giant cell arteritis; PJIA = Polyarticular Juvenile Idiopathic Arthritis; CRS = cytokine release syndrome; SSc-ILD = systemic sclerosis-associated interstitial lung disease; NRAS = non-radiographic axial spondyloarthritis; aGVHD = acute graft versus host disease

POSITION STATEMENT:

Preferred use of biosimilar medically infused therapeutic immunomodulators

Biosimilars have been approved for use in the United States for several disease states that are currently treated with therapeutic immunomodulators. The United States Food and Drug Administration (FDA) defines a biosimilar as a "biological product that is highly similar to and had no clinically meaningful differences from an existing FDA-approved reference product." The Companies have chosen to favor the use of biosimilar products to provide quality clinical care to our members in the most cost-effective manner.

Infliximab

There are currently three approved biosimilars for infliximab: Inflectra® (infliximab-dyyb), Renflexis® (infliximab-abda), and Avsola® (infliximab-axxq). These agents have been FDA approved for all indications that the reference product (Remicade®) has been approved for. Therefore, it is clinically appropriate to use these agents instead of Remicade®. Additionally, there have been several moderate-to-high quality studies that support non-medical switching from Remicade® to infliximab biosimilars.

The NOR-SWITCH trial was a prospective, randomized double-blind study of 482 patients with inflammatory diseases in Norway. Disease states included in this study were: Crohn's disease (CD), ulcerative colitis (UC), spondylarthritis, rheumatoid arthritis, psoriatic arthritis, and chronic plaque psoriasis. This study included patients who had been treated on the reference drug Remicade® for an average of 6.9 years before switching to the biosimilar Inflectra®. Inflectra® was shown to be non-inferior to Remicade® when switching after at least six months of Remicade treatment. There were no significant differences between the groups in terms of safety,

objective measures of disease activity, infliximab trough levels, or immunogenicity (anti-drug antibodies). There was a discontinuation rate of 4% for the Remicade® group and 3% for the Inflectra® group. A notable limitation of the NOR-SWITCH study is that it was not powered to make conclusions about treatment outcomes in the individual indications that were studied, so it is possible that outcomes for certain subgroups may differ. To address this limitation, the authors conducted an open-label extension (OLE) and further subgroup analysis of the inflammatory bowel disease cohorts of the original NOR-SWITCH study. In the OLE, 100 patients who had been in the Remicade® arm of the initial study were switched in an unblinded fashion to Inflectra®. The author's found no difference in clinical outcomes with this open-label switch, adjusted risk of disease worsening with switch to Inflectra for Crohn's disease 7.9% (95% CI –5.2 to 21) and ulcerative colitis 12.4% (-0.1 to 25). Both CD and UC outcomes had wide confidence intervals due to the low number of disease worsening events that occurred. Overall, the NOR-SWITCH study and subsequent open-label extension demonstrates that non-medical change of therapy from Remicade® to a biosimilar is not expected to have an inferior outcome to continuing Remicade®. [2,3]

Bergqvist et al conducted a prospective, observational, open-label study switching 313 consecutive patients receiving Remicade® for inflammatory bowel disease to Inflectra®. This was a multi-center study performed in County of Skåne, Sweden that was funded by a variety of non-industry sponsored grants. All but one of these patients was in the maintenance phase of therapy (i.e., there was one patient still in the induction phase of therapy) and the average time on Remicade® was 4.6 years (range 0.4-16.6 years) for CD and 3.6 years (range 0.2-9.6 years) for UC. At baseline, 33.8% of CD patients and 28.4% of UC patients had clinical disease activity, although no patients would have been considered to have relapsed disease. Comparisons were made between baseline and follow-up clinical disease scores [Harvey-Bradshaw Index (CD) and Simple Clinical Colitis Activity Index (UC)], objective biomarkers [e.g., fecal calprotectin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), etc.], and patient quality of life (Short Health Scale composite scores). The authors found no differences between groups after switching to Inflectra®. In a similar analysis to NOR-SWITCH, 14.0% of patients in the CD group and 13.8% in the UC group had clinical worsening after the switch. This is lower than what was reported in NOR-SWITCH and acts to refute non-inferiority concerns some have expressed regarding NOR-SWITCH. The overall number of patients in remission at baseline increased from 68.2% to 78.9% for CD and 66.2% to 71.6% for UC; these were not statistically significant results.[4]

The DANBIO registry study observed the effects of a nationwide non-medical switch from Remicade® to Inflectra® in Denmark. Patients (n=802) were identified as

switching from Remicade® to Inflectra®; these patients had an average treatment duration of 6.8 years on Remicade®. The authors found no differences in clinical outcomes between the three months before and after the mandated switch. There were similar one-year retention rates between the Inflectra® switch group and a historic Remicade® cohort, 84.1% (95% CI 81.3-86.5) and 86.2% (95% CI 84.8-88.8), respectively. The authors note that compared to the blinded NOR-SWITCH study, the discontinuation rate was higher in this analysis possibly due to the "nocebo" effect in addition to loss of efficacy and side effects. The nocebo effect is the negative counterpart to the placebo effect wherein an active therapy or sham therapy causes a negative outcome based on psychological factors (e.g., negative expectations associated with a change in therapy).[5]

Smolen *et al* conducted a randomized, double-blind, switching study as a continuation of a phase III study of Renflexis® in patients with moderate-to-severe rheumatoid arthritis. Patients (n=396) who completed the initial study which randomized 1:1 initial treatment with Renflexis® vs Remicade® agreed to participate in the follow-up switching study. In the switching study, patients who received Remicade® in the initial study (n=195) were randomized to receive either continued Remicade® (n=101) or switched to Renflexis® (n=94) at week 54 of treatment. Clinical outcomes, safety, and immunogenicity were followed through week 78. Overall, no differences were found between the groups for any of the measured efficacy, safety, or immunogenicity outcomes.[6]

Based on the above moderate-to-high quality studies, a switch from Remicade® to an infliximab biosimilar is expected to have similar clinical efficacy, safety, and immunogenic outcomes as remaining on Remicade®, even in patients who have been long established on Remicade®. Therefore, in the absence of a contraindication, adverse event, or clinical failure of the preferred biosimilar infliximab agents, it is appropriate to transition members from Remicade® to more cost-effective formulations of infliximab.

Inflammatory Bowel Disease

Crohn's Disease (CD)

Based on the available evidence and national practice guidelines, TIMs are effective agents in inducing and maintaining remission in severe, active CD. These agents are typically used when conventional therapies (e.g., corticosteroids, mesalamine, 6-MP and azathioprine) have failed to induce remission. Overall, there is insufficient direct comparative evidence for the efficacy of TIMs in the treatment of severe, active CD; all FDA approved agents have shown to be superior to placebo and are considered to have comparable efficacy.

The American Gastroenterological Association (AGA), in their 2021 guidelines, defines moderate to severe luminal Crohn's disease as any of the following:

- CDAI score of at least 220
- High risk of adverse disease-related complications, such as surgery, hospitalizations, and disability based on a combination of structural damage, inflammatory burden, and impact on quality of life

The AGA recommends the use of infliximab, adalimumab, ustekinumab, or vedolizumab over certolizumab for the induction of remission in patients without previous use of TIMs agents. In primary non-responders to TNF agents, they recommend use of ustekinumab to induce remission (vedolizumab may be considered). For those that loss response to infliximab, they recommend adalimumab or ustekinumab to induce remission (vedolizumab may be considered). For patients with moderate to severe disease, biologic therapy is recommended to induce remission instead of 5-aminosalicylates and/or corticosteroids.[7]

Ulcerative Colitis (UC)

Based on the available evidence and national practice guidelines, TIMs are effective agents in inducing and maintaining remission in moderate to severe UC. These agents are typically used when conventional therapies (e.g., aminosalicylates, topical mesalamine, corticosteroids, 6-mercaptopurine, and azathioprine) have failed to induce remission. Infliximab may be more consistently efficacious for inducing remission and mucosal healing than adalimumab. Vedolizumab is a non-anti-TNF therapy option for the treatment of UC. Overall, there is insufficient direct comparative evidence for the efficacy of TIMs in the treatment of moderate to severe UC; all FDA approved agents have shown to be superior to placebo and are considered to have comparable efficacy.

In 2020, the Institute for Clinical and Economic Review (ICER) published a report on TIMs for UC, assessing the following therapies: adalimumab, golimumab, infliximab and biosimilars, tofacitinib, and ustekinumab. All agents were found to be clinically superior than placebo, and all were found to be comparable to adalimumab. It was noted that vedolizumab was "found to produce greater rates of clinical response and remission over adalimumab, the market leader, in both patients who had used TIMs previously ("biologic-experienced") as well as those who did not ("biologic-naïve")." No agents were found to be cost-effective at current drug costs, but infliximab and its biosimilars represent the best value for money for UC.[8]

The AGA, in their 2020 guidelines, defines moderate to severely active UC as any of the following:

- Patients deemed to be at high-risk for colectomy
- Mayo Clinic Score 6–12, with Mayo Endoscopic Subscore 2 or 3

- Severely active endoscopic disease, with ulcers
- Patients with corticosteroid dependence, or refractory to oral corticosteroids

The AGA recommends infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab over no treatment; however, they suggest the use of infliximab or vedolizumab over adalimumab for the induction of remission in patients without previous use of TIMs agents. They do not recommend the use of tofacitinib in this setting, unless in a clinical trial. In primary non-responders to infliximab, they suggest use of ustekinumab or tofacitinib rather than vedolizumab or adalimumab for induction of remission.[9]

Guidelines:

- American Gastroenterological Association: http://www.gastro.org/guidelines
- American College of gastroenterology: https://gi.org/clinical-guidelines/clinical-guidelines-sortable-list/

Rheumatologic Disorders

Rheumatoid arthritis (RA)

Based on the available evidence and national practice guidelines, TIMs are effective agents in treating moderate to severe RA. These agents are typically used when non-biologic disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, have failed. There is limited direct comparative evidence for the efficacy of TIMs in the treatment of moderate to severe RA; all FDA approved agents have shown to be superior to placebo.[10]

In 2017, the Institute for Clinical and Economic Review (ICER) published a review of the Targeted Immune Modulators for Rheumatoid Arthritis. They reviewed the following therapies:

- TNFα inhibitors: adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), golimumab (Simponi® and Simponi Aria®), infliximab (Remicade®):
- CD20-directed cytolytic B-cell antibody: rituximab (Rituxan®)
- T-cell inhibitor: abatacept (Orencia®)
- IL-6 inhibitors: tocilizumab (Actemra®,), sarilumab (Kevzara™)
- JAK inhibitors: tofacitinib (Xeljanz®), baricitinib (Olumiant™)

Using a network meta-analysis, the review suggests that all agents are superior to conventional DMARD monotherapy. There have been some head-to-head trials conducted between the TIMs agents and adalimumab was found to be inferior to monotherapy with tocilizumab or sarilumab in terms of achieving clinical remission or ACR responses; these agents were rated as B+ over adalimumab (Moderate

certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit). Abatacept was given the same B+ rating over infliximab. Tofacitinib is considered more costly and less effective than adalimumab.[11]

In 2020, ICER published an updated report including newer JAK Inhibitors and biosimilars used for Rheumatoid Arthritis. The review concludes that the JAK inhibitors upadacitinib and tofacitinib are superior to conventional DMARD therapy. These agents both received an A rating over DMARDs (high certainty of substantial net health benefit) in TIM-naïve patients and B+ in TIM-experienced patients. Upadacitinib was rated B+ over adalimumab, tofacitinib was rated C (comparable) to adalimumab, and the infliximab biosimilar (Inflectra®) was rated C to Remicade® in TIM-naïve patients.[12]

Juvenile Idiopathic Arthritis (JIA), Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA)
Based on the available evidence and national practice guidelines, TIMs are effective agents in treating these conditions. There is limited and/or insufficient direct comparative evidence for the efficacy of TIMs in these conditions; all FDA approved agents have shown to be superior to placebo and are considered to have comparable efficacy.[10]

Guidelines:
- American College of Rheumatology: https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines

Dermatologic Disorders
Plaque psoriasis (Ps)
Based on the available evidence and national practice guidelines, TIMs are effective agents in treating moderate to severe plaque psoriasis and are generally initiated when standard conventional therapies (e.g., topical therapy and phototherapy) are inadequate. Low quality evidence suggests that ustekinumab, secukinumab, and ixekizumab may have better efficacy than etanercept, but there were sufficient limitations identified to render the evidence of uncertain validity. At this time, all of the preferred agents have shown to be superior to placebo and are considered to have comparable efficacy.[13,14]

Guidelines:
- American Academy of Dermatology: https://www.aad.org/practicecenter/quality/clinical-guidelines

Immune checkpoint inhibitor (ICI) related diarrhea/colitis

Diarrhea and colitis, inflammatory arthritis, and elevated serum creatinine are a few common symptoms of treatment with ICI therapy. The National Comprehensive Cancer Network (NCCN) recommends addition of infliximab when there is no response to other conventional therapy (if applicable). [15]

Table 3. Conventional Agent Prerequisites by Indication

Compendial Supported Indications	Conventional Agent Prerequisites
Rheumatoid arthritis (RA)	methotrexate leflunomide hydroxychloroquine sulfasalazine
Polyarticular juvenile idiopathic arthritis (PJIA)	methotrexate leflunomide sulfasalazine
Psoriasis (PS)	methotrexate topical corticosteroids coal tar products anthralin calcipotriene calcitriol acitretin tazarotene cyclosporine methoxsalen tacrolimus pimecrolimus PUVA (phototherapy)
Psoriatic arthritis	methotrexate leflunomide sulfasalazine
Uveitis	difluprednate oral prednisone periocular/intraocular glucocorticoid injection Accept but do not offer: azathioprine, mycophenolate, methotrexate, cyclosporine, tacrolimus, cyclophosphamide
Giant Cell Arteritis	Systemic corticosteroid therapy

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Appendix 1. Contraindication(s) for TIMs agents

TIMs Agent	Contraindication(s)
Abatacept (Orencia®)	None
Certolizumab (Cimzia®)	History of hypersensitivity reaction to certolizumab pegol or to any of the excipients. Reactions have included angioedema, anaphylaxis, serum sickness, and urticaria
Golimumab (Simponi Aria®)	None
Infliximab (Remicade®) and infliximab biosimilars	Doses > 5 mg/kg in moderate to severe heart failure; hypersensitivity reaction to infliximab, its inactive components, or to any murine proteins
Mirikizumab-mrkz (Omvoh®)	History of serious hypersensitivity reaction to mirikizumab-mrkz or any of the excipients
risankizumab-rzaa (Skyrizi® Vial)	History of serious hypersensitivity reaction to risankizumab-rzaa or any of the excipients
Tildrakizumab-asmn (Ilumya®)	Previous serious hypersensitivity reaction to tildrakizumab or to any of the excipients
Tocilizumab (Actemra®)	Hypersensitivity to Actemra®
Ustekinumab (Stelara®)	Clinically significant hypersensitivity to ustekinumab or to any of the excipients
Vedolizumab (Entyvio®)	Known serious or severe hypersensitivity reaction to Entyvio® or any of its excipients