Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCOTH021M.1221	**MISCELLANEOUS PRODUCTS** **MEDICALLY INFUSED THERAPEUTIC IMMUNOMODULATORS (TIMs)** See Table 1 for Applicable Medications
Effective Date: 1/1/2022 **Robert Gluckman, M.D.** **Chief Medical Officer**	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, 04/20, 09/20, 05/21, 07/21, 9/21, 11/21 (JLS) P&T Committee Meeting Date: 02/17, 02/17(cv), 03/17(cv), 04/17, 02/18, 03/18 (cv), 06/18, 12/18, 02/19, 04/19, 06/19, 10/19, 12/19 (cv), 02/20, 06/20, 10/20, 10/20 (off-cycle), 06/21, 08/21, 10/21, 10/21 (CV), 12/21 Original Effective Date: 02/17 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 12

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

APPLIES TO:
Medicare Part B

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 MEDICIAL 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 (i.e., American Hospital Formulary Service-Drug Information (AHFS-DI) or Truven Health Analytics’ DRUGDEX® System.)

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 within the previous year: Documentation of response to therapy (e.g., slowing of disease progression or decrease in symptom severity and/or frequency)

b. Patients not established on the requested TIMs agent (new starts), must meet ALL of the following indication-specific criteria:
   i. Requests for non-preferred 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.
   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 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®) may be covered
      2. For non-preferred agents: documentation of trial, failure, intolerance, or contraindication to a preferred infliximab product (Inflectra® or Renflexis®)
   iv. For **Rheumatoid Arthritis**:
      1. For all agents: Documentation of trial and failure, intolerance, or contraindication to at least one conventional therapy (e.g., methotrexate, leflunomide, hydroxychloroquine, sulfasalazine)
      2. 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 (e.g., methotrexate, tazarotene, topical corticosteroids, calcitriol)
      2. 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 (e.g., methotrexate, leflunomide, hydroxychloroquine, sulfasalazine)

2. For non-preferred agents: documentation of trial, failure, intolerance, or contraindication to a preferred infliximab product (Inflectra® or Renflexis®)

vi. 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®)

vii. For **giant cell arteritis**: Tocilizumab (Actemra®) may be approved with documentation of trial and failure, intolerance, or contraindication to at least one conventional therapy (e.g., systemic corticosteroid therapy)

viii. For **systemic sclerosis (SSc-ILD)**, tocilizumab (Actemra®) may be covered if the patient has interstitial lung disease, as evidence by high-resolution computed tomography (HRCT)

ix. For **immune checkpoint inhibitor related diarrhea/colitis**, a preferred infliximab products (Inflectra® and Renflexis®) may be covered if the following criteria are met:
1. Documentation of severe diarrhea/colitis (G3-4)
2. Documentation of inadequate response to a 1-2 day trial of intravenous methylprednisolone

EXCLUSION CRITERIA:
Combination therapy with another therapeutic immunomodulator (TIM) agent or apremilast (Otezla®).

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

PRESCRIBER RESTRICTIONS: Must be prescribed by, or in consultation with, a specialist for the respective indication, such as:
- Rheumatoid arthritis, ankylosing spondylitis: 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
- Giant Cell Arteritis: must be prescribed by, or in consultation with, a rheumatologist or neurologist

- Systemic sclerosis-associated interstitial lung disease: must be prescribed by, or in consultation with, a pulmonologist or rheumatologist
- Immune checkpoint inhibitor related diarrhea/colitis: must be prescribed by, or in consultation with, an oncologist or gastroenterologist

COVERAGE DURATION:
For immune checkpoint inhibitor related diarrhea/colitis: 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.

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.

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

Drug	HCPCS Code
Preferred Agents	
Infliximab-dyyb (Inflectra®)	Q5103
Infliximab-abda (Renflexis®)	Q5104
vedolizumab (Entyvio®) for ulcerative colitis	J3380
Non-Preferred Agents[‡]	
Infliximab (Remicade®)	J1745
Infliximab-axxq (Avsola®)	Q5121

tocilizumab (Actemra®)	J3262
vedolizumab (Entyvio®) for indication(s) other than ulcerative colitis	J3380
abatacept (Orencia®)	J0129
tildrakizumab-asmn (Ilumya®)	J3245
golimumab IV (Simponi Aria®)	J1602
ustekinumab (Stelara®)*	J3358

*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 product under the pharmacy benefit

ŧAny self-administered TIMs agent that is requested for coverage through the medical benefit will be subject to requirements outlined in this policy.

FDA APPROVED INDICATIONS:

Table 2. Infusible therapeutic immunomodulators (TIMs) and their respective FDA-approved Indications

Drug	MOA	RA	CD	UC	Ps	PsA	AS	Other
abatacept (Orencia®)	T-cell inhibitor	X				X		PJIA (age 2+)
golimumab IV (Simponi Aria®)	Anti-TNF	X				X (age 2+)	X	
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	
tildrakizumab-asmn (Ilumya®)	IL-23 inhibitor				X			

Drug	MOA	RA	CD	UC	Ps	PsA	AS	Other
tocilizumab (Actemra®)	IL-6 inhibitor	X						GCA, PJIA/SJIA (age 2+), CRS (age 2+), SSc-ILD
ustekinumab (Stelara® IV)	IL-12/23 inhibitor		X[1]	X[1]				
vedolizumab (Entyvio®)	α4β7 inhibitor		X	X				

[1]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

POSITION STATEMENT:
Due to lack of comparative clinical trials with TIMs agents, comparisons between agents must be based on indirect comparative evidence.

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.

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.

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.

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.

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™)

Newer agents, such as upatacitinib (rinvoq®) were not included in this review.

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.

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.

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 FDA approved agents have shown to be superior to placebo and are considered to have comparable efficacy.

Guidelines:

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

Immune checkpoint inhibitor (ICI) related diarrhea/colitis

Diarrhea and colitis are common symptoms of treatment with ICI therapy. This side effect can present as watery diarrhea, cramping, and fecal urgency. The National Comprehensive Cancer Network (NCCN) recommends that for moderate diarrhea/colitis (G2), ICI therapy be held and the patient be given prednisone/methylprednisolone at 1 mg/kg/day. If there is no improvement in 2-3 days, increase steroids to 2 mg/kg/day and consider addition of infliximab. For patients with severe diarrhea/colitis (G3-4), hold ICI therapy (discontinue for G4), consider whether inpatient care is necessary to provide adequate supportive care, and start prednisone/methylprednisolone at 2 mg/kg/day. If no improvement in two

days, consider addition of infliximab. Vedolizumab may be considered in patients that have infliximab-refractory diarrhea/colitis.

REFERENCE/RESOURCES:

1. Relevant package inserts
2. Institute for Clinical and Economic Review (ICER). Rheumatoid Arthritis: Final Report. Available at https://icer-review.org/material/ra-final-report/ (Accessed September 16, 2020)
3. American College of Rheumatology (ACR). ACR Guideline for the Treatment of Rheumatoid Arthritis, 2015. Available at https://www.rheumatology.org/Portals/0/Files/ACR%202015%20RA%20Guideline.pdf (Accessed September 16, 2020)
4. Oregon State University Drug Use Research & Management Program. Drug Class Update: Targeted Immune Modulators for Autoimmune Diseases. Available at https://www.orpdl.org/durm/meetings/meetingdocs/2021_10_07/finals/BiologicsAutoimmune_ClassUpdate.pdf (Accessed September 14, 2021)
5. ICER. Rheumatoid Arthritis: An assessment of JAK inhibitors. Available at https://icer.org/assessment/rheumatoid-arthritis-2019/ (Accessed September 14, 2021)
6. ICER. An assessment of treatments for ulcerative colitis. Available at https://icer.org/assessment/ulcerative-colitis-2020/ (Accessed September 14, 2021)
7. National Comprehensive Cancer Network (NCCN). NCCN Guidelines Management of Immunotherapy-Related Toxicities Version 3.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf (Accessed September 14, 2021)

Appendix 1. Contraindication(s) for TIMs agents

TIMs Agent	Contraindication(s)
Abatacept (Orencia®)	None
Golimumab (Simponi Aria®)	None
Infliximab (Remicade®)	Doses > 5 mg/kg in moderate to severe heart failure; hypersensitivity reaction to Remicade®, its inactive components, or to any murine proteins
Infliximab-abda (Renlfexis®)	Doses >5 mg/kg in moderate to severe heart failure; previous severe hypersensitivity reaction to infliximab products or known hypersensitivity to inactive components of Renflexis® or to any murine proteins

TIMs Agent	Contraindication(s)
Infliximab-dyyb (Inflectra®)	Doses >5 mg/kg in moderate to severe heart failure; Previous severe hypersensitivity reaction to infliximab products, or known hypersensitivity to inactive components of Inflectra® or to any murine proteins
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

Appendix 2. Conventional Agent Prerequisites by Indication

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

FDA Labeled Indications	Conventional Agent Prerequisites
	cyclosporine, tacrolimus, cyclophosphamide
Giant Cell Arteritis	Systemic corticosteroid therapy