Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCOTH016O.0224	**MISCELLANEOUS AGENTS** **THERAPEUTIC IMMUNOMODULATORS (TIMs)** See Table 1 for Applicable Medications
Effective Date: 4/1/2024	**Review/Revised Date**: 01/17, 08/17, 9/17, 01/18, 05/18, 07/18, 08/1, 11/18, 10/19, 3/19, 4/19, 08/19, 09/19, 01/20, 08/20, 09/20, 01/21, 05/21, 09/21, 11/21, 06/22, 09/22, 01/23, 05/23, 09/23, 12/23, 02/24 (BS)
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Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 25	

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:
Medicaid

POLICY CRITERA:

COVERED USES:
Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services when all applicable indication-specific criteria below are met. The Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit provides comprehensive and preventive health care services for children and adolescents up to their 21st birthday who are enrolled in Medicaid. Management of unfunded conditions falls under this benefit when they impact the ability to grow, develop or participate in school and the applicable indication-specific criteria below are met.

REQUIRED MEDICAL INFORMATION:
1. For **all requests**, the patient must have an FDA labeled indication for the requested agent and is a covered indication according to the Prioritized List of Health Care Services.

AND

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

AND

3. One of the following:
    a. For patients established on the requested therapeutic immunomodulator, the following criteria must be met. 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.

i. For hidradenitis suppurativa, continuation of adalimumab therapy may be covered with clear evidence of response, defined as BOTH of the following:
   1) A reduction of 25% or more in the total abscess and inflammatory nodule count, AND
   2) No increase in abscesses and draining fistulas

ii. For rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, or psoriatic arthritis:
   1) Documentation that patient is adherent to both TIMs agent and DMARD (if DMARD therapy has been prescribed in conjunction with the biologic therapy)
   2) Documentation of response to therapy (such as slowing of disease progression or decrease in symptom severity and/or frequency)

iii. Requests for non-preferred infliximab products (Remicade® or Avsola®) or non-preferred adalimumab products will require failure, intolerance, or contraindication to the preferred infliximab biosimilar products (Inflectra® **AND** Renflexis®) or preferred adalimumab product (Humira®), respectively. 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).

iv. For all other indications: Documentation of response to therapy (such as slowing of disease progression or decrease in symptom severity and/or frequency)

b. Patients not established on the requested therapeutic immunomodulator must meet the following indication-specific criteria:

i. Requests for non-preferred infliximab products (Remicade® or Avsola®) or non-preferred adalimumab products will require failure, intolerance, or contraindication to the preferred infliximab biosimilar products (Inflectra® **AND** Renflexis®) or preferred adalimumab product (Humira®), respectively, in addition to 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 **rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, or psoriatic arthritis**, all the following criteria (1-3) must be met:
    1) Use of disease-modifying anti-rheumatic drugs (DMARDs):
        a) Documented inadequate response to at least one of the following disease-modifying antirheumatic drugs (DMARDs) after at least six months of therapy: methotrexate, leflunomide, sulfasalazine or hydroxychloroquine
        OR
        b) Documented intolerance or contraindication to all of the above DMARDs (methotrexate, leflunomide, sulfasalazine and hydroxychloroquine)
    2) Documentation that the patient is currently using a DMARD and will continue concomitant use (unless contraindicated)
    3) Preferred products (Humira®, Enbrel®, infliximab biosimilars Inflectra® and Renflexis®) may be covered. For non-preferred TIMs agent:
        a) Documented adequate trial and failure (after at least three months of therapy), intolerance or contraindication to at least one of the following preferred TIMs agents: adalimumab (Humira®), etanercept (Enbrel®), or preferred infliximab biosimilar (Inflectra® or Renflexis®)

iii. For **inflammatory bowel diseases** (Crohn's disease, ulcerative colitis), all the following criteria must be met:
    1) Preferred products [(Humira®, infliximab biosimilars (Inflectra® and Renflexis®), or vedolizumab] may be covered. For non-preferred TIMs agent: documented adequate trial and failure (after at least three months of therapy), intolerance or contraindication to at least **two** of the following TIMs agents:
        a) Adalimumab (Humira®)
        b) Preferred infliximab biosimilar (Inflectra® or Renflexis®)
        c) Vedolizumab (Entyvio®)

iv. For **plaque psoriasis**, all the following criteria (1-3) must be met:
    1) Patient must have severe disease, as defined by both of the following:
        a) Documentation of functional impairment as indicated by Dermatology Life Quality Index (DLQI) score of at

least 11, Children's Dermatology Life Quality Index (CDLQI) score of at least 13, or severe score on other validated tool

b) At least one of the following:
   i. At least 10% of body surface area involved
   ii. Hand, foot, face, or mucous membrane involvement

2) Documented adequate trial and failure (after at least three months of therapy), intolerance or contraindication to each of the following first-line agents:
   a) Topical high-potency corticosteroids (such as betamethasone 0.05%, clobetasol 0.05%, fluocinonide 0.05%, halcinonide 0.1%, halobetasol propionate 0.05%, triamcinolone 0.5%)
   b) Another topical agent (such as calcipotriene, tazarotene)
   c) Phototherapy
   d) Systemic therapy (such as methotrexate, cyclosporine)
3) Preferred products (Humira®, Enbrel®, infliximab biosimilars Inflectra® and Renflexis®) may be covered. For non-preferred TIMs agent: Documented adequate trial and failure (after at least three months of therapy), intolerance or contraindication to one of the following preferred agents: Enbrel®, Humira® or preferred infliximab biosimilar (Inflectra® or Renflexis®)

v. For **atopic dermatitis**, upadacitinib (Rinvoq®) may be covered if all the following criteria (1-3) are met:
   1) Patient must have severe disease, as defined by both of the following:
      a) Documentation of functional impairment as indicated by Dermatology Life Quality Index (DLQI) score of at least 11, Children's Dermatology Life Quality Index (CDLQI) score of at least 13, or severe score on other validated tool
      b) At least one of the following:
         i. At least 10% of body surface area involvement
         ii. Hand, foot, face, or mucous membrane involvement

2) Documentation of inadequate efficacy, intolerable side effects, or contraindication to a four-week trial of at least one of the following:
    a) A combination of moderate to high potency topical corticosteroid and a topical non-steroidal agent. See Appendix 4 for potency classifications of topical corticosteroids
    b) Oral immunomodulator (such as cyclosporine, methotrexate, oral corticosteroid)

i. For **ankylosing spondylitis**, preferred agents (Humira®, infliximab biosimilars Inflectra® and Renflexis®, or Enbrel®) may be covered:
    1) For non-preferred TIMs agent: Documented trial and failure (after at least three months of therapy), intolerance or contraindication to at least one of the following preferred agents: adalimumab (Humira®), etanercept (Enbrel®) or preferred infliximab biosimilar (Inflectra® or Renflexis®)

ii. For **hidradenitis suppurativa**, adalimumab (Humira®) may be covered if the following criteria are met:
    1) Documentation of moderate to severe disease (such as Hurley Stage II or Hurley Stage III)
    2) Documented inadequate response to at least one conventional therapy after 90 days of therapy (such as oral antibiotics) unless contraindicated or not tolerated

iii. For **immune checkpoint inhibitor related toxicities** a preferred infliximab product (Inflectra® or Renflexis®) may be covered if one of the following criteria are met:
    1) Moderate to severe diarrhea or colitis unresponsive to high-dose systemic corticosteroids
    2) Moderate to severe pneumonitis if no improvement after 48 hours of high-dose systemic corticosteroids
    3) Severe (stage 3) or life-threatening (stage 4) renal failure or elevated serum creatinine if toxicity remains greater than stage 2 after 4-6 weeks of corticosteroids
    4) Myocarditis if unresponsive to high-dose systemic corticosteroids
    5) Moderate, severe, or life-threatening inflammatory arthritis unresponsive to corticosteroids or anti-inflammatory agents
    6) Grade 1-4 uveitis that is refractory to high-dose systemic corticosteroids

iv. For **polymyalgia rheumatica (PMR),** sarilumab (Kevzara®) may be covered if the following criteria are met:

1) Diagnosis of PMR and documentation of the following:
    a) Age 50 years or older at disease onset AND
    b) One of the following:
        i. Bilateral shoulder or pelvic aching or stiffness lasting longer than 45 minutes and persisting for at least two weeks OR
        ii. If younger than 50 years of age and having asymmetric shoulder or pelvic pain, documentation of PMR with atypical features
    c) Documentation that similar disorders have been ruled out (such as giant cell arteritis rheumatoid arthritis, drug-induced maylgias, fibromyalgia, other muscoloskeletal disease, or other bone disease).
    d) One of the following:
        i. Indadequate response to full dose systemic systemic corticosteroid
        ii. Documented PMR flare while attempting to taper systemic corticosteroid
        iii. Intolerance or contraindication to systemic corticosteroids

v. For **sarcoidosis**, a preferred infliximab product (Inflectra® or Renflexis®) may be covered if one of the following criteria are met:
    1) Trial and failure, contraindication, or intolerance to corticosteroids (such as prednisone, methylprednisolone)
    2) Trial and failure, contraindication, or intolerance to one immunosuppressant (such as methotrexate, cyclophosphamide, azathioprine)

vi. For **all other indications**, the requested agent may be covered if FDA approved for the indication and age of the patient.

Note:

- Conventional therapy requirements may be waived if the patient has previously used another therapeutic immunomodulator agent
- Conventional therapy and preferred agent requirements may be waived with clinically appropriate medical rationale

For quantity limit exception requests (See Appendix 1 for specific quantity limits)

1. For patients already established on the requested dose and frequency, the following criteria must be met: Documentation of response to therapy with increased dosing. 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.

2. For patients not established on requested dose and frequency (such as requesting dose escalation, previous dose escalation sponsored by manufacturer not previously approved by a health plan), one of the following must be met:
    a. Requested dose is FDA-labeled for the indication. For example:
        i. For Crohn's disease: Stelara® and Skyrizi® will be approved for FDA-labeled dosing for this condition (Stelara: 90 mg every eight weeks, Skyrizi: 360 mg every eight weeks)
        ii. For hidradenitis suppurativa: Humira® will be approved for FDA-labeled dosing for this condition (40 mg once weekly)
        iii. For psoriasis: Cimzia® will be approved for FDA-labeled dosing for this condition (800 mg every four weeks)
        iv. For ulcerative colitis: Simponi® will be approved for FDA-labeled dosing for this condition (100 mg every 28 days)
    b. For requests for dose escalation in inflammatory bowel disease (such as Crohn's disease or ulcerative colitis), adalimumab 40 mg once weekly or ustekinumab 90 mg every six weeks may be covered if all of the following criteria are met:
        i. Documentation that patient initially responded to the medication, but has experienced an inadequate response, or waning of response, to the medication. Patient must have used the medication at the FDA-labeled dosing for at least six months.
        ii. Documentation of current and active inflammation on endoscopy or imaging [such as computed tomography enterography (CTE) or magnetic resonance enterography (MRE)] obtained after at least six months of treatment on the FDA-approved dosing outlined above. Results must have been obtained within the last six months prior to this request.
    c. For other disease states: requests for dose escalation are considered experimental/investigational and are not covered

EXCLUSION CRITERIA:

1. Below the line diagnoses (such as alopecia areata)

AGE RESTRICTIONS:

Age must be appropriate based on FDA-approved indication

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:

- Prior Authorization: Authorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes
- Quantity Limitation: Initial authorization will be approved for six months. Reauthorization will be approved for one year.
    - Exception: Authorization for FDA-approved dosing above the quantity limit 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 for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

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.

FDA APPROVED INDICATIONS:

Table 1. Therapeutic immunomodulators (TIMs) requiring prior authorization 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 (age 2+)		PJIA (age 2+) aGVHD (age 2+)
Adalimumab (Humira®)	Anti-TNF	X	X (age 6+)	X (age 5+)	X	X	X	Uveitis (age 2+) HS (age 12+) PJIA (age 2+)
Adalimumab-atto (Amjevita®)	Anti-TNF	X	X (age 6+)	X	X	X	X	HS PJIA (age 2+) Uveitis

Drug	MOA	RA	CD	UC	Ps	PsA	AS	Other
Adalimumab-bwwd (Hadlima®)	Anti-TNF	X	X (age 6+)	X	X	X	X	PJIA (age 2+) HS Uveitis
Adalimumab-adbm (Cyltezo®)	Anti-TNF	X	X (age 6+)	X	X	X	X	PJIA (age 2+) HS Uveitis
Adalimumab (Hulio®)	Anti-TNF	X	X (age 6+)	X	X	X	X	PJIA (age 2+) HS Uveitis
Adalimumab-adaz (Hyrimoz®)	Anti-TNF	X	X (age 6+)	X	X	X	X	PJIA (age 2+)
Adalimumab (Idacio®)	Anti-TNF	X	X (age 6+)	X	X	X	X	PJIA (age 2+) HS Uveitis
Adalimumab-aqvh (Yusimry®)	Anti-TNF	X	X (age 6+)	X	X	X	X	PJIA (age 2+) HS Uveitis
Adalimumab (Yuflyma®)	Anti-TNF	X	X (age 6+)	X	X	X	X	PJIA (age 2+) HS
Anakinra (Kineret®)	IL-1 inhibitor	X						NOMID/CAPS DIRA (age 0+)
Apremilast (Otezla®)	PDE-4 inhibitor				X	X		BD
Baricitinib (Olumiant®)	JAK Inhibitor	X						AA COVID-19
Brodalumab (Siliq®)	IL-17 inhibitor				X			
Certolizumab (Cimzia®)	Anti-TNF	X	X**		X	X	X	NRAS
Deucravacitinib (Sotyktu®)	TYK-2 inhibitor				X			
Etanercept (Enbrel®)	Anti-TNF	X			X (age 4+)	X (age 2+)	X	PJIA (age 2+)
Golimumab (Simponi®/ Simponi Aria®)	Anti-TNF	X		X*		X (age 2+)	X	PJIA (age 2+)
Guselkumab (Tremfya®)	IL-23 inhibitor				X	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	
Ixekizumab	IL-17				X	X	X	NRAS

Drug	MOA	RA	CD	UC	Ps	PsA	AS	Other
(Taltz®)	inhibitor				(age 6+)			
Risankizumab-rzaa (Skyrizi®)	IL-23 Inhibitor		X		X	X		
Sarilumab (Kevzara®)	IL-6 inhibitor	X						PMR
Secukinumab (Cosentyx®)	IL-17 inhibitor				X (age 6+)	X (age 2+)	X	NRAS ERA (age 4+) HS
Tildrakizumab-asmn (Ilumya®)	IL-23 inhibitor				X			
Tocilizumab (Actemra®)	IL-6 inhibitor	X						GCA CRS (age 2+) PJIA (age 2+) SJIA (age 2+) SSc-ILD COVID-19
Tofacitinib (Xeljanz® and Xeljanz XR®)	JAK inhibitor	X		X		X	X	PJIA (age 2+)
Upadacitinib (Rinvoq®)	JAK inhibitor	X	X	X		X	X	AD (age 12+) NRAS
Ustekinumab (Stelara®)	IL-12/23 inhibitor		X**	X*	X (age 6+)	X (age 6+)		
Vedolizumab (Entyvio®)	α4β7 inhibitor		X**	X*				

*Does not have FDA indication for pediatric ulcerative colitis
**Does not have FDA indication for pediatric Crohn's disease
Abbreviations: MOA = mechanism of action; JAK = Janus kinase; IL = interleukin; PDE-4 = Phosphodiesterase 4; TYK-2 = Tyrosine kinase-2; RA = rheumatoid arthritis; SJIA = Systemic juvenile idiopathic arthritis; PJIA = Polyarticular Juvenile Idiopathic Arthritis CD = Crohn's disease; UC = ulcerative colitis; Ps = psoriasis; PsA = psoriatic arthritis; AS = ankylosing spondylitis; HS = Hidradenitis Suppurativa; NOMID/CAPS = neonatal onset multi-systemic inflammatory disease/Cryopyrin-Associated Periodic Syndromes; BD = oral ulcers associated with Behçet's Disease; GCA = giant cell arteritis; CRS = cytokine release syndrome; NRAS = non-radiographic axial spondyloarthritis; DIRA = Deficiency of Interleukin-1 Receptor Antagonist; SSc-ILD = systemic sclerosis-associated interstitial lung disease; AD = atopic dermatitis; aGVHD = Prophylaxis of acute graft versus host disease; ERA = Enthesitis-related arthritis; AA = alopecia areata; PMR = polymyalgia rheumatica

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. Some systematic reviews and meta-analyses suggest that infliximab and adalimumab may have superior efficacy over other TIMs agents from indirect comparisons. 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.[10]

Dose escalation requests are common for this disease state. Adalimumab (Humira®) maintenance dosing is every other week, but evidence suggests that once weekly dosing can be helpful for patients that have not achieved a full response to every other week dosing (this dosing regimen is covered per policy). Ustekinumab (Stelara®) is covered at every eight weeks for CD, Two recent retrospective evaluations of patients that were dose escalated to every four weeks

have been published.[8,9] However, these studies are of low-quality; retrospective in nature (non-standardized treatment protocols and follow-up procedures) and did not adequately compare changes seen with dose escalation to that of standard therapy. In addition, surrogate markers were used for determining disease activity (lack of robust endoscopic evaluations). Endoscopy/colonoscopy and/or imaging are used to measure active inflammation and can be useful in determining whether dose escalation is reasonable. Per the American College of Gastroenterology (ACG) 2018 Clinical Guideline on the Management of Crohn's Disease in Adults, endoscopy/colonoscopy may show evidence of ulcerations and granulomatous inflammation. Common forms of imaging in Crohn's disease are computed tomography enterography (CTE) and magnetic resonance enterography (MRE). Signs of active inflammation through on CTE consist of mucosal enhancement, mesenteric hypervascularity, and mesenteric fat stranding. In MRE, the signs are similar to CTE, but also can detect wall enhancement, mucosal lesions, and T2 hypersensitivity.[11]

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 (6-MP) 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.

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.[12]

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.[13]

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 and/or insufficient 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.[14]

In 2017, 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.[15]

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.[16]

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.[14]

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. Secukinumab and brodalumab may have better efficacy than ustekinumab with reference to Psoriasis Area Severity Index (PASI) 90 and 100. Brodalumab has significant safety concerns that limit its usability. At this time, all FDA approved agents have shown to be superior to placebo and are considered to have comparable efficacy.[17]

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

Atopic *Dermatitis (AD):*
Atopic dermatitis (also known as eczema) is a chronic, and relapsing inflammatory skin condition that typically causes red, swollen, itchy, and dry skin (erythema, edema, pruritis, and xerosis). This can lead to breakdown of the skin barrier and skin thickening from scratching (erosions/excoriations, oozing/crusting, and lichenification). This condition occurs most frequently in young children and many young patients will have resolution of symptoms by adulthood. However, some will continue to have symptoms into adulthood and some cases start in adulthood.[18]

The American Academy of Dermatology (AAD) guidelines for the management of AD recommend topical therapies as first-line treatment options due to their efficacy and safety profiles. Topical therapies that should be tried include skin hydration with moisturizers, wet-wrap therapy techniques for flares, and eliminating/avoiding triggers. Topical corticosteroids and topical calcineurin inhibitors are recommended for both adults and children. They can be used for acute treatment (typically twice daily) and for maintenance (1-2 times per week).[18,19] For adults, topical Janus kinase (JAK) inhibitors and topical phosphodiesterase-4 (PDE-4) inhibitors are also considered strong recommendations for use in mild to moderate atopic dermatitis.[19,20] For moderate to severe AD that is not controlled with use of topical agents, the 2017 consensus statement from the American Academy of Allergy, Asthma & Immunology (AAAI) recommends dupilumab as the first-line systemic option, as it has shown to be effective and safe. Systemic immunomodulatory agents (such as cyclosporine, methotrexate) are not FDA-approved for AD and can have considerable side effects that limit maintenance therapy. Phototherapy can be used as a treatment, but is not always accessible or practical.[21] Of note, this consensus statement was published prior to the approval of upadacitinib for atopic dermatitis.

Alopecia Areata (AA):
Alopecia areata (AA) is an inflammatory autoimmune condition that causes non-scarring hair loss. The clinical presentation can vary significantly including age of onset (typically between 20-50 years of age), type of hair loss (well demarcated patch of hair loss, multiple patches, or extensive hair loss or scalp, or hair loss of entire scalp and body hair), and other manifestations (such as nail involvement). AA is often associated with spontaneous remission (hair regrowth within one year), so treatment is not typically warranted. However, this is a relapsing condition with most patients experiencing more than one episode.[22,23] This indication is not covered by the health plan, as the treatment of alopecia areata (AA) is considered cosmetic in nature and has “no direct impact on general health that justifies the use of hazardous treatments.”[23] This indication is considered “unfunded” by the Oregon Health Authority. While there are limited treatment options for AA, no treatment has been shown to improve function or reduce morbidity/mortality.[22,23]

Coverage of these products for adults with Medicaid is limited to conditions that have been designated as covered line-item numbers by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services. Per guideline note 21, severe inflammatory skin disease is defined as having functional impairment as indicated by a Dermatology Life Quality Index (DLQI) ≥11 or Children's Dermatology Life Quality Index (CDLQI) ≥13 (or severe score on other validated tool) and one or more of the following: at least 10% of body surface area involved; and/or hand, foot or mucous membrane involvement. The DLQI is a validated measure developed to provide a standard and easy process for determining the impact of skin disease on a patient's quality of life (See a sample of DLQI). The CDLQI is a questionnaire that is geared towards children and has the rate symptoms of the condition using pictorial representations (See a version of the CDLQI).[24,25]

The Medicaid Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit was introduced in 1967 as a part of the Social Security Act Amendments. The goal of the EPSDT benefit is to ensure that children under the age of 21 who are enrolled in Medicaid receive appropriate preventative, dental, mental health, and developmental specialty services. The EPSDT standard requires states to cover all medically necessary and medically appropriate treatment for children and adolescents on Medicaid, including medications, regardless of what services states provide to adults. Under EPSDT, the Prioritized List is a guidance tool for assessment of coverage. Medically appropriate and medically necessary services are defined in Oregon Administrative Rule (OAR) 410-120-000.[26]

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). [27]

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Appendix 1. Quantity limitations for self-administered medications

Drug	Quantity Limit
Abatacept (Orencia®)	4 doses per 28 days
Adalimumab (Humira®)	2 doses per 28 days
Anakinra (Kineret®)	30 syringes per 30 days
Apremilast (Otezla®)	60 tablets per 30 days
Baricitinib (Olumiant®)	30 tablets per 30 days
Brodalumab (Siliq®)	2 injections per 28 days
Certolizumab (Cimzia®)	1 kit per 28 days
Etanercept (Enbrel®)	200 mg per 28 days
Golimumab (Simponi®)	1 dose per 28 days
Guselkumab (Tremfya®)	1 dose every 56 days
Ixekizumab (Taltz®)	1 dose per 28 days
Risankizumab-rzaa (Skyrizi®)	1 dose per 84 days (syringe/pen) 2.4 mL per 56 days (on-body injector)
Sarilumab (Kevzara®)	1.66 mL (2 injections) per 28 days
Secukinumab (Cosentyx®)	300 mg per 28 days
Tildrakizumab-asmn (Ilumya®)	100 mg per 84 days
Tocilizumab (Actemra®)	4 doses per 28 days
Tofacitinib (Xeljanz® and Xeljanz XR®)	IR: 60 tablets per 30 days ER: 30 tablets per 30 days
Ustekinumab (Stelara®)	1 dose per 84 days

Appendix 2. Contraindication(s) for TIMs agents

TIMs Agent	Contraindication(s)
Abatacept (Orencia®)	None
Adalimumab (Humira®)	None
Anakinra (Kineret®)	Hypersensitivity to *E coli* proteins
Baricitinib (Olumiant®)	None
Brodalumab (Siliq®)	Crohn's disease
Certolizumab (Cimzia®)	None
Etanercept (Enbrel®)	Sepsis
Golimumab (Simponi/Simponi Aria®)	None
Guselkumab (Tremfya®)	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

TIMs Agent	Contraindication(s)
	Renflexis® or to any murine proteins
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
Ixekizumab (Taltz®)	Previous serious hypersensitivity reaction, such as anaphylaxis, to ixekizumab or to any of the excipients
Risankizumab-rzaa (Skyrizi®)	None
Sarilumab (Kevzara®)	Known hypersensitivity to sarilumab or any of the inactive ingredients.
Secukinumab (Cosentyx®)	Serious hypersensitivity reaction to secukinumab or to any of the excipients
Tildrakizumab-asmn (Ilumya®)	Serious hypersensitivity reaction to tildrakizumab or to any of the excipients
Tocilizumab (Actemra®)	Hypersensitivity to Actemra®
Tofacitinib (Xeljanz® and Xeljanz XR®)	None
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 3. Coding for medically infused therapies

Drug	HCPCS Code
Preferred Agents	
Infliximab-dyyb (Inflectra®)	Q5103
Infliximab-abda (Renflexis®)	Q5104
Non-Preferred Agents[t]	
abatacept (Orencia®)	J0129
golimumab IV (Simponi Aria®)	J1602
Infliximab (Remicade®)	J1745
Infliximab-axxq (Avsola®)	Q5121
risankizumab-rzaa (Skyrizi® Vial)	J2327
tildrakizumab-asmn (Ilumya®)	J3245
tocilizumab (Actemra®)	J3262
ustekinumab (Stelara®)	J3358
vedolizumab (Entyvio®)	J3380

Appendix 4. Potency of topical corticosteroid preparations[28]

Potency Group	Corticosteroid	Strength	Formulation
Lowest Potency	Hydrocortisone Base and Hydrocortisone Acetate	0.5%, 1.0%, 2.0%	cream, ointment, gel, lotion, solution
Low Potency	Alcometasone dipropionate	0.05%	cream, ointment
	Betamethasone valerate	0.05%	lotion
	Desonide	0.05%	cream
	Fluocinolone acetonide	0.01%	cream, oil, shampoo, solution
	Triamcinolone acetonide	0.1%	cream
Medium-Low Potency	Betamethasone dipropionate	0.05%	lotion
	Betamethasone valerate	0.1%	cream
	Betamethasone valerate	0.01%	cream, lotion
	Desonide	0.05%	lotion, ointment
	Fluocinolone acetonide	0.025%	cream
	Flurandrenolide	0.05%	cream
	Fluticasone propionate	0.05%	cream
	Hydrocortisone butyrate	0.1%	cream
	Hydrocortisone valerate	0.2%	cream
	Prednicarbate	0.1%	cream
	Triamcinolone acetonide	0.1%	lotion
Medium Potency	Betamethasone valerate	0.12%	foam
	Desoximetasone	0.05%	cream
	Fluocinolone acetonide	0.025%	ointment
	Fluocinolone acetonide	0.2%	cream
	Flurandrenolide	0.05%	ointment
	Halcinonide	0.025%	cream
	Hydrocortisone probutate	0.1%	cream
	Hydrocortisone valerate	0.2%	cream
	Mometasone furoate	0.1%	cream, lotion, solution
	Prednicarbate	0.1%	ointment
Medium-High Potency	Amcinonide	0.1%	cream, lotion
	Betamethasone valerate	0.1%	ointment
	Diflorasone diacetate	0.05%	cream
	Fluocinonide	0.05%	cream
	Fluticasone propionate	0.005%	ointment
	Halcinonide	0.1%	ointment, solution
	Triamcinolone acetonide	0.5%	cream

	Triamcinolone acetonide	0.1%	ointment
High Potency	Amcinonide	0.1%	ointment
	Betamethasone dipropionate, augmented (Diprolene®)	0.05%	cream, lotion
	Betamethasone dipropionate, unaugmented (Diprosone®)	0.05%	cream, ointment
	Desoximetasone	0.25%	cream, ointment, spray
	Desoximetasone	0.05%	gel
	Diflorasone diacetate	0.05%	ointment
	Fluocinonide	0.05%	cream, gel, ointment, solution
	Halcinonide	0.1%	cream
	Mometasone furoate	0.1%	ointment
	Triamcinolone acetonide	0.5%	ointment
Super-High Potency	Betamethasone dipropionate, augmented (Diprolene®)	0.05%	gel, ointment
	Clobetasol propionate	0.05%	cream, foam, gel, lotion, ointment, shampoo, spray
	Diflorasone diacetate	0.05%	ointment
	Fluocinonide	0.1%	cream
	Flurandrenolide	4 mcg/cm^2	tape
	Halobetasol propionate	0.05%	cream, ointment