

Policy and Procedure

PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCOTH016O.0622

MISCELLANEOUS AGENTS THERAPEUTIC IMMUNOMODULATORS (TIMs)

See [Table 1](#) for Applicable Medications

Effective Date: 8/1/2022



Robert Gluckman, M.D.
Chief Medical Officer

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 (MA)

P&T Committee Meeting Date: 02/17, 08/17, 10/17, 02/18, 06/18, 08/18, 10/18, 12/18, 02/19, 04/19, 06/19, 08/19, 10/19, 02/20, 08/20, 10/20, 02/21, 06/21, 10/21, 10/21 (CV), 12/21, 02/22 (cv), 04/22, 06/22

Original Effective Date: 03/17

Approved by: Oregon Region Pharmacy and Therapeutics Committee

Page
1 of 19

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 CRITERIA:

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.

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.

**PHARMACY PRIOR AUTHORIZATION
POLICY AND CRITERIA
ORPTCOTH0160**

**MISCELLANEOUS AGENTS
THERAPEUTIC IMMUNOMODULATORS
(TIMs)**

See [Table 1](#) for Applicable Medications

- 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, 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 (e.g., slowing of disease progression or decrease in symptom severity and/or frequency)
 - iii. Requests for non-preferred infliximab product (Remicade® or Avsola®) will require failure, intolerance, or contraindication to the preferred infliximab biosimilar products (Inflectra® **AND** Renflexis®). 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 (e.g., 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 product (Remicade® or Avsola®) will require failure, intolerance, or contraindication to the preferred infliximab biosimilar 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 **Rheumatoid Arthritis, 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

**PHARMACY PRIOR AUTHORIZATION
POLICY AND CRITERIA
ORPTCOTH0160**

**MISCELLANEOUS AGENTS
THERAPEUTIC IMMUNOMODULATORS
(TIMs)**

See [Table 1](#) for Applicable Medications

- b. Documented intolerance or contraindication to all of the above DMARDs (such as 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 (adalimumab, etanercept, 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** (e.g., Crohn's disease, ulcerative colitis), all the following criteria (1 and 2) must be met:
 1. Use of conventional immunosuppressive therapies:
 - a. Documented inadequate response to at least one of the following conventional immunosuppressive therapies for at least six months: mercaptopurine, azathioprine, or budesonide

OR

 - b. Documented intolerance or contraindication to these therapies

OR

 - c. Medical rationale is provided for escalating to biologic therapy without previous trial of conventional therapies (e.g., severity of disease activity)
 2. Preferred products [(adalimumab, 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 **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

**PHARMACY PRIOR AUTHORIZATION
POLICY AND CRITERIA
ORPTCOTH0160**

**MISCELLANEOUS AGENTS
THERAPEUTIC IMMUNOMODULATORS
(TIMs)**

See [Table 1](#) for Applicable Medications

- 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:
- At least 10% of body surface area involve
 - Hand, foot 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:
- Topical high-potency corticosteroids (e.g., betamethasone 0.05%, clobetasol 0.05%, fluocinonide 0.05%, halcinonide 0.1%, halobetasol propionate 0.05%, triamcinolone 0.5%)
 - Another topical agent (e.g., calcipotriene, tazarotene)
 - Phototherapy
 - Systemic therapy (e.g., methotrexate, cyclosporine)
3. Preferred products (adalimumab, etanercept, infliximab biosimilars Inflectra® and Renflexis®, or secukinumab) may be covered. For non-preferred TIMs agent: Documented adequate trial and failure (after at least three months of therapy), intolerance or contraindication to the following preferred agents:
- One of the following TNF inhibitor agents: adalimumab (Humira®) or preferred infliximab biosimilar (Inflectra® or Renflexis®)
- AND**
- Secukinumab (Cosentyx®)
- v. For **ankylosing spondylitis**, preferred agents (adalimumab, infliximab biosimilars Inflectra® and Renflexis®, or etanercept) may be covered:
- 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®)
- vi. For **Hidradenitis Suppurativa**, adalimumab (Humira®) may be covered if the following criteria are met:
- Documentation of moderate to severe disease (e.g., Hurley Stage II or Hurley Stage III)
 - Documented inadequate response to at least one conventional therapy after 90 days of therapy (e.g., oral antibiotics) unless contraindicated or not tolerated

**PHARMACY PRIOR AUTHORIZATION
POLICY AND CRITERIA
ORPTCOTH0160**

**MISCELLANEOUS AGENTS
THERAPEUTIC IMMUNOMODULATORS
(TIMs)**

See [Table 1](#) for Applicable Medications

- vii. 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 (e.g., 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® will be approved for FDA-labeled dosing for this condition (90 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.

**PHARMACY PRIOR AUTHORIZATION
POLICY AND CRITERIA
ORPTCOTH0160**

**MISCELLANEOUS AGENTS
THERAPEUTIC IMMUNOMODULATORS
(TIMs)**

See [Table 1](#) for Applicable Medications

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
2. Combination therapy with another therapeutic immunomodulator (TIM) agent or apremilast (Otezla®)

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

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:

**PHARMACY PRIOR AUTHORIZATION
POLICY AND CRITERIA
ORPTCOTH0160**

**MISCELLANEOUS AGENTS
THERAPEUTIC IMMUNOMODULATORS
(TIMs)**

See [Table 1](#) for Applicable Medications

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		PJIA (age 2+) aGVHD
Adalimumab (Humira®)	Anti-TNF	X	X	X*	X	X	X	Uveitis (age 2+), HS (age 12+), PJIA (age 2+)
Anakinra (Kineret®)	IL-1 inhibitor	X						NOMID/CAPS (age 0+), DIRA
Apremilast (Otezla®)	PDE-4 inhibitor				X	X		BD
Baricitinib (Olumiant®)	JAK Inhibitor	X						
Brodalumab (Siliq®)	IL-17 inhibitor				X			
Certolizumab (Cimzia®)	Anti-TNF	X	X**		X	X	X	NRAS
Etanercept (Enbrel®)	Anti-TNF	X			X (age 4+)	X	X	PJIA (age 2+)
Golimumab (Simponi®)	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	

**PHARMACY PRIOR AUTHORIZATION
POLICY AND CRITERIA
ORPTCOTH0160**

**MISCELLANEOUS AGENTS
THERAPEUTIC IMMUNOMODULATORS
(TIMs)**

See [Table 1](#) for Applicable Medications

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

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

**PHARMACY PRIOR AUTHORIZATION
POLICY AND CRITERIA
ORPTCOTH0160**

**MISCELLANEOUS AGENTS
THERAPEUTIC IMMUNOMODULATORS
(TIMs)**

See [Table 1](#) for Applicable Medications

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}

**PHARMACY PRIOR AUTHORIZATION
POLICY AND CRITERIA
ORPTCOTH0160**

**MISCELLANEOUS AGENTS
THERAPEUTIC IMMUNOMODULATORS
(TIMs)**

See [Table 1](#) for Applicable Medications

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

**PHARMACY PRIOR AUTHORIZATION
POLICY AND CRITERIA
ORPTCOTH0160**

**MISCELLANEOUS AGENTS
THERAPEUTIC IMMUNOMODULATORS
(TIMs)**

See [Table 1](#) for Applicable Medications

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

**PHARMACY PRIOR AUTHORIZATION
POLICY AND CRITERIA
ORPTCOTH0160**

**MISCELLANEOUS AGENTS
THERAPEUTIC IMMUNOMODULATORS
(TIMs)**

See [Table 1](#) for Applicable Medications

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:

**PHARMACY PRIOR AUTHORIZATION
POLICY AND CRITERIA
ORPTCOTH0160**

**MISCELLANEOUS AGENTS
THERAPEUTIC IMMUNOMODULATORS
(TIMs)**

See [Table 1](#) for Applicable Medications

- 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

**PHARMACY PRIOR AUTHORIZATION
POLICY AND CRITERIA
ORPTCOTH0160**

**MISCELLANEOUS AGENTS
THERAPEUTIC IMMUNOMODULATORS
(TIMs)**

See [Table 1](#) for Applicable Medications

In 2017, ICER published a review of the Targeted Immune Modulators for Rheumatoid Arthritis. They reviewed the following therapies:

- TNF α 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>

**PHARMACY PRIOR AUTHORIZATION
POLICY AND CRITERIA
ORPTCOTH0160**

**MISCELLANEOUS AGENTS
THERAPEUTIC IMMUNOMODULATORS
(TIMs)**

See [Table 1](#) for Applicable Medications

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.^{17,18}

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.¹⁹

REFERENCE/RESOURCES:

1. Relevant package inserts
2. Jørgensen KK, Olsen IC, Goll GL et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet*. 2017;389:2304-16.

**PHARMACY PRIOR AUTHORIZATION
POLICY AND CRITERIA
ORPTCOTH0160**

**MISCELLANEOUS AGENTS
THERAPEUTIC IMMUNOMODULATORS
(TIMs)**

See [Table 1](#) for Applicable Medications

3. Jørgensen KK, Goll GL, Sexton J. Efficacy and safety of CT-P13 in inflammatory bowel disease after switching from originator infliximab: exploratory analyses from the NOR-SWITCH main and extension trials. *BioDrugs*. 2020;34:681-94.
4. Bergqvist V, Kadivar M, Molin D et al. Switching from originator infliximab to the biosimilar CT-P13 in 313 patients with inflammatory bowel disease. *Ther Adv Gastroenterol*. 2018;11:1-13.
5. Glintborg B, Sørensen IJ, Loft AG et al. A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. *Ann Rheum Dis* 2017;76:1426-31.
6. Smolen JS, Choe JY, Prodanovic N et al. Safety, immunogenicity and efficacy after switching from reference infliximab to biosimilar SB2 compared with continuing reference infliximab and SB2 in patients with rheumatoid arthritis: results of a randomised, double-blind, phase III transition study. *Ann Rheum Dis*. 2018;77:234-40.
7. American Gastroenterological Association (AGA). AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. Available at [https://www.gastrojournal.org/article/S0016-5085\(21\)00645-4/fulltext](https://www.gastrojournal.org/article/S0016-5085(21)00645-4/fulltext) (Accessed September 14, 2021).
8. Ollech, JE, Normatov I, Peleg N et al. Effectiveness of Ustekinumab Dose Escalation in Patients With Crohn's Disease. *Clin Gastroenterol Hepatol*. 2020;S1542-3565(20)30205-6. doi: 10.1016/j.cgh.2020.02.035.
9. Kopylove U, Hanzel J, Liefferinckx C et al. Effectiveness of ustekinumab dose escalation in Crohn's disease patients with insufficient response to standard-dose subcutaneous maintenance therapy. *Aliment Pharmacol Ther*. 2020 Jul;52(1):135-142. doi: 10.1111/apt.15784.
10. American Gastroenterological Association (AGA). AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. Available at [https://www.gastrojournal.org/article/S0016-5085\(21\)00645-4/fulltext](https://www.gastrojournal.org/article/S0016-5085(21)00645-4/fulltext) (Accessed September 14, 2021).
11. American College of Gastroenterology (ACG). ACG Clinical Guideline: Management of Crohn's Disease in Adults. Available at https://journals.lww.com/ajg/Fulltext/2018/04000/ACG_Clinical_Guideline_Management_of_Crohn_s.10.aspx (Accessed September 14, 2021).
12. American Gastroenterological Association (AGA). AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis.

**PHARMACY PRIOR AUTHORIZATION
POLICY AND CRITERIA
ORPTCOTH0160**

**MISCELLANEOUS AGENTS
THERAPEUTIC IMMUNOMODULATORS
(TIMs)**

See [Table 1](#) for Applicable Medications

- Available at [https://www.gastrojournal.org/article/S0016-5085\(20\)30018-4/fulltext](https://www.gastrojournal.org/article/S0016-5085(20)30018-4/fulltext) (Accessed September 14, 2021)
13. ICER. An assessment of treatments for ulcerative colitis. Available at <https://icer.org/assessment/ulcerative-colitis-2020/> (Accessed September 14, 2021)
 14. 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)
 15. 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)
 16. ICER. Rheumatoid Arthritis: An assessment of JAK inhibitors. Available at <https://icer.org/assessment/rheumatoid-arthritis-2019/> (Accessed September 14, 2021)
 17. Oregon State University Drug Use Research & Management Program. Drug Class Update: Targeted Immune Modulators for Autoimmune Diseases. Available at https://www.orpd.org/durm/meetings/meetingdocs/2021_10_07/finals/BiologicsAutoimmune_ClassUpdate.pdf (Accessed September 14, 2021)
 18. American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF). Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. Available at [https://www.jaad.org/article/S0190-9622\(18\)33001-9/fulltext](https://www.jaad.org/article/S0190-9622(18)33001-9/fulltext). Accessed (September 14, 2021)
 19. 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.

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

**PHARMACY PRIOR AUTHORIZATION
POLICY AND CRITERIA
ORPTCOTH0160**

**MISCELLANEOUS AGENTS
THERAPEUTIC IMMUNOMODULATORS
(TIMs)**

See [Table 1](#) for Applicable Medications

Drug	Quantity Limit
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®)	150 mg per 84 days
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 <i>E coli</i> 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 (Renflexis®)	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
Infliximab-dyyb (Inflectra®)	Doses >5 mg/kg in moderate to severe heart failure; Previous severe

**PHARMACY PRIOR AUTHORIZATION
POLICY AND CRITERIA
ORPTCOTH0160**

**MISCELLANEOUS AGENTS
THERAPEUTIC IMMUNOMODULATORS
(TIMs)**

See [Table 1](#) for Applicable Medications

TIMs Agent	Contraindication(s)
	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
<i>Preferred Agents</i>	
Infliximab-dyyb (Inflectra®)	Q5103
Infliximab-abda (Renflexis®)	Q5104
<i>Non-Preferred Agents[†]</i>	
abatacept (Orencia®)	J0129
golimumab IV (Simponi Aria®)	J1602
Infliximab (Remicade®)	J1745
Infliximab-axxq (Avsola®)	Q5121
risankizumab-rzaa (Skyrizi® Vial)	J3590
tildrakizumab-asmn (Ilumya®)	J3245
tocilizumab (Actemra®)	J3262
ustekinumab (Stelara®)	J3358
vedolizumab (Entyvio®)	J3380