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Subject: Apremilast (Otezla®) Tablet

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Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Apremilast (Otezla) was approved by the US Food and Drug Administration (FDA) for the treatment of adults with active psoriatic arthritis (PsA) in March 2014 and then moderate-to-severe plaque psoriasis in September 2014. In July 2019, the indications were expanded to include the treatment of adult patients with oral ulcers associated with Behçet's Disease. The treatment of Behçet's disease was a previously granted orphan drug designation by the FDA in 2013. Apremilast, as sponsored by the innovator drug company, also was granted orphan drug designation by the FDA for the treatment of pediatric patients with ulcerative colitis in 2018. In December 2021, the plaque psoriasis indication was expanded to include mild-to-moderate disease, with the revised indication now worded as "for the treatment of adult patients with plaque psoriasis who are candidates for phototherapy or systemic therapy". Apremilast exerts its therapeutic activity through inhibition of phosphodiesterase-4 (PDE-4). PDE-4 inhibition promotes intracellular accumulation of cyclic adenosine monophosphate; this accumulation results in a downregulation of inflammatory responses and ultimately reduces inflammation. The National Comprehensive Cancer Network (NCCN) guidelines on the Management of Immunotherapy-Related-Toxicities include apremilast as a consideration for the management of immunotherapy-related moderate (10 to 30% body surface area [BSA]) psoriasis and psoriasiform diseases if not responsive to recommended treatments and severe (>30% BSA) psoriasis and psoriasiform diseases.

Psoriasis (PS)

Psoriasis (PS) is a chronic inflammatory skin condition that is often associated with systemic manifestations, especially arthritis. Diagnosis is usually clinical, based on the presence of typical erythematous scaly patches, papules, and plaques that are often pruritic and sometimes painful.

Treatment goals for psoriasis include improvement of skin, nail, and joint lesions plus enhanced quality of life.

The American Academy of Family Physicians (AAFP) categorizes psoriasis severity into mild to moderate (less than 5% of body surface area [BSA]) and moderate to severe (5% or more of BSA). The AAFP psoriasis treatment guidelines recommend basing treatment on disease severity:

- Mild to moderate (less than 5% of BSA and sparing the genitals, hands, feet, and face):
 - Candidate for intermittent therapy: topical corticosteroids, vitamin D analogs (calcipotriene and calcitriol), or tazarotene (Tazorac)
 - Candidate for continuous therapy: calcineurin inhibitors (tacrolimus and pimecrolimus)
- Severe (5% or more of BSA or involving the genitals, hands, feet, and face):
 - Less than 20% of BSA affected: vitamin D analogs (calcipotriene and calcitriol) with or without phototherapy. These agents have a slower onset of action but a longer disease-free interval than topical corticosteroids
 - 20% or more of BSA affected: systemic therapy with MTX, cyclosporine, acitretin, or biologics. Biologics are recommended for those with concomitant PsA
- Less commonly used topical therapies include non-medicated moisturizers, salicylic acid, coal tar, and anthralin

The American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) categorize psoriasis severity as limited or mild (less than 3% of BSA), moderate (3% to 10% of BSA), or severe (greater than 10% of BSA). The AAD/NPF guidelines also note that psoriasis can be considered severe irrespective of BSA when it occurs in select locations (e.g., hands, feet, scalp, face, or genital area) or when it causes intractable pruritus. The AAD psoriasis treatment guidelines recommend the following:

- Limited disease (less than 5% of BSA):
 - Topical corticosteroids are first line as either monotherapy or in conjunction with non-steroidal topical agents
 - Vitamin D analogs, calcipotriene, calcipotriol, and calcitriol, are other first line agents and are often used in combination with topical corticosteroids
 - Tazarotene is a corticosteroid sparing agent and can be used in combination with topical corticosteroids to produce a synergistic effect and longer durations of treatment benefit and remission
 - Phototherapy is another first line option for limited disease, and allows for selective targeting of localized lesions and resistant areas such as the scalp and skin folds, leaving surrounding, non-lesional skin unaffected
 - Calcineurin inhibitors (tacrolimus and pimecrolimus) may also be considered first line for intertriginous, inverse, face, and genital psoriasis
 - Systemic agents are considered second line and only for short term use
- Moderate to severe disease without PsA (more than 5% of BSA or psoriasis in vulnerable areas [e.g., face, genitals, hands, and feet] that adversely affects quality of life):

- UV-therapy is considered first line as monotherapy or in combination with acitretin or MTX
- If UV-therapy is unavailable first line therapies include MTX, cyclosporine, acitretin, and biologics
- Second line systemic agents include leflunomide, sulfasalazine, and tacrolimus
- Biologics are routinely used when one or more traditional systemic agents fail to produce adequate response, but are considered first line in patients with moderate to severe psoriasis with concomitant severe PsA

The National Psoriasis Foundation (NPF) medical board recommend a treat-to-target approach to therapy for psoriasis that include the following:

- The preferred assessment instrument for determining disease severity is BSA
- Target response after treatment initiation should be BSA $\leq 1\%$ after 3 months
- Acceptable response is either a BSA $\leq 3\%$ or a BSA improvement $\geq 75\%$ from baseline at 3 months after treatment initiation

Psoriatic Arthritis (PsA)

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease associated with psoriasis, most commonly presenting with peripheral arthritis, dactylitis, enthesitis, and spondylitis. Treatment involves the use of a variety of interventions, including many agents used for the treatment of other inflammatory arthritis, particularly spondyloarthritis and RA, and other management strategies of the cutaneous manifestations of psoriasis.

The American Academy of Dermatology (AAD) recommends initiating MTX in most patients with moderate to severe PsA. After 12 to 16 weeks of MTX therapy with appropriate dose escalation, the AAD recommends adding or switching to a TNF inhibitor if there is minimal improvement on MTX monotherapy.

The American College of Rheumatology (ACR) and the National Psoriasis Foundation (NPF) guidelines for PsA recommend a treat-to-target approach in therapy, regardless of disease activity, and the following:

- Active PsA is defined as symptoms at an unacceptably bothersome level as reported by the patient and health care provider to be due to PsA based on the presence of one of the following:
 - Actively inflamed joints
 - Dactylitis
 - Enthesitis
 - Axial disease
 - Active skin and/or nail involvement
 - Extraarticular manifestations such as uveitis or inflammatory bowel disease
- Disease severity includes level of disease activity at a given time point and the presence/absence of poor prognostic factors and long-term damage
- Severe PsA disease includes the presence of 1 or more of the following:

- Erosive disease
- Elevated markers of inflammation (ESR, CRP) attributable to PsA
- Long-term damage that interferes with function (i.e., joint deformities)
- Highly active disease that causes a major impairment in quality of life
- Active PsA at many sites including dactylitis, enthesitis
- Function limiting PsA at a few sites
- Rapidly progressive disease
- Symptomatic treatments include nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, local glucocorticoid injections
- Treatment recommendations for active disease:
 - Treatment naïve patients first line options include oral small molecules (OSM), TNF biologics, IL-17 inhibitor, and IL-12/23 inhibitor
 - OSM (i.e., methotrexate [MTX], sulfasalazine, cyclosporine, leflunomide, apremilast) should be considered if the patient does not have severe PsA, does not have severe psoriasis, prefers oral therapy, has concern over starting a biologic, or has contraindications to TNF inhibitor
 - Biologics (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor) are recommended as a first line option in patients with severe PsA and/or severe psoriasis
 - Previous treatment with OSM and continued active disease:
 - Switch to a different OSM (except apremilast) in patients without severe PsA or severe PS, contraindications to TNF biologics, prefers oral therapy OR add on apremilast to current OSM therapy
 - May add another OSM (except apremilast) to current OSM therapy for patients that have exhibited partial response to current OSM in patients without severe PsA or severe PS, contraindications to TNF biologics, or prefers oral therapy
 - Biologic (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor) monotherapy
 - Previous treatment with a biologic (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor) and continued active disease:
 - Switch to another biologic (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor, abatacept, or tofacitinib) monotherapy or add MTX to the current TNF biologic

Behcet's Disease (BD)

Behcet's disease (BD) is a type of vasculitis that involves numerous organ systems, such as the skin, mucosa, joints, eyes, veins, arteries, nervous system, and gastrointestinal system. BD runs a relapsing and remitting course and a multidisciplinary approach is necessary for optimal care. The goal of treatment is to suppress inflammatory exacerbations and recurrences to prevent irreversible organ damage.

Chronic oral ulceration can cause scarring requiring vigorous treatment to prevent oropharyngeal narrowing. The European League Against Rheumatism recommends topical measures, such as steroids, for the treatment of oral and genital ulcers. Colchicine is recommended for the prevention of recurrent mucocutaneous lesions. Patients with lesions that continue to recur despite colchicine may use immunomodulatory or immunosuppressive agents, such as azathioprine, tumor necrosis factor (TNF) inhibitors, or apremilast.

Efficacy

The efficacy of Otezla for the treatment of oral ulcers associated with BD was established in a multicenter, randomized, placebo-controlled trial. Patients were required to have active oral ulcers at the time of enrollment, have had at least 3 occurrences of oral ulcers within the previous 12 months, and have received treatment with at least one non-biologic therapy. All subjects had a history of recurrent oral ulcers that were currently active. Otezla had a greater reduction in the number of oral ulcers and patient reported ulcer pain when compared to placebo.

Safety

Otezla is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

NOTE: The self-administered products with prerequisites for certain indications are as follows:

Table 1

Disease State	Step 1		Step 2 (Directed to ONE step 1 agent)	Step 3a (Directed to TWO step 1 agents)	Step 3b (Directed to TWO agents from step 1 and/or step 2)	Step 3c (Directed to THREE step 1 agents)
	Step 1a	Step 1b (Directed to ONE TNF inhibitor) NOTE: Please see Step 1a for preferred TNF inhibitors				
Rheumatoid Disorders						
Ankylosing Spondylitis (AS)	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL	Oral: Rinvoq, Xeljanz, Xeljanz XR	N/A	SQ: Cimzia, Simponi, Taltz	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL **,

	Cosentyx, Enbrel, Hadlima, Humira					Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Nonradiographic Axial Spondyloarthritis (nr-axSpA)	SQ: Cimzia, Cosentyx	Oral: Rinvoq	N/A	SQ: Taltz	N/A	N/A
Polyarticular Juvenile Idiopathic Arthritis (PJIA)	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Enbrel, Hadlima, Humira	Oral: Xeljanz	SQ: Actemra (Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, or Humira is a required Step 1 agent)	N/A	SQ: Orencia	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Psoriatic Arthritis (PsA)	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Cosentyx, Enbrel, Humira, Hadlima, Skyrizi, Stelara, Tremfya Oral: Otezla	Oral: Rinvoq, Xeljanz, Xeljanz XR	N/A	SQ: Cimzia, Orencia, Simponi, Taltz	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Rheumatoid Arthritis	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Enbrel, Hadlima, Humira	Oral: Rinvoq, Xeljanz, Xeljanz XR	SQ: Actemra (Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, or Humira is a required Step 1 agent)	Oral: Olumiant SQ: Cimzia, Kevzara, Kineret, Orencia, Simponi	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Dermatological Disorders						
Hidradenitis Suppurativa (HS)	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Cosentyx, Hadlima, Humira	N/A	N/A	N/A	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Yuflyma**, Yusimry**

						Idacio**, Yuflyma**, Yusimry**
Psoriasis (PS)	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Cosentyx, Enbrel, Hadlima, Humira, Skyrizi, Stelara, Tremfya Oral: Otezla	N/A	N/A	SQ: Cimzia	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Bimzelx, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Siliq, Taltz, Yuflyma**, Yusimry** Oral: Sotyktu
Inflammatory Bowel Disease						
Crohn's Disease	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, Humira, Skyrizi, Stelara	Oral: Rinvoq	N/A	SQ: Cimzia (Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, or Humira are required Step 1 agents)	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Ulcerative Colitis	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, Humira, Stelara	Oral: Rinvoq, Xeljanz, Xeljanz XR	SQ: Simponi (Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, or Humira is a required Step 1 agent)	N/A	Zeposia (Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, Humira, Rinvoq, Stelara, OR Xeljanz/Xeljanz XR are required Step agents)	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Entyvio, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry** Oral: Velsipity
Other						
Uveitis	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, Humira	N/A	N/A	N/A	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**,

						Yuflyma**, Yusimry**
Indications Without Prerequisite Biologic Immunomodulators						
Alopecia Areata (AA)						
Atopic Dermatitis						
Deficiency of IL-1 Receptor Antagonist (DIRA)						
Enthesitis Related Arthritis (ERA)						
Giant Cell Arteritis (GCA)						
Neonatal-Onset Multisystem Inflammatory Disease (NOMID)	N/A	N/A	N/A	N/A	N/A	N/A
Polymyalgia Rheumatica (PMR)						
Systemic Juvenile Idiopathic Arthritis (SJIA)						
Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD)						

***Note:** A trial of either or both Xeljanz products (Xeljanz and Xeljanz XR) collectively counts as **ONE** product

****Note:** Amjevita (one of: 10 mg/0.2 mL, 20 mg/0.4 mL, 40 mg/0.8 mL), Hadlima, and Humira are required Step 1 agents

Note: Branded generic available for Cyltezo, Hulio, Hyrimoz, and Idacio and are included as a target at same step level in this program

Initiation of apremilast (Otezla) **meets the definition of medical necessity** when **ALL** of the following are met (“1” to “5”):

1. **ONE** of the following (“a”, “b”, or “c”):
 - a. Information has been provided that indicates the member has been treated with apremilast (starting on samples is not approvable) within the past 90 days
 - b. The prescriber states the member has been treated with apremilast (starting on samples is not approvable) within the past 90 days **AND** is at risk if therapy is changed
 - c. **BOTH** of the following (“i” and “ii”):
 - i. Apremilast will be used for the treatment of an indication listed in Table 2, and **ALL** of the indication-specific criteria are met
 - ii. **EITHER** of the following if the member has an FDA-approved indication (“I” or “II”)
 - I. The member’s age is within FDA labeling for the requested indication for apremilast

- II. The prescriber has provided information in support of using apremilast for the member's age
2. The prescriber is a specialist in the area of the member's diagnosis (e.g., dermatologist, rheumatologist) or has consulted with a specialist in the area of the member's diagnosis
3. Member does **NOT** have any FDA labeled contraindications to apremilast
4. Member will **NOT** be using apremilast in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Litfulo (ritlecitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Rinvoq (upadacitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]
5. **ANY** of the following ("a", "b", or "c"):
 - a. The dosage does not exceed:
 - Titration dose: Day 1: 10 mg in the morning, Day 2: 10 mg in morning and 10 mg in evening, Day 3: 10 mg in morning and 20 mg in evening, Day 4: 20 mg in morning and 20 mg in evening, Day 5: 20 mg in morning and 30 mg in evening, Day 6 and beyond: 30 mg twice daily
 - 10 mg, 20 mg & 30 mg tablet starter pack (4 week) - 1 starter kit (55 tablets)/180 days
 - Maintenance dose – 30 mg twice daily
 - QL: 30 mg tablets - 60 tablets/30 days (2 tablets/day)
 - b. The requested quantity (dose) exceeds the program quantity limit but does **NOT** exceed the maximum FDA labeled dose OR the maximum compendia-supported dose (i.e., DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a) for the requested indication, AND the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit
 - c. The requested quantity (dose) exceeds the program quantity limit and exceeds the maximum FDA labeled dose AND the maximum compendia-supported dose (i.e., DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a) for the requested indication, **AND** the prescriber has provided information in support of therapy with a higher dose for the requested indication (submitted copy required, e.g., clinical trials, phase III studies, guidelines required)

Approval duration: 12 months

Table 2

Diagnosis	Criteria
Active psoriatic arthritis (PsA)	<p>ONE of the following:</p> <ol style="list-style-type: none"> 1. The member has tried and had an inadequate response to ONE conventional agent (i.e., cyclosporine, leflunomide, methotrexate, sulfasalazine) used in the treatment of PsA for at least 3 months <p>OR</p>

	<ol style="list-style-type: none"> The member has an intolerance or hypersensitivity to ONE of the conventional agents used in the treatment of PsA <p>OR</p> <ol style="list-style-type: none"> The member has an FDA labeled contraindication to ALL of the conventional agents used in the treatment of PsA <p>OR</p> <ol style="list-style-type: none"> The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of PsA
Plaque psoriasis (PS)	<p>ONE of the following:</p> <ol style="list-style-type: none"> The member has tried and had an inadequate response to ONE conventional agent (i.e., acitretin, anthralin, calcipotriene, calcitriol, coal tar products, cyclosporine, methotrexate, pimecrolimus, PUVA [phototherapy], tacrolimus, tazarotene, topical corticosteroids) used in the treatment of PS for at least 3 months <p>OR</p> <ol style="list-style-type: none"> The member has an intolerance or hypersensitivity to ONE conventional agent used in the treatment of PS <p>OR</p> <ol style="list-style-type: none"> The member has an FDA labeled contraindication to ALL conventional agents used in the treatment of PS <p>OR</p> <ol style="list-style-type: none"> The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of PS
Behcet's disease (BD)	<p>ALL of the following:</p> <ol style="list-style-type: none"> The member has active oral ulcers associated with BD <p>AND</p> <ol style="list-style-type: none"> The member has had at least 3 occurrences of oral ulcers in the last 12 months <p>AND</p> <ol style="list-style-type: none"> ONE of the following: <ol style="list-style-type: none"> The member has tried and had an inadequate response to ONE conventional agent (i.e., topical oral corticosteroids [i.e.,

	<p>triamcinolone dental paste], colchicine, azathioprine) used in the treatment of BD</p> <p>OR</p> <p>b. The member has an intolerance or hypersensitivity to ONE conventional agent used in the treatment of BD</p> <p>OR</p> <p>c. The member has an FDA labeled contraindication to ALL conventional agents used in the treatment of BD</p> <p>OR</p> <p>d. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of BD.</p>
Other indications	The member has another FDA labeled indication or an indication supported in DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a.

Continuation of apremilast (Otezla) **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "6"):

1. An authorization or reauthorization for apremilast has been previously approved by Florida Blue
2. Member has had clinical benefit with apremilast therapy
3. The prescriber is a specialist in the area of the member's diagnosis (e.g., dermatologist, rheumatologist) or has consulted with a specialist in the area of the member's diagnosis
4. Member does **NOT** have any FDA labeled contraindications to apremilast
5. Member will **NOT** be using apremilast in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Litfulo (ritlecitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Rinvoq (upadacitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]
6. **ANY** of the following ("a", "b", or "c"):
 - a. The dosage does not exceed 30 mg twice daily
 - QL: 30 mg tablets - 60 tablets/30 days (2 tablets/day)
 - b. The requested quantity (dose) exceeds the program quantity limit but does **NOT** exceed the maximum FDA labeled dose **OR** the maximum compendia-supported dose (i.e., DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a) for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit

- c. The requested quantity (dose) exceeds the program quantity limit and exceeds the maximum FDA labeled dose **AND** the maximum compendia-supported dose (i.e., DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a) for the requested indication, **AND** the prescriber has provided information in support of therapy with a higher dose for the requested indication (submitted copy required, e.g., clinical trials, phase III studies, guidelines required)

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

Apremilast is indicated for (1) the treatment of adult patients with active psoriatic arthritis, (2) the treatment of adult patients with plaque psoriasis who are candidates for phototherapy or systemic therapy, and (3) the treatment of adult patients with oral ulcers associated with Behçet's Disease.

To reduce the risk of gastrointestinal symptoms, the following titration schedule is recommended:

- Day 1: 10 mg in the morning
- Day 2: 10 mg in morning and 10 mg in evening
- Day 3: 10 mg in morning and 20 mg in evening
- Day 4: 20 mg in morning and 20 mg in evening
- Day 5: 20 mg in morning and 30 mg in evening
- Day 6: 30 mg twice daily

Dose Adjustments

Reduce the dose to 30 mg once daily for persons with severe renal impairment (i.e., creatinine clearance less than 30 ml/min). For initial dose titration, titrate using only the morning schedule and skip evening doses. No dose adjustment is necessary in patients with hepatic impairment.

Product Availability

Apremilast is supplied as 10-, 20-, and 30-mg tablets.

PRECAUTIONS:

Boxed Warning

- None

Contraindication

- Known hypersensitivity to apremilast or any excipients in the formulation

Precautions/Warnings

- **Hypersensitivity:** Hypersensitivity reactions, including cases of angioedema and anaphylaxis, have been reported during post marketing surveillance. Avoid the use in patients with known hypersensitivity to apremilast or to any of the excipients in the formulation. If signs or symptoms of serious hypersensitivity reactions develop during treatment, discontinue apremilast and institute appropriate therapy.
- **Diarrhea, Nausea, and Vomiting:** There have been postmarketing reports of severe diarrhea, nausea, and vomiting associated with the use of apremilast. Most events occurred within the first few weeks of treatment. Monitor patients who are more susceptible to complications of diarrhea or vomiting. Patients who reduced dosage or discontinued treatment generally improved quickly. Consider dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting.
- **Depression:** Advise patients, their caregivers, and families to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes and if such changes occur to contact their healthcare provider. Carefully weigh risks and benefits of treatment with apremilast in persons with a history of depression and/or suicidal thoughts or behavior.
- **Weight Decrease:** Monitor weight regularly. If unexplained or clinically significant weight loss occurs, evaluate weight loss and consider discontinuation of apremilast.
- **Drug Interactions:** Use with strong cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended because loss of efficacy may occur.

BILLING/CODING INFORMATION:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, NOS
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ICD-10 Diagnosis Codes That Support Medical Necessity

L27.0	Generalized skin eruption due to drugs and medicaments taken internally [for immunotherapy-related psoriasis and psoriasiform diseases ONLY]
L27.1	Localized skin eruption due to drugs and medicaments taken internally [for immunotherapy-related psoriasis and psoriasiform diseases ONLY]
L27.9	Dermatitis due to unspecified substance taken internally [for immunotherapy-related psoriasis and psoriasiform diseases ONLY]
L40.0	Psoriasis vulgaris
L40.1	Generalized pustular psoriasis [for immunotherapy-related psoriasis and psoriasiform diseases ONLY]
L40.2	Acrodermatitis continua [for immunotherapy-related psoriasis and psoriasiform diseases ONLY]
L40.3	Pustulosis palmaris et plantaris [for immunotherapy-related psoriasis and psoriasiform diseases ONLY]
L40.50	Arthropathic psoriasis, unspecified
L40.51	Distal interphalangeal psoriatic arthropathy

L40.52	Psoriatic arthritis mutilans
L40.53	Psoriatic spondylitis
L40.59	Other psoriatic arthropathy
L40.8	Other psoriasis [for immunotherapy-related psoriasis and psoriasiform diseases ONLY]
L40.9	Psoriasis, unspecified [for immunotherapy-related psoriasis and psoriasiform diseases ONLY]
M35.2	Behçet's disease

REIMBURSEMENT INFORMATION:

Refer to section entitled [POSITION STATEMENT](#).

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

DEFINITIONS:

DMARDs: An acronym for disease-modifying antirheumatic drugs. These are drugs that modify the rheumatic disease processes, and slow or inhibit structural damage to cartilage and bone. These drugs are unlike symptomatic treatments such as NSAIDs that do not alter disease progression. DMARDs can be further subcategorized. With the release of biologic agents (e.g., anti-TNF drugs), DMARDs were divided into either: (1) conventional, traditional, synthetic, or non-biological DMARDs; or as (2) biological DMARDs. However, with the release of newer targeted non-biologic drugs and biosimilars, DMARDs are now best categorized as: (1) conventional synthetic DMARDs (csDMARD) (e.g., MTX, sulfasalazine), (2) targeted synthetic DMARDs (tsDMARD) (e.g., baricitinib, tofacitinib, apremilast), and (3) biological DMARDs (bDMARD), which can be either a biosimilar DMARD (bsDMARD) or biological originator DMARD (boDMARD).

Plaque psoriasis: It is the most common form of psoriasis. It affects 80 to 90% of people with psoriasis. Plaque psoriasis typically appears as raised areas of inflamed skin covered with silvery white scaly skin. These areas are called plaques.

Psoriatic arthritis: joint inflammation that occurs in about 5% to 10% of people with psoriasis (a common skin disorder). It is a severe form of arthritis accompanied by inflammation, psoriasis of the skin or nails, and a negative test for rheumatoid factor. Enthesitis refers to inflammation of entheses, the site where ligaments or tendons insert into the bones. It is a distinctive feature of PsA and does not occur with other forms of arthritis. Common locations for enthesitis include the bottoms of the feet, the Achilles' tendons, and the places where ligaments attach to the ribs, spine, and pelvis.

RELATED GUIDELINES:

[Abatacept \(Orencia\), 09-J0000-67](#)

[Adalimumab \(Humira\), 09-J0000-46](#)

[Brodalumab \(Siliq\) Injection, 09-J2000-74](#)

[Certolizumab Pegol \(Cimzia\), 09-J0000-77](#)

[Etanercept \(Enbrel\), 09-J0000-38](#)

[Golimumab \(Simponi, Simponi Aria\), 09-J1000-11](#)

[Guselkumab \(Tremfya\), 09-J2000-87](#)

[Infliximab Products \[infliximab \(Remicade\), infliximab-dyyb \(Inflectra\), and infliximab-abda \(Renflexis\)\], 09-J0000-39](#)

[Ixekizumab \(Taltz\), 09-J2000-62](#)

[Psoralens with Ultraviolet A \(PUVA\), 09-10000-16](#)

[Risankizumab \(Skyrizi\), 09-J3000-45](#)

[Secukinumab \(Cosentyx\), 09-J2000-30](#)

[Tildrakizumab-asmn \(Ilumya\), 09-J3000-04](#)

[Ustekinumab \(Stelara\), 09-J1000-16](#)

OTHER:

Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy

Abrilada (adalimumab-afzb)

Actemra (tocilizumab)

Adalimumab

Adbry (tralokinumab-ldrm)

Amjevita (adalimumab-atto)

Arcalyst (rilonacept)

Avsola (infliximab-axxq)

Benlysta (belimumab)

Bimzelx (bimekizumab-bkzx)

Cimzia (certolizumab)

Cinqair (reslizumab)

Cosentyx (secukinumab)

Cyltezo (adalimumab-adbm)

Dupixent (dupilumab)

Enbrel (etanercept)

Entyvio (vedolizumab)

Fasenra (benralizumab)

Hadlima (adalimumab-bwwd)

Hulio (adalimumab-fkjp)

Humira (adalimumab)

Hyrimoz (adalimumab-adaz)

Idacio (adalimumab-aacf)

Ilaris (canakinumab)

Ilumya (tildrakizumab-asmn)

Inflectra (infliximab-dyyb)
 Infliximab
 Kevzara (sarilumab)
 Kineret (anakinra)
 Nucala (mepolizumab)
 Omvoh (mirikizumab-mrkz)
 Orencia (abatacept)
 Remicade (infliximab)
 Renflexis (infliximab-abda)
 Riabni (rituximab-arrx)
 Rituxan (rituximab)
 Rituxan Hycela (rituximab/hyaluronidase human)
 Ruxience (rituximab-pvvr)
 Siliq (brodalumab)
 Simponi (golimumab)
 Simponi Aria (golimumab)
 Skyrizi (risankizumab-rzaa)
 Stelara (ustekinumab)
 Taltz (ixekizumab)
 Tezspire (tezepelumab-ekko)
 Tofidence (tocilizumab-bavi)
 Tremfya (guselkumab)
 Truxima (rituximab-abbs)
 Tysabri (natalizumab)
 Wezlana (ustekinumab-auub)
 Xolair (omalizumab)
 Yuflyma (adalimumab-aaty)
 Yusimry (adalimumab-aqvh)
 Zymfentra (infliximab-dyyb)

Table 1: Conventional Synthetic DMARDs

DMARD Generic Name	DMARD Brand Name
Auranofin (oral gold)	Ridaura
Azathioprine	Imuran
Cyclosporine	Neoral, Sandimmune
Hydroxychloroquine	Plaquenil
Leflunomide	Arava
Methotrexate	Rheumatrex, Trexall
Sulfasalazine	Azulfidine, Azulfidine EN-Tabs

REFERENCES:

1. Armstrong AW, Siegel MP, Bagel J, et al. From the Medical Board of the National Psoriasis Foundation: Treatment targets for plaque psoriasis. J Am Acad Dermatol. 2017 Feb;76(2):290-298.

2. Canadian Psoriasis Guidelines Addendum Committee. 2016 Addendum to the Canadian Guidelines for the Management of Plaque Psoriasis 2009. *J Cutan Med Surg*. 2016 Sep;20(5):375-431.
3. Clinical Pharmacology powered by ClinicalKey [Internet]. Tampa, FL: Elsevier.; 2022. Available at: <https://www.clinicalkey.com/pharmacology/>. Accessed 10/24/23.
4. Coates LC, Kavanaugh A, Mease PJ et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis: Treatment Recommendations for Psoriatic Arthritis 2015. *Arthritis Rheumatol* 2016; 68:1060–71.
5. Crowley J, Thaçi D, Joly P, et al. Long-term safety and tolerability of apremilast in patients with psoriasis: Pooled safety analysis for ≥156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2). *J Am Acad Dermatol*. 2017 Aug;77(2):310-317.e1.
6. Dogra S, Jain A, Kanwar AJ. Efficacy and safety of acitretin in three fixed doses of 25, 35 and 50 mg in adult patients with severe plaque type psoriasis: a randomized, double blind, parallel group, dose ranging study. *J Eur Acad Dermatol Venereol*. 2013 Mar;27(3): e305-11.
7. Dogra S, Krishna V, Kanwar AJ. Efficacy and safety of systemic methotrexate in two fixed doses of 10 mg or 25 mg orally once weekly in adult patients with severe plaque-type psoriasis: a prospective, randomized, double-blind, dose-ranging study. *Clin Exp Dermatol*. 2012 Oct;37(7):729-34.
8. Edwards CJ, Blanco FJ, Crowley J, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). *Ann Rheum Dis*. 2016 Jun;75(6):1065-73.
9. FDA Orphan Drug Designations and Approvals [Internet]. Washington, D.C. [cited 2023 Oct 24]. Available from: <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/>.
10. Griffiths CEM, Armstrong AW, Gudjonsson JE, Barker JNWN. Psoriasis. *Lancet*. 2021;397(10281): 1301-1315.
11. Hatemi G, Christensen R, Bang D, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. *Ann Rheum Dis*. 2018 Jun;77(6):808-818. Epub 2018 Apr 6.
12. Hatemi G, Melikoglu M, Tunc R, et al. Apremilast for Behçet's syndrome--a phase 2, placebo-controlled study. *N Engl J Med*. 2015 Apr 16;372(16):1510-8.
13. Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Treatment of psoriatic arthritis in a phase 3 randomized, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis*. Mar 4 2014.
14. Krause ML, Amin A, and Makol A. Use of DMARDs and biologics during pregnancy and lactation in rheumatoid arthritis: what the rheumatologist needs to know. *Ther Adv Musculoskelet Dis*. 2014 Oct; 6(5): 169–184.
15. Leccese P, Ozguler Y, Christensen R, et al. Management of skin, mucosa and joint involvement of Behçet's syndrome: A systematic review for update of the EULAR recommendations for the management of Behçet's syndrome. *Semin Arthritis Rheum*. 2018 May 19.
16. Mentor A, Korman NJ, Elmetts CA, et al. Guidelines for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. *J Am Acad Dermatol* 2011; 65:137-74.
17. Menter A, Strober BE, Kaplan DH et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2019 Apr;80(4):1029-1072. Epub 2019 Feb 13.
18. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 10/24/23.

19. National Comprehensive Cancer Network. Cancer Guidelines. Cancer Guidelines and Drugs and Biologics Compendium. Accessed 10/24/23.
20. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Management of Immunotherapy-Related-Toxicities. Version 3.2023 - October 11, 2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed 10/26/23.
21. Otezla (apremilast) [package insert]. Amgen Inc. Thousand Oaks, CA. July 2023.
22. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). *J Am Acad Dermatol*. 2015 Jul;73(1):37-49.
23. Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). *Br J Dermatol*. 2015 Dec;173(6):1387-99.
24. Rahimi R, Nikfar S, Rezaie A, et al. Pregnancy outcome in women with inflammatory bowel disease following exposure to 5-aminosalicylic acid drugs: a meta-analysis. *Reprod. Toxicol*; 2008;25,271–275.
25. Rich P, Gooderham M, Bachelez H, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with difficult-to-treat nail and scalp psoriasis: Results of 2 phase III randomized, controlled trials (ESTEEM 1 and ESTEEM 2). *J Am Acad Dermatol*. 2016 Jan;74(1):134-42.
26. Sbidian E, Chaimani A, Garcia-Doval, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database Syst Rev*. 2021 Apr 19;4(4):CD011535. Update in: *Cochrane Database Syst Rev*. 2022 May 23;5:CD011535.
27. Schett G, Wollenhaupt J, Papp K, et al. Oral apremilast in the treatment of active psoriatic arthritis: Results of a multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum*. 2012;64(10):3156-3167.
28. Singh JA, Guyatt G, Ogdie A, et al. Special Article: 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. *Arthritis Rheumatol*. 2019 Jan;71(1):5-32. Epub 2018 Nov 30.
29. Smith CH, Jabbar-Lopez JK, Yiu ZZ, et al. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017. *Br J Dermatol* 2017; 177: 628-136.
30. Wells AF, Edwards CJ, Kivitz AJ, et al. Apremilast monotherapy in DMARD-naïve psoriatic arthritis patients: results of the randomized, placebo-controlled PALACE 4 trial. *Rheumatology (Oxford)*. 2018 Apr 4.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/08/23.

GUIDELINE UPDATE INFORMATION:

09/15/14	New Medical Coverage Guideline.
12/15/14	Revision to guideline.
04/15/15	Revision of guideline; consisting of position statement to exclude combination therapy.

09/15/15	Review and revision of guidelines; consisting of updating description section, position statement, dosage/administration, billing/coding, related guidelines, definitions, and references.
11/01/15	Revision: ICD-9 Codes deleted.
09/15/16	Review and revision of guidelines consisting of updating description section, position statement, billing/coding, related guidelines, and references.
02/01/17	Revision to guideline consisting of removing the two preferred agent prerequisite requirement.
10/15/17	Review and revision to guideline consisting of updating description, position statement, dosage/administration, definitions, related guidelines, and references.
07/01/18	Revision to guideline consisting of updating the position statement.
10/15/18	Review and revision to guideline consisting of updating the position statement, billing/coding, and references.
10/15/19	Review and revision to guideline consisting of updating description, position statement, dosage/administration, related guidelines, and references.
07/01/20	Revision to guideline consisting of updating the description, position statement, billing/coding, related guidelines, and definitions.
01/01/21	Review and revision to guideline consisting of updating the position statement and references.
03/15/21	Revision to guideline consisting of updating Table 1 in the position statement.
11/15/21	Revision to guideline consisting of updating the position statement.
01/01/22	Review and revision to guideline consisting of updating the position statement, other section, and references.
02/15/22	Update to Table 1 in Position Statement.
03/15/22	Revision to guidelines consisting of updating the description, position statement, dosage/administration, precautions, other section, and references.
05/15/22	Update to Table 1 in Position Statement.
07/15/22	Update to Table 1 in Position Statement.
09/15/22	Update to Table 1 in Position Statement.
01/01/23	Review and revision to guideline consisting of updating the position statement, other section, and references. New drugs were added to the list of drugs that are not permitted for use in combination.
04/15/23	Update to Table 1 in Position Statement. New drugs were added to the list of drugs that are not permitted for use in combination.
07/01/23	Revision to guideline consisting of updating the position statement and other section. Amjevita and Hadlima added as Step 1a agents. Humira biosimilar products added to list of Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy.
01/01/24	Review and revision to guideline consisting of updating the description section (NCCN info), position statement, other section, billing/coding, and references. Update to Table 1 in Position Statement. New drugs were added to the list of drugs that are not permitted for use in combination.