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Subject: Ustekinumab (Stelara[®]) Injection and Infusion

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DESCRIPTION:

Ustekinumab (Stelara), an interleukin (IL)-12 and IL-23 antagonist, was first approved by the US Food and Drug Administration (FDA) in September 2009 for the treatment of adults with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy, and then approved for the treatment of active psoriatic arthritis (PsA) in September 2013. In September 2016, ustekinumab received an additional approval for the treatment of adult patients with moderately to severely active Crohn's disease (CD) who have: (1) failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed a tumor necrosis factor (TNF) blocker, or (2) failed or were intolerant to treatment with one or more TNF blockers. In October 2017, the plaque psoriasis indication was expanded to include adolescent patients (12 to 18 years of age). In October 2019, ustekinumab received approval for the treatment of adult patients with moderately to severely active ulcerative colitis (UC). In addition, the CD indication was modified to no longer include prior treatment failure (i.e., now reads "for the treatment of adult patients with moderately to severely active CD"). In July 2020, the plaque psoriasis indication was expanded to include pediatric patients (6 to 11 years of age). Unlike for treatment of psoriasis and PsA, treatment for CD and UC requires a single, initial weight-based IV loading dose. Ustekinumab (as sponsored by the innovator drug company) has been granted orphan drug designation by the FDA for "treatment of type 1 diabetes mellitus patients with residual beta-cell function" in November 2010, for "treatment of pediatric Crohn's disease (0 through 16 years of age)" in May 2016, for "treatment of pediatric ulcerative colitis" in February 2017, and for "treatment of pediatric systemic lupus erythematosus" in July 2017.

RHEUMATOID DISORDERS

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

DERMATOLOGICAL DISORDERS

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

INFLAMMATORY BOWEL DISEASE

Crohn's Disease (CD)

Crohn's Disease (CD) is an inflammatory condition that can affect any portion of the gastrointestinal tract from the mouth to the perianal area. Choice of therapy is dependent on the anatomic location of disease, the severity of disease, and whether the treatment goal is to induce remission or maintain remission.^{21,36} The American Gastroenterological Association (AGA) 2013 guideline recommends the following:²¹

- Induction of remission in moderately severe CD:
 - Anti-TNF (i.e., infliximab or adalimumab), as monotherapy or in combination with thiopurines, is recommended in patients refractory to standard therapies (mesalamine, antibiotics, corticosteroids and immunomodulators) in moderately severe disease
 - Thiopurines or methotrexate may be added to corticosteroids for induction to maintain a steroid induced remission in moderately severe disease
- Maintenance of remission in moderately severe CD:

- Following steroid-induced remission, thiopurine or MTX are preferred over no therapy
- Following steroid induced or anti-TNF drug induced remission, anti-TNF with or without thiopurine to maintain remission is preferred over no therapy

The 2018 American College of Gastroenterology (ACG) guidelines recommend the following:

- Mild to moderately severe disease/low risk disease:
 - Sulfasalazine (in doses of 3-6 grams daily) is effective in colonic and/or ileocolonic CD, but not those with isolated small bowel disease
 - 5-aminosalicylic (ASA) suppositories and enema preparations are effective for induction and maintenance of remission in rectal and sigmoid disease
 - Conventional corticosteroids are primarily used for the treatment of flares, and are often used as a bridge until immunomodulators and/or biologic agents become effective
 - Controlled ileal release budesonide is effective for induction of remission in ileocecal disease
- Moderate to severe disease/moderate to high risk disease
 - Corticosteroids are effective for short-term use in alleviating signs and symptoms of moderate to severely active CD, but do not induce mucosal healing and should be used sparingly
 - Azathioprine, 6-mercaptopurine, or MTX (15 mg once weekly) may be used in treatment of active disease and as adjunctive therapy for reducing immunogenicity against biologic therapy
 - TNF inhibitors should be used to treat CD that is resistant to treatment with corticosteroids and that is refractory to thiopurines or MTX
 - Vedolizumab with or without an immunomodulator should be considered for induction of symptomatic remission for patients with moderate to severely active CD and objective evidence of active disease
 - Ustekinumab should be used in patients that have failed previous treatment with corticosteroids, thiopurines, MTX, or TNF inhibitors, or in patients with no prior TNF inhibitor exposure
- Severe/fulminant disease:
 - IV corticosteroids should be used
 - TNF inhibitors can be considered
- Maintenance therapy:
 - Thiopurines or methotrexate should be considered once remission is induced with corticosteroids
 - TNF inhibitors, specifically infliximab, adalimumab, and certolizumab pegol, should be used in combination with azathioprine, MTX, or 6-mercaptopurine to maintain remission of TNF induced remission
 - Vedolizumab should be used for maintenance of remission of vedolizumab induced remission
 - Ustekinumab should be used for maintenance of remission of ustekinumab induced remission

Ulcerative Colitis (UC)

Ulcerative colitis (UC) is a chronic immune-mediated inflammatory condition affecting the large intestine associated with inflammation of the rectum, but that can extend to involve additional areas of the colon. The American College of Gastroenterology (ACG) recommends a treat-to-target approach and recommend therapeutic management should be guided by diagnosis (i.e., Montreal classification), assessment of disease activity (i.e., mild, moderate, and severe), and disease prognosis. The ACG treatment recommendations are further broken down into induction therapies and maintenance of

remission. The 2019 ACG treatment guidelines recommend the following for therapeutic management of UC³⁷:

Induction of remission:

- Mildly active disease:
 - Rectal 5-ASA at a dose of 1 g/day with or without oral 5-ASA at a dose of at least 2 g/day for left-sided UC
 - Rectal 5-ASA at a dose of 1 g/day for ulcerative proctitis
 - Oral 5-ASA at a dose of at least 2 g/day for extensive UC
 - Add oral budesonide multi-matrix (MMX) 9 mg/day for patients that are intolerant or non-responsive to oral and/or rectal and oral 5-ASA at appropriate doses
- Moderately active disease:
 - Oral budesonide multi-matrix (MMX) 9 mg/day for induction of remission
- Moderately to severely active disease:
 - Oral systemic corticosteroids, TNF inhibitors (i.e., adalimumab, golimumab, or infliximab), tofacitinib, or vedolizumab to induce remission
 - Combination of infliximab with thiopurine therapy when using infliximab for induction
 - Switch to tofacitinib or vedolizumab for induction in patients that have failed TNF inhibitors
 - Patients with initial response to TNF inhibitors that lose response should have antibody levels and serum drug levels tested to assess reason for loss of response. If serum levels are adequate, use of another TNF inhibitor is not likely to be of benefit.

Maintenance of remission:

- Previously mildly active disease:
 - Rectal 5-ASA at a dose of 1 g/day in patients with ulcerative proctitis
 - Oral 5-ASA at a dose of at least 2 g/day in patients with left-sided or extensive UC
- Previously moderately to severely active disease:
 - Thiopurines in patients that achieved remission due to corticosteroid induction
 - Continue TNF inhibitors (i.e., adalimumab, golimumab, or infliximab) for remission due to TNF induction
 - Continue vedolizumab for remission due to vedolizumab induction
 - Continue tofacitinib for remission due to tofacitinib induction

The American Gastroenterology Association (AGA) published recommendations for the management of mild to moderate UC:

- Use either standard-dose mesalamine (2-3 g/day) or diazo-bonded 5-ASA for patients with extensive UC for induction of remission and maintenance of remission
- May add rectal mesalamine to oral 5-ASA in patients with extensive or left-sided UC for induction of remission and maintenance of remission
- Use high dose mesalamine (>3 g/day) with rectal mesalamine in patients with suboptimal response to standard-dose mesalamine, diazo-bonded 5-ASA, or with moderate disease activity for induction of remission and maintenance of remission

- Add either oral prednisone or budesonide MMX in patients that are refractory to optimized oral and rectal 5-ASA regardless of disease extent

The American Gastroenterology Association (AGA) published recommendations for the management of moderate to severe UC.

- Standard of care is to continue agents initiated for induction therapy as maintenance therapy, if they are effective (excluding corticosteroids and cyclosporine)
- Adult outpatients with moderate to severe UC:
 - Infliximab, adalimumab, golimumab, vedolizumab, tofacitinib or ustekinumab are strongly recommended over no treatment
 - Biologic naïve patients:
 - infliximab or vedolizumab are conditionally recommended over adalimumab for induction of remission
 - Recommend tofacitinib only be used in the setting of a clinical or registry study
 - Previous exposure to infliximab, particularly those with primary non-response, ustekinumab or tofacitinib are conditionally recommended over vedolizumab or adalimumab for induction of remission
 - Conditionally recommend against use of thiopurine monotherapy for induction, but may be used for maintenance of remission over no treatment

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the subcutaneous formulations of 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) of the subcutaneous formulations in certain provider-administered setting such as an outpatient hospital, ambulatory surgical suite, or emergency facility is not considered medically necessary.

NOTE: The preferred and non-preferred, self-administered products for certain indications are as follows:

Table 1

Disease State	Step 1 (Preferred)	Step 2 (Non-preferred directed to ONE step 1 agent)	Step 3a (Non-preferred directed to TWO step 1 agents)	Step 3b (Non-preferred directed to TWO agents from step 1 and/or step 2)	Step 3c (Non-preferred directed to THREE step 1 agents)
Rheumatoid Disorders					
Ankylosing Spondylitis (AS)	SQ: Cosentyx, Enbrel, Humira	N/A	SQ: Cimzia, Simponi, Taltz	N/A	N/A
Nonradiographic Axial Spondyloarthritis (nr-axSpA)	SQ: Cimzia, Cosentyx	N/A	SQ: Taltz	N/A	N/A
Polyarticular Juvenile Idiopathic Arthritis (PJIA)	SQ: Enbrel, Humira Oral: Xeljanz	SQ: Actemra (Humira is required Step 1 agent)	N/A	SQ: Orencia	N/A

Psoriatic Arthritis (PsA)	SQ: Cosentyx, Enbrel, Humira, Stelara , Tremfya Oral: Otezla, Xeljanz, Xeljanz XR	N/A	SQ: Cimzia, Oencia, Simponi, Taltz	N/A	N/A
Rheumatoid Arthritis	SQ: Enbrel, Humira, Oral: Rinvoq, Xeljanz, Xeljanz XR	SQ: Actemra (Humira is required Step 1 agent)	Oral: Olumiant SQ: Cimzia, Kevzara, Kineret, Oencia, Simponi	N/A	N/A
Dermatological Disorders					
Hidradenitis Suppurativa (HS)	SQ: Humira	N/A	N/A	N/A	N/A
Psoriasis (PS)	SQ: Cosentyx, Enbrel, Humira, Skyrizi, Stelara , Tremfya Oral: Otezla	N/A	SQ: Cimzia, Ilumya, Siliq	N/A	SQ: Taltz
Inflammatory Bowel Disease					
Crohn's Disease	SQ: Humira, Stelara	SQ: Cimzia (Humira is required Step 1 agent)	N/A	N/A	N/A
Ulcerative Colitis	SQ: Humira, Stelara	SQ: Simponi Oral: Xeljanz, Xeljanz XR	N/A	N/A	N/A
Other					
Uveitis	SQ: Humira	N/A	N/A	N/A	N/A
Indications Without Preferred Agents Required					
Giant Cell Arteritis (GCA)					
Neonatal-Onset Multisystem Inflammatory Disease (NOMID)	N/A	N/A	N/A	N/A	N/A
Systemic Juvenile Idiopathic Arthritis (SJIA)					

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

SUBCUTANEOUS STELARA (MEDICAL AND PHARMACY BENEFIT)

Initiation of subcutaneous ustekinumab (Stelara) **meets the definition of medical necessity** when **ALL** of the following are met (“1” to “6”):

1. **ONE** of the following (“a”, “b”, or “c”):
 - a. Information has been provided that indicates the member has been treated with subcutaneous ustekinumab (starting on samples is not approvable) within the past 90 days
 - b. The prescriber states the member has been treated with subcutaneous ustekinumab (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. Subcutaneous ustekinumab 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 (“I” or “II”)
 - I. The member’s age is within FDA labeling for the requested indication for subcutaneous ustekinumab
 - II. The prescriber has provided information in support of using subcutaneous ustekinumab for the member’s age
2. The prescriber is a specialist in the area of the member’s diagnosis (e.g., rheumatologist for PsA; gastroenterologist for CD, UC; dermatologist for PS) or the prescriber has consulted with a specialist in the area of the member’s diagnosis
 3. Member does **NOT** have any FDA labeled contraindications to subcutaneous ustekinumab
 4. Member has been tested for latent tuberculosis (TB) **AND**, if positive, the member has begun therapy for latent TB
 5. Member will **NOT** be using subcutaneous ustekinumab in combination with another biologic immunomodulator agent or Otezla
 6. **ANY** of the following (“a”, “b”, or “c”):
 - a. The dosage does not exceed:
 - Loading dose:
 - CD or UC: Initial dose is a single IV weight-based dose, followed by maintenance doses starting 8 weeks after the initial IV dose
 - PS and PsA: 90 mg at day 0 and week 4, followed by maintenance doses starting 12 weeks later (week 16)
 - Maintenance dose: 90 mg every 8 weeks (56 days)
 - QL: 45 mg/0.5 mL vial - 1 vial (0.5 mL)/84 days
 - QL: 45 mg/0.5 mL syringe - 1 syringe (0.5 mL)/84 days
 - QL: 90 mg/1 mL syringe - 1 syringe (1 mL)/56 days
 - Maintenance dose – **EITHER** of the following
 - 45 mg every 12 week (84 days)
 - QL: 45 mg/0.5 mL vial - 1 vial (0.5 mL)/84 days
 - QL: 45 mg/0.5 mL syringe - 1 syringe (0.5 mL)/84 days
 - 90 mg every 8 weeks (56 days), **AND ONE** of the following:
 - Member has a diagnosis of psoriasis **AND** weighs >100 kg, **OR**
 - The member has a dual diagnosis of psoriasis AND psoriatic arthritis **AND** the member is >100kg, **OR**
 - Member has a diagnosis of Crohn’s disease or ulcerative colitis
 - QL: 90 mg/1 mL syringe - 1 syringe (1 mL)/56 days
 - b. The requested quantity (dose) is greater than program’s 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) is greater than the program's quantity limit and greater than 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:

- PS and PsA - Loading dose (doses on week 0 and 4) for 4 months, then maintenance dose for 8 additional months [12 months for total duration of approval]
- Other indications - 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 OR 2. The member has an intolerance or hypersensitivity to ONE of the conventional agents used in the treatment of PsA OR 3. The member has an FDA labeled contraindication to ALL of the conventional agents used in the treatment of PsA OR 4. The member has severe active PsA (e.g., erosive disease, elevated markers of inflammation [e.g., ESR, CRP] attributable to PsA, long-term damage that interferes with function [i.e., joint deformities], rapidly progressive) OR 5. The member has concomitant severe psoriasis (PS) (e.g., greater than 10% body surface area involvement, occurring on select locations [i.e., hands, feet, scalp, face, or genitals], intractable pruritus, serious emotional consequences) OR 6. The member's medication history indicates use of another biologic immunomodulator agent OR Otezla that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence AHFS, or NCCN compendium recommended use 1 or 2a for the treatment of PsA

<p>Moderate to severe plaque psoriasis (PS)</p>	<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., 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 style="text-align: center;">OR</p> 2. The member has an intolerance or hypersensitivity to ONE conventional agent used in the treatment of PS <p style="text-align: center;">OR</p> 3. The member has an FDA labeled contraindication to ALL conventional agents used in the treatment of PS <p style="text-align: center;">OR</p> 4. The member has severe active PS (e.g., greater than 10% body surface area involvement, occurring on select locations [i.e., hands, feet, scalp, face, or genitals], intractable pruritus, serious emotional consequences) <p style="text-align: center;">OR</p> 5. The member has concomitant severe psoriatic arthritis (PsA) (e.g., erosive disease, elevated markers of inflammation [e.g., ESR, CRP] attributable to PsA, long-term damage that interferes with function [i.e., joint deformities], rapidly progressive) <p style="text-align: center;">OR</p> 6. The member's medication history indicates use of another biologic immunomodulator agent OR Otezla that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence,, AHFS, or NCCN compendium recommended use 1 or 2a for the treatment of PS
<p>Moderately to severely active Crohn's disease (CD)</p>	<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., 6-mercaptopurine, azathioprine, corticosteroids [e.g., prednisone, budesonide EC capsule], methotrexate, sulfasalazine) used in the treatment of CD for at least 3 months <p style="text-align: center;">OR</p> 2. The member has an intolerance or hypersensitivity to ONE of the conventional agents used in the treatment of CD <p style="text-align: center;">OR</p> 3. The member has an FDA labeled contraindication to ALL of the conventional agents used in the treatment of CD <p style="text-align: center;">OR</p> 4. 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, AHFS, or NCCN compendium recommended use 1 or 2a for the treatment of CD
Moderately to severely active ulcerative colitis (UC)	<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., 6-mercaptopurine, azathioprine, balsalazide, corticosteroids, cyclosporine, mesalamine, steroid suppositories, sulfasalazine) used in the treatment of UC for at least 3 months <p>OR</p> <ol style="list-style-type: none"> 2. The member has an intolerance or hypersensitivity to ONE of the conventional agents used in the treatment of UC <p>OR</p> <ol style="list-style-type: none"> 3. The member has an FDA labeled contraindication to ALL of the conventional agents used in the treatment of UC <p>OR</p> <ol style="list-style-type: none"> 4. 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, AHFS, or NCCN compendium recommended use 1 or 2a for the treatment of UC
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 subcutaneous ustekinumab (Stelara) **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "6"):

1. An authorization or reauthorization for subcutaneous ustekinumab has been previously approved by Florida Blue (*please note Stelara renewal must be for the same strength as the initial approval)
2. Member has had clinical benefit with subcutaneous ustekinumab therapy
3. The prescriber is a specialist in the area of the member's diagnosis (e.g., rheumatologist for PsA, gastroenterologist for CD, UC; dermatologist for PS) or the prescriber has consulted with a specialist in the area of the member's diagnosis
4. Member does **NOT** have any FDA labeled contraindications to subcutaneous ustekinumab
5. Member will **NOT** be using subcutaneous ustekinumab in combination with another biologic immunomodulator agent or Otezla
6. **ANY** of the following ("a", "b", or "c"):
 - a. The dosage does not exceed 90 mg every 8 weeks (56 days)
 - QL: 45 mg/0.5 mL vial - 1 vial (0.5 mL)/84 days
 - QL: 45 mg/0.5 mL syringe - 1 syringe (0.5 mL)/84 days
 - QL: 90 mg/1 mL syringe - 1 syringe (1 mL)/56 days

- b. The requested quantity (dose) is greater than program's 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) is greater than the program's quantity limit and greater than 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)

INTRAVENOUS STELARA (MEDICAL BENEFIT)

Initiation of intravenous (IV) ustekinumab (Stelara) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "6"):

- 1. Intravenous ustekinumab will be used for the treatment of an indication listed in **Table 3**, and **ALL** of the indication-specific and maximum-allowable dose criteria are met
- 2. The prescriber is a specialist in the area of the member's diagnosis (e.g., gastroenterologist for CD, UC) or the prescriber has consulted with a specialist in the area of the member's diagnosis
- 3. Member does **NOT** have any FDA labeled contraindications to IV ustekinumab
- 4. Member has been tested for latent tuberculosis (TB) **AND**, if positive, the member has begun therapy for latent TB
- 5. Member will **NOT** be using ustekinumab in combination with another biologic immunomodulator agent or Otezla
- 6. Member has not received a previous dose of ustekinumab (IV or SC) in the past 12 months

Table 3

Indication	Criteria	Max Allowable Dosage
Moderately to severely active Crohn's disease (CD)	<p>ONE of the following:</p> <ul style="list-style-type: none"> 1. The member has tried and had an inadequate response to ONE conventional agent (i.e., 6-mercaptopurine, azathioprine, corticosteroids [e.g., prednisone, budesonide EC capsule], methotrexate, sulfasalazine) used in the treatment of CD for at least 3 months <p>OR</p> <ul style="list-style-type: none"> 2. The member has an intolerance or hypersensitivity to ONE of the conventional agents used in the treatment of CD 	<ul style="list-style-type: none"> • ≤55 kg: 260 mg (two 130 mg vials) X 1 dose • >55 to 85 kg: 390 mg (three 130 mg vials) X 1 dose • >85 kg: 520 mg (four 130 mg vials) X 1 dose

	<p>OR</p> <p>3. The member has an FDA labeled contraindication to ALL of the conventional agents used in the treatment of CD</p> <p>OR</p> <p>4. 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, AHFS, or NCCN compendium recommended use 1 or 2a for the treatment of CD</p>	
Moderately to severely active ulcerative colitis (UC)	<p>ONE of the following:</p> <p>1. The member has tried and had an inadequate response to ONE conventional agent (i.e., 6-mercaptopurine, azathioprine, balsalazide, corticosteroids, cyclosporine, mesalamine, steroid suppositories, sulfasalazine) used in the treatment of UC for at least 3-months</p> <p>OR</p> <p>2. The member has an intolerance or hypersensitivity to ONE of the conventional agents used in the treatment of UC</p> <p>OR</p> <p>3. The member has an FDA labeled contraindication to ALL of the conventional agents used in the treatment of UC</p> <p>OR</p> <p>4. 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, AHFS, or NCCN compendium recommended use 1 or 2a for the treatment of UC</p>	<ul style="list-style-type: none"> • ≤55 kg: 260 mg (two 130 mg vials) X 1 dose • >55 to 85 kg: 390 mg (three 130 mg vials) X 1 dose • >85 kg: 520 mg (four 130 mg vials) X 1 dose
Other indications	The member has another FDA labeled indication or an indication supported in DrugDex with 1 or 2a level of evidence,	Maximum dose supported by the FDA labeled indication or maximum dose supported in

	AHFS, or NCCN compendium recommended use 1 or 2a	DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a [not to exceed an approval duration of 1 year]
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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: ustekinumab is indicated for: (1) the treatment of patients 6 years or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy, (2) the treatment of adult patients with active psoriatic arthritis, alone or in combination with methotrexate, (3) the treatment of adult patients with moderately to severely active Crohn's disease, and (4) the treatment of adult patients with moderately to severely active ulcerative colitis (UC).

The recommended dose is based on weight for the treatment of plaque psoriasis:

- Adults dosage (18 years and older)
 - 100 kg or less: 45 mg at week 0 and 4 week later at week 4, followed by 45 mg every 12 weeks beginning at week 16.
 - Greater than 100 kg: 90 mg at week 0 and 4 week later at week 4, followed by 90 mg every 12 weeks beginning at week 16.
- Pediatric/Adolescent dosage (6 to less than 18 years)
 - Less than 60 kg: 0.75 mg/kg at week 0 and 4 week later at week 4, followed by 0.75 mg/kg every 12 weeks beginning at week 16 – refer to the prescribing information for a table of the injection volumes based on weight
 - 60 to 100 kg: 45 mg at week 0 and 4 week later at week 4, followed by 45 mg every 12 weeks beginning at week 16
 - Greater than 100 kg: 90 mg at week 0 and 4 weeks at weeks 4, followed by 90 mg every 12 weeks beginning at week 16

The recommended dose for the treatment of active psoriatic arthritis is 45 mg every 4 weeks at weeks 0 and 4, followed by 45 mg every 12 weeks beginning at week 16. In persons with co-existent moderate to severe plaque psoriasis who weight greater than 100 kg, the recommended dose is 90 mg every 4 weeks at weeks 0 and 4, followed by 90 mg every 12 weeks beginning at week 16.

The recommended dosage for the treatment of Crohn's disease and UC is weight-based for the initial IV loading dose but then a fixed maintenance dosage. The loading dose is: ≤55 kg: 260 mg (two 130 mg vials) X 1 dose; >55 to 85 kg: 390 mg (three 130 mg vials) X 1 dose; >85 kg: 520 mg (four 130 mg vials) X 1 dose (on week 0) given as an IV infusion in 250 mL (using normal saline) over at least one hour. The maintenance dose is 90 mg given as a subcutaneous injection 8 weeks after the initial IV dose (week 8), then every 8 weeks thereafter.

Ustekinumab should be administered as a subcutaneous injection with the exception of the initial IV infusion loading dose for Crohn's disease and UC. Although initially approved only for administration by a healthcare professional, ustekinumab was approved for subcutaneous self-administration in June 2013.

Drug availability: ustekinumab is supplied in the following dosage forms and strengths

- Single-dose prefilled syringe: 45 mg/0.5 mL, 90 mg/1 mL (both for SQ use)
- Single-dose vial: 45 mg/0.5 mL (for SQ use), 130 mg/26 mL (5 mg/mL) (for IV infusion)

PRECAUTIONS:

Boxed Warning:

- None

Contraindication:

- Persons with clinically significant hypersensitivity to ustekinumab or any of the excipients.

Precautions/Warnings

- **Infections:** Serious infections have occurred. Do not start ustekinumab during any clinically important active infection. If a serious infection develops, discontinue therapy until the infection resolves.
- **Theoretical Risk for Vulnerability to Particular Infections:** Serious infections from mycobacteria, salmonella and [Bacillus Calmette-Guerin \(BCG\)](#) vaccinations have been reported in persons genetically deficient in IL-12/IL-23. Diagnostic tests for these infections should be considered as dictated by clinical circumstances.
- **Pre-treatment Evaluation for Tuberculosis (TB):** Evaluate individuals for TB prior to initiating treatment with ustekinumab. Initiate treatment of latent TB before administering ustekinumab
- **Malignancies:** ustekinumab may increase risk of malignancy. The safety of ustekinumab in persons with a history of or a known malignancy has not been evaluated.
- **Hypersensitivity Reactions:** Anaphylaxis or other clinically significant hypersensitivity reactions may occur.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** One case was reported. If suspected, treat promptly and discontinue ustekinumab.
- **Immunization:** do not administer live vaccines with ustekinumab.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** One case was reported. If suspected, treat promptly and discontinue ustekinumab.
- **Concomitant Therapies:** In clinical studies of psoriasis the safety of ustekinumab in combination with other immunosuppressive agents or phototherapy was not evaluated
- **Noninfectious Pneumonia:** Cases of interstitial pneumonia, eosinophilic pneumonia and cryptogenic organizing pneumonia have been reported during post-approval use of ustekinumab. Clinical presentations included cough, dyspnea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalization. Patients improved with discontinuation of therapy and in certain cases administration of corticosteroids. If diagnosis is confirmed, discontinue ustekinumab and institute appropriate treatment,

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding:

J3357	Ustekinumab, for subcutaneous injection, 1 mg
J3358	Ustekinumab, for intravenous injection, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity of Intravenous Injection (J3358):

K50.00 – K50.919	Crohn's disease [regional enteritis]
K51.00 – K51.919	Ulcerative colitis

ICD-10 Diagnosis Codes That Support Medical Necessity of Subcutaneous Injection (J3357):

K50.00 – K50.919	Crohn's disease [regional enteritis]
K51.00 – K51.919	Ulcerative colitis
L40.0	Psoriasis vulgaris
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

[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:](#)

Bacillus Calmette-Guérin (BCG): a vaccine against tuberculosis that is prepared from a strain of the attenuated (weakened) live bovine tuberculosis bacillus, *Mycobacterium bovis*.

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.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): a neurological disorder, which is not caused by demyelination or a known infectious agent. RPLS can present with headache, seizures, confusion and visual disturbances. Conditions with which it has been associated include preeclampsia, eclampsia, acute hypertension, cytotoxic agents and immunosuppressive therapy. Fatal outcomes have been reported.

RELATED GUIDELINES:

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

[Apremilast \(Otezla\) Tablet, 09-J2000-19](#)

[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](#)

[Natalizumab \(Tysabri\) Injection, 09-J0000-73](#)

[Psoralens with Ultraviolet A \(PUVA\), 02-10000-16](#)

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

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

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

[Vedolizumab \(Entyvio\) Injection, 09-J2000-18](#)

OTHER:

Table 4: Conventional Synthetic DMARDs

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

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 10/14/20.

GUIDELINE UPDATE INFORMATION:

02/15/10	New Medical Coverage Guideline.
04/15/10	Revision to guideline; consisting of adding specific continuation criteria.
01/01/11	Revision to guideline; consisting of updating coding.
09/15/11	Review and revision to guideline; consisting of updating position statement, coding and references.
09/15/12	Review and revision to guideline; consisting of modifying continuation criteria, reformatting position statement and updating precautions and references.
09/15/13	Review and revision to guideline; consisting of revising description, position statement, dosage/administration, and precautions; updated program exceptions and references.
01/01/14	Revision to guideline; consisting of revising position statement, updating coding and references.
04/15/14	Revision to guideline; consisting of revising position statement.
09/15/14	Review and revision to guideline; consisting of updating position statement and references.
09/15/15	Review and revision to guideline; consisting of revising position statement, updating

	coding and references.
11/01/15	Revision: ICD-9 Codes deleted.
11/15/15	Revision to guideline consisting of updating maximum starting dosage in the position statement.
02/24/16	Revision to guideline consisting of updating the position statement.
09/15/16	Review and revision to guideline consisting of updating position statement, related guidelines, and references.
11/15/16	Revision to guideline, based on a new FDA-approved indication and IV formulation, consisting of updating the description section, position statement, dosage/administration section, billing/coding, related guidelines, and references.
01/01/17	Revision: updated HCPCS code J3357 description.
01/15/17	Revision to guideline to separate the authorizations for the IV and SC formulations for Crohn's disease.
04/01/17	Revision to guideline consisting of adding HCPCS code C9487.
07/01/17	Addition of HCPCS code Q9989 that replaces codes C9487 and J3590
07/15/17	Revision to guideline consisting of updating the position statement.
10/15/17	Review and revision to guideline consisting of updating description, position statement, coding/billing, definitions, related guidelines, and references.
01/01/18	Revision to guideline consisting of updating the description section, position statement, and references after expanded FDA-approved indication for plaque psoriasis to include adolescent patients. The preferred self-administered biologic products were also updated according to indication for use. Addition of HCPCS code J3358 and deletion of code Q9989.
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, precautions, and references.
10/15/19	Review and revision to guideline consisting of updating the description, position statement, billing/coding, related guidelines, and references.
01/01/20	Revision to guideline consisting of updating the description section, position statement, dosage/administration section, and references, based on the new FDA-approved indication of ulcerative colitis.
07/01/20	Revision to guideline consisting of updating the description, position statement, billing/coding, and definitions.
01/01/21	Review and revision to guideline consisting of updating the description, position statement, and references.