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Subject: Adalimumab (Humira[®]) Injection

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DESCRIPTION:

Adalimumab (Humira) is one of five commercially available tumor necrosis factor (TNF)-alpha inhibitors, not counting biosimilars as separate products, available in the United States, and was first approved in December 2002. Tumor necrosis factor, a proinflammatory cytokine, initiates the body's defense response to local injury by stimulating the production of inflammatory mediators and signaling immune cells. TNF may augment host defense mechanisms when in low concentration, but large amounts of TNF can lead to excessive inflammation and tissue deterioration. In rheumatoid arthritis, activated T-cells migrate into the synovial lining of the joint where TNF is released and joint destruction begins. The intestinal mucosa from patients with Crohn's disease or ulcerative colitis has been associated with high levels of TNF as compared to healthy individuals; a similar elevation in TNF has been demonstrated in patients with psoriasis.

Adalimumab is approved by the US Food and Drug Administration (FDA) for the treatment of nine indications (the most of any TNF inhibitor): ankylosing spondylitis (2006), Crohn's disease (2007), hidradenitis suppurativa (2015), polyarticular juvenile idiopathic arthritis (2008), plaque psoriasis (2008), [psoriatic arthritis](#) (2005), [rheumatoid arthritis](#) (2002), ulcerative colitis (2012), and uveitis (2016). In October 2018, the indications for uveitis and hidradenitis suppurativa were expanded to include pediatric patients (2 years of age and older) and adolescent patients (12 years of age and older), respectively. Humira also has orphan drug designation for the treatment of pediatric patients with ulcerative colitis (2011). In 2019, AbbVie released a citrate-free formulation of Humira that includes a thinner needle and half the injection volume as compared the original Humira formulation. The changes are intended to reduce the amount of pain immediately following injection. As of September 2019, both formulations are available in the market. In September 2016 the first biosimilar to adalimumab, adalimumab-atto (Amjevita), was FDA approved. Additional biosimilars have followed: adalimumab-adbm (Cyltezo)

approved in August 2017, adalimumab-adaz (Hyrimoz) approved in October 2018, adalimumab-bwwd (Hadlima) approved in July 2019, adalimumab-afzb (Abrilada) approved in November 2019, and adalimumab-fkjp (Hulio) approved in July 2020. As of October 2020, none of the biosimilar products have launched. Projected launches are not expected until at least 2023. The TNF-alpha inhibitors as a class are considered to have similar efficacy and safety for the majority of indications. Similar to other TNF-alpha inhibitors, the package labeling contains a Boxed Warning regarding potential increased risk of serious infections (e.g., tuberculosis) and certain malignancies during therapy.

RHEUMATOID DISORDERS

Ankylosing spondylitis (AS)

Ankylosing spondylitis (AS) is a form of chronic inflammatory arthritis characterized by sacroiliitis, enthesitis, and a marked propensity for sacroiliac joint and spinal fusion. AS is distinguished by universal involvement with sacroiliac joint inflammation or fusion and more prevalent spinal ankylosis. Goals of treatment for AS are to reduce symptoms, maintain spinal flexibility and normal posture, reduce functional limitations, maintain work ability, and decrease disease complications. The mainstay of treatment has been NSAIDs and exercise, with the additional use of DMARDs in patients with peripheral arthritis. The American College of Rheumatology (ACR), Spondylitis Association of America (SAA), and Spondyloarthritis Research and Treatment Network (SPARTAN) recommend the following pharmacological treatment for AS:

- Stable AS: First line therapy with on demand NSAIDs; there is also a conditional recommendation for continuation of TNF inhibitor as monotherapy
- Active AS:
 - First line therapy with continuous NSAIDs and physical therapy
 - TNF inhibitor recommended for patients with active AS despite an adequate trial with NSAIDs
 - Lack of response (or intolerance) to at least 2 different NSAIDs over 1 month or incomplete response to at least 2 different NSAIDs over 2 months would be an adequate NSAID trial to judge response
 - Recommendations for nonresponse to TNF therapy (all conditional):
 - Primary nonresponse: switch to secukinumab or ixekizumab over another TNF
 - Secondary nonresponse: switch to another TNF over a non-TNF biologic
 - Recommend against addition of sulfasalazine or MTX
 - Recommend against switching to a biosimilar of the failed TNF
 - TNF-inhibitors are conditionally recommended over secukinumab or ixekizumab
 - Secukinumab or ixekizumab are conditionally recommended over DMARDs in patients that have failed NSAIDs and have contraindications to TNF-inhibitors
 - DMARDs (i.e., methotrexate [MTX], sulfasalazine, leflunomide, pamidronate, thalidomide, apremilast) are only conditionally recommended in patients that have failed NSAIDs and have contraindications to TNF-inhibitors
 - Methotrexate is not recommended as add on therapy to TNF inhibitors in stable and active AS
 - If patient has concomitant inflammatory bowel disease (IBD) or recurrent uveitis, TNF-inhibitors are recommended over other biologics
 - Glucocorticoids are not recommended

Rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) is the most common inflammatory autoimmune arthritis in adults. The main goal of therapy is to achieve remission, but additional goals include decrease inflammation, relieve symptoms, prevent joint and organ damage, improve physical function/overall well-being, and reduce long term complications. The choice of therapy depends on several factors, including the severity of disease activity when therapy is initiated and the response of the patient to prior therapeutic interventions.

American College of Rheumatology (ACR) guidelines recommend a treat-to-target approach in therapy, regardless of disease activity. ACR guidelines categorize therapy for those with early RA (disease duration <6 months) or established RA (disease duration ≥6 months) as follows:

- In general, MTX is the preferred initial DMARD therapy for most patients with RA with active disease.
- For early RA patients, the ACR recommends the following:
 - Naïve to therapy: DMARDs, methotrexate (MTX) preferred, as initial, monotherapy therapy unless contraindicated. Other DMARD monotherapy options include sulfasalazine, hydroxychloroquine, and leflunomide.
 - Moderate or high disease activity despite DMARD monotherapy: treatment with combination DMARDs or a TNF-inhibitor (e.g., adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab) or a non-TNF inhibitor (abatacept, rituximab, or tocilizumab [excludes anakinra]), with or without MTX.
 - Moderate or high disease activity despite the previous DMARD or biologic therapy: addition of low-dose glucocorticoid (≤10 mg/day of prednisone or equivalent) to bridge therapy until therapeutic effects of DMARD is reached. ACR also recommends short-term (<3 months) with lowest dose of glucocorticoids for flares.
- For established RA patients, the ACR recommends the following:
 - Low disease activity and is DMARD naïve: DMARD monotherapy, MTX preferred, is recommended over a TNF-inhibitor.
 - Moderate or high disease and is DMARD naïve: DMARD monotherapy, MTX preferred, is recommended over double or triple DMARD therapy and tofacitinib.
 - Moderate-high disease activity despite DMARD monotherapy: combination DMARD therapy OR the addition of TNF inhibitor, non-TNF biologic, or tofacitinib with or without MTX is recommended rather than continuing DMARD monotherapy. Combination biologic therapy and MTX is recommended over biologic monotherapy.
 - Moderate or high disease despite TNF-inhibitor and not on DMARD: addition of one or two DMARD, rather than TNF-inhibitor monotherapy

Early use of DMARD, particularly MTX, is recommended as soon as possible following diagnosis of RA. Dosing of MTX for RA is once weekly dosing with starting doses at 7.5 mg or 15 mg once weekly.²⁶⁻²⁸

MTX dose is increased as tolerated and as needed to control symptoms and signs of RA disease. The usual target dose is at least 15 mg weekly and the usual maximum dose is 25 mg weekly.^{27,28} ACR defines optimal dosing for RA treatments as 1) dosing to achieve a therapeutic target derived from mutual patient-clinician consideration of patient priorities and 2) given for at least 3 months before therapy escalation or switching. For patients who are unable to take MTX, hydroxychloroquine, sulfasalazine, or leflunomide are other DMARD options. In patients resistant to initial MTX treatment, combination DMARD (e.g., MTX plus sulfasalazine or hydroxychloroquine or a TNF-inhibitor) is recommended.

For patients who are resistant to MTX after 3 months of treatment at optimal doses (usually 25 mg per week), it is recommended to either use DMARD triple therapy with MTX plus sulfasalazine and

hydroxychloroquine or combination of MTX with TNF inhibitor. Triple therapy regimen has been found to be of similar clinical efficacy to MTX with biologics in several randomized trials, including in patients with high level of disease activity or with adverse prognostic features. The use of triple therapy has been shown to be highly cost-effective compared with combining a biologic with MTX, providing comparable or near comparable clinical benefit. The use of biologic with MTX combination is preferred when patients have high disease activity and clinical benefit from a more rapid response is needed and when patients who do not achieve satisfactory response within 3 months with non-biologic triple therapy following an inadequate response to MTX therapy.

Polyarticular Juvenile Idiopathic Arthritis (PJIA)

Juvenile idiopathic arthritis (JIA) is arthritis that begins before the 16th birthday and persists for at least 6 weeks with other known conditions excluded. Polyarticular juvenile idiopathic arthritis (PJIA) is a subset of JIA. The ACR defines PJIA as arthritis in more than 4 joints during their disease course and excludes systemic JIA. Treatment goals are aimed at achieving clinically inactive disease and to prevent long-term morbidities, including growth disturbances, joint contractures and destruction, functional limitations, and blindness or visual impairment from chronic uveitis.

The ACR 2019 guidelines recommend the following treatment approach for PJIA:

- NSAIDs are conditionally recommended as adjunct therapy
- DMARD therapy:
 - Methotrexate (MTX) is conditionally recommended over leflunomide and sulfasalazine
 - Subcutaneous MTX is conditionally recommended over oral MTX
- Intraarticular glucocorticoids are conditionally recommended as adjunct therapy and conditionally recommended for bridging only in patients with moderate to high disease activity
- Strongly recommend against chronic low-dose glucocorticoid use, irrespective of disease activity and/or risk factors
- Strongly recommend combination use of a DMARD and infliximab
- Initial therapy for all patients:
 - DMARD is strongly recommended over NSAID monotherapy
 - MTX monotherapy is conditionally recommended over triple DMARD therapy
 - DMARD is conditionally recommended over a biologic
 - Initial biologic therapy may be considered for patients with risk factors and involvement of high-risk joints (e.g., cervical spine, wrist, hip), high disease activity, and/or those judged by their physician to be at high risk of disabling joint damage
- Subsequent therapy:
 - Low disease activity:
 - Escalating therapy (e.g., intraarticular glucocorticoid injections, optimization of DMARD dose, trial of MTX if not already done, and adding or changing biologic agent)
 - Moderate to high disease activity:
 - Add a biologic to original DMARD over changing to a second DMARD or changing to triple DMARD therapy
 - Switch to a non-TNF biologic if currently treated with first TNF ± DMARD over switching to another TNF (unless the patient had good initial response to first TNF)

- TNF, abatacept, or tocilizumab (depending on prior biologics received) over rituximab after trial of second biologic

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

Hidradenitis Suppurativa (HS)

Hidradenitis suppurativa (HS) is a chronic inflammatory disease causing painful, nodules to form in the folds of the skin and often secrete puss and blood. HS can be described as mild (single or few lesions in one area of the skin, Hurley Stage I), moderate (repeated cycles of enlarged lesions that break open and occur in more than one area of the skin, Hurley Stage II), and severe (widespread lesions, scarring, and chronic pain; Hurley Stage III).

Pharmacological treatment for mild HS includes topical clindamycin, oral tetracyclines, hormonal treatment, retinoids, intralesional corticosteroid injections (i.e., triamcinolone), and deroofing. Oral

tetracyclines are recommended for mild to moderate HS for at least a 12 weeks course or as long-term maintenance. Combination clindamycin and rifampin is effective second-line therapy for mild to moderate HS, or as first-line or adjunct therapy for severe HS. Combination rifampin, moxifloxacin, and metronidazole are recommended as second or third-line therapy for moderate to severe disease. Dapsone may be effective for a minority of patients with mild to moderate HS as long-term maintenance therapy. Oral retinoids, such as acitretin and isotretinoin, have also been used for mild HS as second or third-line therapy. Hormonal therapy may be considered in female patients for mild to moderate disease as monotherapy, or as adjunct therapy for severe disease. such as hormonal contraceptives, metformin, finasteride, and spironolactone.

Treatment recommendations for moderate to severe and refractory HS include immunosuppressants (e.g., cyclosporine and low dose systemic corticosteroids) and biologic agents. The TNF-inhibitors that are recommended are adalimumab, at doses within FDA labeling, and infliximab, but optimal doses have not been established. Anakinra and ustekinumab may be effective, but require dose ranging studies to determine optimal doses for management.

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

OTHER DISORDERS

Uveitis

Uveitis is inflammation of the uvea, which is the middle layer of the eye, leading to tissue damage and vision loss. There are three types of uveitis: anterior, intermediate and posterior. Uveitis frequently occurs in association with other systemic medical conditions, especially infections and inflammatory disease, but may occur as an isolated process. Treatment of non-infectious uveitis depends on the location of inflammation. Anterior uveitis is generally treated with topical glucocorticoids, such as prednisolone ophthalmic drops. Uveitis that is primarily posterior to the lens is generally not responsive to topical medication, although some experts are increasingly using difluprednate. Oral corticosteroids continue to be the mainstay of treatment for noninfectious intermediate, posterior, and pan uveitis. Intraocular and periocular injections of triamcinolone or glucocorticoids are also options, although patients may decline the injections. Systemic treatment is generally reserved for resistant inflammation and may be indicated in patients with glaucoma who cannot be treated with local injection. If remission has been achieved for 6 to 12 months with systemic glucocorticoids, the maintenance dose may be gradually discontinued. The American Academy of Ophthalmology recommends the use of immunosuppressive agents, such as methotrexate, azathioprine, mycophenolate, cyclosporine, and tacrolimus, for patients that are intolerant and/or resistant to systemic corticosteroids. TNF-inhibitors, such as adalimumab, are recommended if the patient is inadequately controlled by corticosteroids and non-corticosteroid systemic immunomodulatory therapies.

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 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	SQ: Cimzia, Cosentyx	N/A	SQ: Taltz	N/A	N/A

Spondyloarthritis (nr-axSpA)					
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, Orencia, 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, Orencia, 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

Initiation of adalimumab (Humira) 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 adalimumab (starting on samples is not approvable) within the past 90 days
 - b. The prescriber states the member has been treated with adalimumab (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. Adalimumab 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 adalimumab
 - II. The prescriber has provided information in support of using adalimumab for the member’s age
2. The prescriber is a specialist in the area of the member’s diagnosis (e.g., rheumatologist for JIA, PsA, RA; 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 adalimumab
 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 adalimumab 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
 - Adult AS, PsA, RA: no loading dose required
 - PJIA, adolescent uveitis: no loading dose required
 - Adult CD, UC: Initial dose of 160 mg on day 1, 80 mg on day 15, then maintenance dose starting on day 29
 - QL: Crohn’s Disease, Ulcerative Colitis, or Hidradenitis Starter kit 40 mg/0.8 mL pen - 1 kit (6 pens)/180 days
 - QL: 80 mg/0.8 mL pen, Crohn’s disease, ulcerative colitis, or hidradenitis suppurativa Starter kit - 1 kit (3 pens)/180 days
 - Pediatric CD:
 - 17kg to <40kg: Initial dose of 80 mg on day 1, 40 mg on day 15, then maintenance dose starting on day 29
 - QL: Pediatric Crohn’s Starter Kit 40 mg/0.8mL (Both 3 and 6 syringe pack) - 1 kit/180 day [1 kit (3 syringes), 1 kit (6 syringes)]
 - QL: Pediatric Crohn’s Disease Starter kit (40 mg/0.4 mL and 80 mg/0.8 mL syringe) - 1 kit (2 syringes)/180 days
 - ≥40kg: 160 mg on day 1, 80 mg on day 15, then maintenance dose starting on day 29
 - QL: Pediatric Crohn’s Starter Kit 40 mg/0.8mL (Both 3 and 6 syringe pack) - 1 kit/180 day [1 kit (3 syringes), 1 kit (6 syringes)]
 - QL: Pediatric Crohn’s Disease Starter kit (80 mg/0.8 mL syringe) - 1 kit (3 syringes)/180 days

- PS, Adult uveitis: Initial dose of 80 mg, then maintenance dose starting one week after the initial dose
 - QL: Psoriasis, Uveitis Starter kit 40 mg/0.8 mL pen - 1 kit (4 pens)/180 days
 - QL: 80 mg/0.8 mL and 40 mg/0.4 mL pen, Psoriasis, uveitis Starter kit - 1 kit (3 pens)/180 days
- Adult HS: Initial dose of 160 mg day 1, 80 mg on day 15, then maintenance dose starting on day 29
 - QL: Crohn's Disease, Ulcerative Colitis, or Hidradenitis Starter kit 40 mg/0.8 mL pen - 1 kit (6 pens)/180 days
 - QL: 80 mg/0.8 mL pen, Crohn's disease, ulcerative colitis, or hidradenitis suppurativa Starter kit - 1 kit (3 pens)/180 days
- Pediatric HS:
 - 30 kg to <60 kg: Initial dose of 80 mg on day 1, then maintenance dose starting on day 8
 - QL: Psoriasis, Uveitis Starter kit 40 mg/0.8 mL pen - 1 kit (4 pens)/180 days
 - QL: 80 mg/0.8 mL and 40 mg/0.4 mL pen, Psoriasis, uveitis Starter kit - 1 kit (3 pens)/180 days
 - ≥60 kg: 160 mg on day 1, 80 mg on day 15, then maintenance dose starting on day 29
 - QL: Crohn's Disease, Ulcerative Colitis, or Hidradenitis Starter kit 40 mg/0.8 mL pen - 1 kit (6 pens)/180 days
- Maintenance dose - 40 mg every 2 weeks (14 days) [for HS and RA monotherapy ONLY - 40 mg once a week (every 7 days)]
 - QL: 10 mg/0.1 mL syringe - 2 syringes/28 days
 - QL: 10 mg/0.2 mL syringe - 2 syringes/28 days
 - QL: 20 mg/0.2 mL syringe - 2 syringes/28 days
 - QL: 20 mg/0.4 mL syringe, kit - 2 syringes/28 days
 - QL: 40 mg/0.8 mL syringe, kit - 2 syringes/28 days
 - QL: 40 mg/0.4 mL syringe - 2 syringes/28 days
 - QL: 40 mg/0.8 mL pen - 2 pens/28 days
 - QL: 40 mg/0.4 mL pen - 2 pens/28 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:

- Adult AS, PsA, and RA - 12 months
- PJIA and adolescent uveitis - 12 months
- UC - Loading dose (doses on day 1 and 15) for 4 weeks, then maintenance dose for 8 additional weeks [12 weeks for total duration of approval]
- CD - Loading dose (doses on day 1 and 15) for 1 month, then maintenance dose for 11 additional months [12 months for total duration of approval]
- PS and adult uveitis - Loading dose (doses on day 1, 8, 22) for 1 month, then maintenance dose for 11 additional months [12 months for total duration of approval]
- Adult HS and pediatric HS (≥ 60 kg) - Loading dose (doses on day 1 and 15) for 1 month, then maintenance dose for 11 additional months [12 months for total duration of approval]
- Pediatric HS (30 kg to < 60 kg) - Loading dose (doses on day 1, 8, 22) for 1 month, then maintenance dose for 11 additional months [12 months for total duration of approval]
- Other indications - 12 months

Table 2

Diagnosis	Criteria
Moderately to severely active rheumatoid arthritis (RA)	<p>ONE of the following:</p> <ol style="list-style-type: none"> <li data-bbox="526 947 1385 1035">1. The member has tried and had an inadequate response to maximally tolerated methotrexate (e.g., titrated to 25 mg weekly) for at least 3 months <p>OR</p> <ol style="list-style-type: none"> <li data-bbox="526 1119 1352 1207">2. The member has tried and had an inadequate response to another conventional agent (i.e., hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA for at least 3-months <p>OR</p> <ol style="list-style-type: none"> <li data-bbox="526 1287 1385 1402">3. The member has an intolerance or hypersensitivity to ONE of the following conventional agents (i.e., maximally tolerated methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA <p>OR</p> <ol style="list-style-type: none"> <li data-bbox="526 1486 1385 1575">4. The member has an FDA labeled contraindication to ALL of the following conventional agents (i.e., methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA <p>OR</p> <ol style="list-style-type: none"> <li data-bbox="526 1654 1385 1770">5. 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 RA
Active psoriatic arthritis (PsA)	<p>ONE of the following:</p> <ol style="list-style-type: none"> <li data-bbox="526 1871 1320 1896">1. The member has tried and had an inadequate response to ONE

	<p>conventional agent (i.e., cyclosporine, leflunomide, methotrexate, sulfasalazine) used in the treatment of PsA 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 PsA</p> <p>OR</p> <p>3. The member has an FDA labeled contraindication to ALL of the conventional agents used in the treatment of PsA</p> <p>OR</p> <p>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)</p> <p>OR</p> <p>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)</p> <p>OR</p> <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 PsA</p>
<p>Moderate to severe plaque psoriasis (PS)</p>	<p>ONE of the following:</p> <p>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> <p>OR</p> <p>2. The member has an intolerance or hypersensitivity to ONE conventional agent used in the treatment of PS</p> <p>OR</p> <p>3. The member has an FDA labeled contraindication to ALL conventional agents used in the treatment of PS</p> <p>OR</p> <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>

	<p>OR</p> <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> <p>OR</p> <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>
<p>Moderately to severely active Crohn's disease (CD)</p>	<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, corticosteroids [e.g., prednisone, budesonide EC capsule], methotrexate, sulfasalazine) used in the treatment of CD 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 CD</p> <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>
<p>Moderately to severely active ulcerative colitis (UC)</p>	<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</p>

	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
Non-infectious intermediate uveitis, posterior uveitis, or panuveitis	<p>ONE of the following:</p> <p>1. BOTH of the following:</p> <p>A. ONE of the following:</p> <ul style="list-style-type: none"> i. The member has tried and had an inadequate response to oral corticosteroids used in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis for a minimum of 2 weeks <p>OR</p> <ul style="list-style-type: none"> ii. The member has tried and had an inadequate response to periocular or intravitreal corticosteroid injections in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis <p>OR</p> <ul style="list-style-type: none"> iii. The member has an intolerance or hypersensitivity to oral corticosteroids OR periocular or intravitreal corticosteroid injections used in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis <p>OR</p> <ul style="list-style-type: none"> iv. The member has an FDA labeled contraindication to BOTH oral corticosteroids and periocular/intravitreal corticosteroids <p>AND</p> <p>B. ONE of the following:</p> <ul style="list-style-type: none"> i. The member has tried and had an inadequate response to ONE conventional systemic agent (i.e., azathioprine, mycophenolate, methotrexate, cyclosporine, tacrolimus) used in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis for at least 3 months <p>OR</p> <ul style="list-style-type: none"> ii. The member has an intolerance or hypersensitivity to ONE conventional systemic agent used in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis <p>OR</p> <ul style="list-style-type: none"> iii. The member has an FDA labeled contraindication to ALL conventional systemic agents used in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis <p>OR</p> <p>2. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex</p>

	with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a for the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis
Active ankylosing spondylitis (AS)	<p>ONE of the following:</p> <ol style="list-style-type: none"> 1. The member has tried and had an inadequate response to TWO different NSAIDs used in the treatment of AS for at least a 4-week total trial <p>OR</p> <ol style="list-style-type: none"> 2. The member has an intolerance or hypersensitivity to TWO different NSAIDs used in the treatment of AS <p>OR</p> <ol style="list-style-type: none"> 3. The member has an FDA labeled contraindication to ALL NSAIDs used in the treatment of AS <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 AS
Moderately to severely active polyarticular juvenile idiopathic arthritis (PJIA)	<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., methotrexate, leflunomide) used in the treatment of PJIA 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 PJIA <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 PJIA <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 PJIA
Moderate to severe hidradenitis suppurative (HS)	<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., oral tetracyclines [doxycycline, minocycline, tetracycline]; oral contraceptives [females only]; metformin [females only]; finasteride [females only]; spironolactone [females only]; intralesional corticosteroids [triamcinolone]; clindamycin in combination with rifampin; combination of rifampin, moxifloxacin, and metronidazole;

	<p>cyclosporine, oral retinoids) used in the treatment of HS for at least 3 months</p> <p>OR</p> <p>2. The member has an intolerance or hypersensitivity to ONE conventional agent used in the treatment of HS</p> <p>OR</p> <p>3. The member has an FDA labeled contraindication to ALL conventional agents used in the treatment of HS</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 HS</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 adalimumab (Humira) meets the definition of medical necessity when **ALL** of the following are met ("1" to "6"):

1. An authorization or reauthorization for adalimumab has been previously approved by Florida Blue
2. Member has had clinical benefit with adalimumab therapy
3. The prescriber is a specialist in the area of the member's diagnosis (e.g., rheumatologist for PsA, RA; 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 adalimumab
5. Member will **NOT** be using adalimumab in combination with another biologic immunomodulator agent or Otezla
6. **ANY** of the following ("a", "b", or "c"):
 - a. The dosage does not exceed 40 mg every 2 weeks (14 days) [for HS and RA monotherapy **ONLY** - 40 mg once a week (every 7 days)]
 - QL: 10 mg/0.1 mL syringe - 2 syringes/28 days
 - QL: 10 mg/0.2 mL syringe - 2 syringes/28 days
 - QL: 20 mg/0.2 mL syringe - 2 syringes/28 days
 - QL: 20 mg/0.4 mL syringe, kit - 2 syringes/28 days
 - QL: 40 mg/0.8 mL syringe, kit - 2 syringes/28 days
 - QL: 40 mg/0.4 mL syringe - 2 syringes/28 days
 - QL: 40 mg/0.8 mL pen - 2 pens/28 days
 - QL: 40 mg/0.4 mL pen - 2 pens/28 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: 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.

Table 3

Table 2: FDA-approved indications and recommended dosing	
Indication	Dosage[†]
Ankylosing Spondylitis	<ul style="list-style-type: none"> 40 mg every other week
Crohn's Disease (CD)	<p>Weight 17 kg to less than 40 kg:</p> <ul style="list-style-type: none"> Initial: 80 mg at week 0, and 40 mg at week 2 (day 15) Maintenance: 20 mg every other week beginning at week 4 <p>Weight 40 kg or greater:</p> <ul style="list-style-type: none"> Initial: 160 mg at week 0, and 80 mg at week 2 (day 15) Maintenance: 40 mg every other week beginning at week 4
Hidradenitis Suppurativa	<p>≥60 kg (132 lbs.):</p> <ul style="list-style-type: none"> Initial: 160 mg at week 0, followed by 80 mg at week 2 (day 15) Maintenance: 40 mg every week beginning at week 4 (day 29) <p>30 kg (66 lbs.) to <60 kg (132 lbs.):</p> <ul style="list-style-type: none"> Initial: 80 mg at week 0, followed by 40 mg at week 1 (day 8) Maintenance: 40 mg every 2 weeks beginning at week 3 (day 22)
Juvenile Idiopathic Arthritis (JIA)	<p>Dose is based on weight:</p> <ul style="list-style-type: none"> 15 kg to 29.9 kg (33-66 lbs): 20 mg every other

	<p>week</p> <ul style="list-style-type: none"> 30 kg or more: 40 mg every other week
Plaque Psoriasis	<ul style="list-style-type: none"> Initial: 80 mg at week 0 Maintenance: 40 mg every other week beginning at week 1
Psoriatic Arthritis (PsA)	<ul style="list-style-type: none"> 40 mg every other week
Rheumatoid Arthritis (RA)	<ul style="list-style-type: none"> Concomitant DMARD: 40 mg every other week Monotherapy: 40 mg weekly
Ulcerative Colitis (UC)	<ul style="list-style-type: none"> Initial: 160 mg at week 0, followed by 80 mg at week 2 (day 15) Maintenance: 40 mg every other week beginning at week 4 (day 29)
Uveitis (non-infectious intermediate, posterior and panuveitis)	<p>Adult (≥18 years old):</p> <ul style="list-style-type: none"> Initial: 80 mg at week 0 Maintenance: 40 mg every other week beginning at week 1 <p>Pediatric</p> <ul style="list-style-type: none"> ≥30 kg (66 lbs.): 40 mg every other week 15 kg (33 lbs.) to <30 kg (66 lbs.): 20 mg every other week 10 kg (22 lbs.) to <15 kg (33 lbs.): 10 mg every other week
†Administered as a subcutaneous injection	

- **Dose Adjustments:** dosage adjustments are not required for members with hepatic or renal impairment.
- **Drug Availability:**
 - Starter Packs
 - Starter Pack for Plaque Psoriasis and Uveitis
 - Starter Pack for Plaque Psoriasis and Uveitis (citrate-free)
 - Starter Pack for Crohn's Disease, Ulcerative Colitis, and Hidradenitis Suppurativa
 - Starter Pack for Crohn's Disease, Ulcerative Colitis, and Hidradenitis Suppurativa (citrate-free)
 - Starter Pack for Pediatric Crohn's Disease (<40 kg)
 - Starter Pack for Pediatric Crohn's Disease (<40 kg) (citrate-free)
 - Starter Pack for Pediatric Crohn's Disease (≥40 kg)
 - Starter Pack for Pediatric Crohn's Disease (≥40 kg) (citrate-free)
 - **Pen**
 - 80 mg/0.8 mL single-use pen (citrate-free) - only available in starter packs
 - 40 mg/0.8 mL single-use pen - carton of two pens
 - 40 mg/0.4 mL single-use pen (citrate-free) - carton of two pens
 - **Prefilled Syringe**

- 80 mg/0.8 mL single-use syringe (citrate-free) – only available in starter packs
- 40 mg/0.8 mL single-use syringe - carton of two syringes
- 40 mg/0.4 mL single-use syringe (citrate-free) - carton of two syringes
- 20 mg/0.4 mL single-use syringe - carton of two syringes
- 20 mg/0.2 mL single-use syringe (citrate-free) - carton of two syringes
- 10 mg/0.2 mL single-use syringe - carton of two syringes
- 10 mg/0.1 mL single-use syringe (citrate-free) - carton of two syringes
- **Single-Use Institutional Use Vial**
 - 40 mg/0.8 mL single-use vial – carton of one vial

PRECAUTIONS:

Boxed Warning

- **Infections:** tuberculosis (TB), invasive fungal, and other opportunistic infections, some fatal, have occurred. Perform test for latent TB; if positive, start treatment for TB prior to starting therapy. Monitor all patients for active TB, even if initial tuberculin skin test is negative.
- **Malignancy:** lymphoma and other malignancies, some fatal have been reported in children and adolescent individuals treated with TNF blockers including adalimumab. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have occurred in adolescents and young adults with inflammatory bowel disease.

Contraindications

- None

Warnings/Precautions

Serious Infections: adalimumab should not be initiated in members during an active infection. If an infection develops, monitor carefully, and discontinue adalimumab if infection becomes serious.

- **Invasive fungal infections:** If a member develops a systemic infection while on adalimumab therapy, consider empiric antifungal therapy for those who reside or travel to regions where mycoses are endemic
- **Anaphylaxis:** anaphylaxis or serious allergic reactions may occur.
- **Hepatitis B virus reactivation:** members who are HBV carriers should be monitored during and several months after therapy. If reactivation occurs during therapy, discontinue adalimumab and initiate anti-viral therapy.
- **Demyelinating disease:** exacerbation of new onset may occur
- **Cytopenia, pancytopenia:** advise members to seek immediate medical attention if symptoms develop and consider discontinuing adalimumab.
- **Heart failure:** worsening or new onset heart failure may occur.
- **Lupus-like syndrome:** discontinue adalimumab if syndrome develops.
- **Drug Interactions:** avoid concomitant use with abatacept (Orencia®) and anakinra (Kineret®), due to increased risk of serious infection.
- **Live vaccines:** Avoid administration of live vaccines (e.g., varicella and MMR) in members taking adalimumab.

- **Pregnancy and Lactation**

- Adalimumab is classified as pregnancy category B. Developmental toxicity studies performed in animals have revealed no evidence of harm to the fetus. There are no studies in pregnant women and use during pregnancy should only occur if clearly needed.
- Because many immunoglobulins are secreted in milk and the potential for serious adverse reactions exists, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

BILLING/CODING INFORMATION:

HCPSC Coding:

J0135	Adalimumab (Humira) Injection 20 mg
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ICD-10 Diagnosis Codes That Support Medical Necessity:

H20.041 – H20.049	Secondary noninfectious iridocyclitis
H44.111 – H44.119	Panuveitis
K50.00 – K50.919	Crohn's disease [regional enteritis]
K51.00 – K51.919	Ulcerative colitis
K52.3	Indeterminate colitis
L40.0	Psoriasis vulgaris
L40.50 – L40.59	Arthropathic psoriasis
L73.2	Hidradenitis suppurativa
M05.00 – M05.09	Felty's syndrome
M05.10 – M05.19	Rheumatoid lung disease with rheumatoid arthritis
M05.20 – M05.29	Rheumatoid vasculitis with rheumatoid arthritis
M05.30 – M05.39	Rheumatoid heart disease with rheumatoid arthritis
M05.40 – M05.49	Rheumatoid myopathy with rheumatoid arthritis
M05.50 – M05.59	Rheumatoid polyneuropathy with rheumatoid arthritis
M05.60 – M05.69	Rheumatoid arthritis with involvement of other organs and systems
M05.70 – M05.79	Rheumatoid arthritis with rheumatoid factor without organ or systems involvement
M05.80 – M05.89	Other rheumatoid arthritis with rheumatoid factor
M05.9	Rheumatoid arthritis with rheumatoid factor, unspecified
M06.00 – M06.09	Rheumatoid arthritis without rheumatoid factor
M06.20 – M06.29	Rheumatoid bursitis
M06.30 – M06.39	Rheumatoid nodule
M06.80 – M06.89	Other specified rheumatoid arthritis
M06.9	Rheumatoid Arthritis, unspecified
M08.09	Unspecified Juvenile rheumatoid arthritis, multiple sites
M08.1	Juvenile ankylosing spondylitis
M08.3	Juvenile Rheumatoid polyarthritis (seronegative)
M08.89	Other juvenile arthritis, multiple sites
M35.2	Behçet's disease
M45.0 – M45.9	Ankylosing spondylitis
M46.81 – M46.89	Other specified inflammatory spondylopathies

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:

Crohn's disease: A chronic granulomatous inflammatory disease of unknown etiology, involving any part of the gastrointestinal tract from mouth to anus, but commonly involving the terminal ileum with scarring and thickening of the bowel wall.

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).

Hidradenitis suppurativa (HS) (a.k.a., acne inversa): a chronic, inflammatory, recurrent, debilitating skin disease of the hair follicle that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillae, inguinal and anogenital regions. HS may have a large impact on quality of life, often causing depression, impaired sexual health, and embarrassment. Squamous cell carcinoma may arise from chronic (10-30 years of evolution) lesions. The main goals of treatment are to prevent the formation of new lesion, treat new lesions, and eliminate existing nodules and sinus tract to limit or prevent scar formation.

Moderate to Severe Crohn's Disease: Moderate to severe disease applies to patients who have failed to respond to treatment for mild to moderate disease or those with more prominent symptoms of fevers, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia.

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 (PsA): 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.

Rheumatoid arthritis: An inflammatory disease of the synovium, or lining of the joint which results in pain, stiffness, and swelling of multiple joints. The inflammation may extend to other joints and cause bone and cartilage erosion, joint deformities, movement problems, and activity limitations.

RELATED GUIDELINES:

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

[Baricitinib \(Olumiant\), 09-J3000-10](#)

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

[Canakinumab \(Ilaris\) Injection, 09-J1000-14](#)

[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](#)

[Rilonacept \(Arcalyst\) Injection, 09-J0000-89](#)

[Rituximab \(Rituxan\), 09-J0000-59](#)

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

[Sarilumab \(Kevzara\), 09-J2000-87](#)

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

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

[Tocilizumab \(Actemra\) Injection, 09-J1000-21](#)

[Tofacitinib \(Xeljanz, Xeljanz XR\) Tablets, 09-J1000-86](#)

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

[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

Table 5: Grading of Severity of Rheumatoid Arthritis

Severity	Criteria
Mild	<p>Joint pain</p> <p>Inflammation of at least 3 joints</p> <p>No inflammation in tissues other than the joints</p> <p>Usually, a negative result on a rheumatoid factor test</p> <p>An elevated erythrocyte sedimentation rate (ESR) or C reactive protein (CRP) level</p> <p>No evidence of bone or cartilage damage on x-rays</p>
Moderate	<p>Between 6 and 20 inflamed joints</p> <p>Usually no inflammation in tissues other than the joints</p> <p>An elevated ESR or CRP levels</p> <p>A positive rheumatoid factor test or anti-cyclic citrullinated peptide (anti-CCP) antibodies</p> <p>Evidence of inflammation but no evidence of bone damage on x-rays</p>
Severe	<p>More than 20 persistently inflamed joints or a rapid loss of functional abilities</p> <p>Elevated ESR or CRP levels</p> <p>Anemia related to chronic illness</p> <p>Low blood albumin level</p> <p>A positive rheumatoid factor test, often with a high level</p> <p>Evidence of bone and cartilage damage on x-ray</p> <p>Inflammation in tissues other than joints</p>

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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:

01/01/05	New Medical Coverage Guideline.
08/15/05	Revised and Updated: Updated description, dosage/administration. Deleted precautions, updated when services are not covered, billing/coding information, and definitions, table 1, references.
11/15/05	Updated when services are covered for psoriatic arthritis, updated ICD-9 codes, definitions, and references.
11/15/06	Scheduled review: added indication of ankylosing spondylitis, added ICD-9 code, corrected CPT-4 coding and updated references.
01/01/07	MCG revised to include Medicare Part D as program exception.
04/15/07	Revision; consisting of adding Crohn's disease indication and ICD-9 code, related guidelines and definitions.
06/15/07	Review and revision; consisting of reformatting, updating related guidelines and references.

03/15/08	Revision; consisting of adding plaque psoriasis and juvenile idiopathic arthritis (JIA) as covered indications, rewording coverage criteria for Crohn's disease, updated dosage and administration section, added ICD-9 codes and updated references.
05/15/08	Review and revision; consisting of reformatting, adding a black box warning under "PRECAUTIONS", adding related guideline and updating references.
09/15/08	Revision of guideline; consisting of adding 3 ICD-9 codes.
01/01/09	Annual HCPCS coding update: deleted code 90772; added code 96372.
09/15/09	Review and revision; consisting of updating references, boxed warning and ICD-9 coding.
04/15/10	Revision; consisting of adding specific continuation criteria.
08/15/10	Review and revision; consisting of adding age criteria to all indications, updated precautions and references.
01/15/11	Revision; consisting of adding ICD-10 codes.
04/01/11	Revision; consisting of adding dosage limitations.
08/15/11	Review and revision to guideline; consisting of updating the precautions section, coding and references.
08/15/12	Review and revision to guideline; consisting of reformatting position statement, updating precautions and references.
09/15/12	Revision to guideline consisting of modifying plaque psoriasis criteria and continuation criteria.
11/15/12	Revision to guideline consisting of adding new indication of ulcerative colitis.
01/15/13	Revision to guideline; consisting of revising/reformatting/updating position statement, description, dosage/administration sections; reformatting precautions section; updating references.
04/15/13	Revision to guideline; consisting of revising position statement to include Orphan Drug indications and duration of approval
09/15/13	Review and revision to guideline; consisting of reformatting position statement, updating program exceptions section and references.
01/01/14	Revision to guideline; consisting of updating position statement.
04/15/14	Revision to guideline; consisting of reformatting and revising position statement to include clarifying language.
09/15/14	Review and revision to guideline; consisting of updating position statement, references, coding and related guidelines.
12/15/14	Revision to guideline; consisting of position statement, dosage/administration, references
09/15/15	Review and revision to guideline; consisting of consisting of updating description section, position statement, billing/coding, related guidelines, and references.
11/01/15	Revision: ICD-9 Codes deleted.
11/15/15	Revision to guideline; consisting of updating description section, position statement, dosage/administration, and references based on a new FDA-approved indication.
02/15/16	Revision to guideline consisting of updating maximum dosages for pediatric patients in the position statement.
09/15/16	Review and revision to guideline consisting of consisting of updating description section, position statement, billing/coding, definitions, related guidelines, and references.
10/01/16	Revision: ICD-10 code updates
10/15/17	Review and revision to guideline consisting of updating description, position statement, definitions, related guidelines, and references
01/01/18	Revision to guideline consisting of updating the preferred self-administered biologic products according to indication for use.

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, related guidelines, and references.
12/15/18	Revision to guideline consisting of updating the description, position statement, dosage/administration, and references based on new pediatric/adolescent indications.
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 position statement "Note" due to changes in preferred products.
03/15/20	Revision to guideline consisting of updating the description section.
07/01/20	Review and revision to guideline consisting of updating the description section, position statement, definitions, billing/coding, and other.
01/01/21	Review and revision to guideline consisting of updating the description, position statement and references.