Original Effective Date: 11/01/2012
Current Effective Date: 07/04/2024
Last P&T Approval/Version: 10/30/2024
Next Review Due By: 10/2025
Policy Number: C10421-A

Infliximab and Biosimilars

PRODUCTS AFFECTED

Avsola (infliximab-axxq), Inflectra (infliximab-dyyb), infliximab, Remicade (infliximab), Renflexis (infliximab-abda), Zymfentra (infliximab-dyyb)

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Rheumatoid Arthritis, Psoriatic Arthritis, Psoriasis, Ulcerative Colitis, Plaque Psoriasis, Ankylosing Spondylitis, Crohn's Disease, Behcet's Syndrome, Hidradenitis Suppurativa, Active Still's Disease, Juvenile Idiopathic Arthritis, Kawasaki Disease, Takayasu's Disease, Non- infectious Uveitis

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

FOR ALL INDICATIONS:

1. Prescriber attests member does not have an active or latent untreated infection (e.g., Hepatitis B, tuberculosis, etc.), including clinically important localized infections, according to the FDA label AND

2. Member is not on concurrent treatment or will not be used in combination with other TNF-inhibitor, biologic response modifier or other biologic DMARDs, Janus kinase Inhibitors, or Phosphodiesterase 4 inhibitor (i.e., apremilast, tofacitinib, baricitinib) as verified by prescriber attestation, member medication fill history, or submitted documentation
   AND
3. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to infliximab include: doses of infliximab greater than 5 mg/kg in members with moderate or severe heart failure, history of severe hypersensitivity reaction to infliximab or any inactive ingredients or to any murine proteins.]
   AND
4. (a) IF THIS IS A PHARMACY BENEFIT REQUEST FOR A NON-FORMULARY/NON-PREFERRED PRODUCT: Documentation of trial/failure of or serious side effects to a majority (not more than 3) of the preferred formulary/PDL alternatives for the given diagnosis. Documentation of medication(s) tried, dates of trial(s) and reason for treatment failure(s) is required.
   AND
   (b) If request is for reference product with a biosimilar available for initial or continuation of therapy requests: Documentation of a trial and failure, serious side effects or contraindication to a majority (not more than 3) biosimilar product(s) is required (unless otherwise specified per applicable state regulations and/or there is data demonstrating clinical superiority of reference drugs over the FDA approved biosimilar drugs). [DOCUMENTATION REQUIRED: Document when the preferred biologic product or biosimilar was tried and the length of the trial period. Provide specific clinical documentation of therapeutic failure on the preferred biologic product or biosimilar whenever possible. Describe the medical problem caused by the preferred referenced biologic. Vague and non-descriptive symptoms are not adequate rationale (e.g., stomachache).]
   OR
5. FOR INITIAL OR CONTINUATION OF THERAPY REQUESTS OF A PHYSICIAN ADMINISTERED MEDICATION: BIOSIMILAR DRUGS are preferred when requested as a physician administered drug per applicable state regulations and/or there is a lack of data demonstrating clinical superiority of reference drugs over the FDA approved biosimilar drugs. A reference medication is approved under the following conditions:
   a. Treatment with at least two associated biosimilar drug(s) has been ineffective, resulted in serious side effects, or is contraindicated (i.e. an allergic reaction to a specific inactive ingredient in the preferred biologic product or biosimilar OR an adverse reaction to a specific inactive ingredient in the preferred biologic product or biosimilar OR therapeutic success while taking a non-preferred biologic product or biosimilar and therapeutic failure while taking the preferred biologic product or biosimilar documented by patient diary or medical charted notes)

   [DOCUMENTATION REQUIRED: Document when the preferred biologic product or biosimilar was tried and the length of the trial period. Provide specific clinical documentation of therapeutic failure on the preferred biologic product or biosimilar whenever possible. Describe the medical problem caused by the preferred referenced biologic. Vague and non-descriptive symptoms are not adequate rationale (e.g., stomachache).]

A. MODERATE TO SEVERE RHEUMATOID ARTHRITIS (IV ONLY):
   1. Documentation of moderate to severe rheumatoid arthritis diagnosis
      AND
   2. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal [DOCUMENTATION REQUIRED]
      AND
   3. (a) Member is currently receiving maximally tolerated dose of methotrexate and is not at goal disease activity
      OR
      (b) Member has an FDA labeled contraindication or serious side effects to methotrexate, as determined by the prescribing physician AND Member has tried one additional disease- modifying antirheumatic drug (DMARD) (brand or generic; oral or injectable) for at least 3 months

(NOTE: An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the member has already had a 3-month trial of at least one biologic. These members who have already tried a biologic for RA are not required to "step back" and try a conventional synthetic DMARD.)

B. PSORIATIC ARTHRITIS (PsA) (IV ONLY):
1. Documentation of active psoriatic arthritis
   AND
2. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy [DOCUMENTATION REQUIRED]
   AND
3. (a) Documented treatment failure, serious side effects or clinical contraindication to a minimum 3-month trial of ONE of the following: Leflunomide, Methotrexate, Sulfasalazine, Cyclosporine
   OR
   (b) Documentation member has severe psoriatic arthritis [erosive disease, elevated markers of inflammation, long term damage that interferes with function, 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 or rapidly progressive disease]
   OR
   (c) Documentation of member has severe psoriasis [PASI ≥12, BSA of >5-10%, significant involvement in specific areas (e.g., face, hands or feet, nails, intertriginous areas, scalp), impairment of physical or mental functioning with lower amount of surface area of skin involved]

C. ULCERATIVE COLITIS:
1. Documentation of ulcerative colitis diagnosis with evidence of moderate to severe disease activity
   AND
2. (a) Documentation of treatment failure, serious side effects or clinical contraindication to a 2-month trial of one systemic agent (e.g., 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone, methylprednisolone) for ulcerative colitis or will continue to take concurrently.
   NOTE: A previous trial of a biologic (e.g., an adalimumab product [e.g., Humira], Simponi SC [golimumab SC injection], or Entyvio [vedolizumab IV infusion]) also counts as a trial of one systemic agent for UC
   OR
   (b) The Member has pouchitis AND has tried therapy with an antibiotic (e.g., metronidazole, ciprofloxacin), probiotic, corticosteroid enema [for example, Cortenema® (hydrocortisone enema, generics)], or topical mesalamine
   AND
3. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal [DOCUMENTATION REQUIRED]
   AND
4. FOR SQ REQUESTS FOR ADULTS ONLY: Member has completed an intravenous infliximab induction regimen and request is for maintenance treatment starting week 10 or later

D. CHRONIC PLAQUE PSORIASIS (IV ONLY):
1. Documented diagnosis of moderate to severe psoriasis (BSA ≥ 3%) OR < 3% body surface area with plaque psoriasis that involves sensitive areas of the body or areas that would significantly impact daily function (e.g., face, neck, hands, feet, genitals)
   AND
2. (a) Documentation of treatment failure, serious side effects, or clinical contraindication to TWO of the following systemic therapies for ≥ 3 months: Methotrexate (oral or IM at a minimum dose of 15 mg/week), cyclosporine, acitretin, azathioprine, hydroxyurea, leflunomide, mycophenolate mofetil, or tacrolimus
   OR
   (b) Documentation of treatment failure to Phototherapy for ≥3 months with either psoralens with ultraviolet A (PUVA) or ultraviolet B (UVB) radiation (provider to submit documentation of duration of treatment, dates of treatment, and number of sessions; contraindications include type1 or type 2 skin, history of photosensitivity, treatment of facial lesions, presence of premalignant lesions,

history of melanoma or squamous cell carcinoma, or physical inability to stand for the required exposure time)
AND

3. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal [DOCUMENTATION REQUIRED]

E. MODERATE TO SEVERE ANKYLOSING SPONDYLITIS (IV ONLY):

1. Documented diagnosis of ankylosing spondylitis
AND
2. Documentation of treatment failure, serious side effects or clinical contraindication to TWO NSAIDs (e.g., ibuprofen, naproxen, etodolac, meloxicam, indomethacin) for ≥3 consecutive months at maximal recommended or tolerated anti-inflammatory doses
AND
3. FOR MEMBER WITH PROMINENT PERIPHERAL ARTHRITIS: Documentation of treatment failure, serious side effects or clinical contraindication to a trial (≥3 consecutive months) of methotrexate OR sulfasalazine
AND
4. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal [DOCUMENTATION REQUIRED]

F. MODERATE TO SEVERE ACTIVE CROHN'S DISEASE:

1. Documentation of a diagnosis of Crohn's Disease
AND
2. Member has one or more high risk feature:
   i. Diagnosis at a younger age (<30 years old)
   ii. History of active or recent tobacco use
   iii. Elevated C-reactive protein and/or fecal calprotectin levels
   iv. Deep ulcers on colonoscopy
   v. Long segments of small and/or large bowel involvement
   vi. Perianal disease
   vii. Extra-intestinal manifestations
   viii. History of bowel resections
   AND
3. (a) Documentation of treatment failure, serious side effects or clinical contraindication to an adequate trial (>3 months) of ONE immunomodulator (e.g., azathioprine, 6- mercaptopurine, methotrexate) up to maximally indicated doses
   OR
   (b) Prescriber provides documented medical justification that supports the inability to use immunomodulators
      i. Inability to induce short-term symptomatic remission with a 3-month trial of systemic glucocorticoids
      ii. High-risk factors for intestinal complications may include: Initial extensive ileal, ileocolonic, or proximal GI involvement, Initial extensive perianal/severe rectal disease, Fistulizing disease (e.g., perianal, enterocutaneous, and rectovaginal fistulas), Deep ulcerations, Penetrating, stricturing or stenosis disease and/or phenotype, Intestinal obstruction or abscess
      iii. High risk factors for postoperative recurrence may include: Less than 10 years duration between time of diagnosis and surgery, Disease location in the ileum and colon, Perianal fistula, Prior history of surgical resection, Use of corticosteroids prior to surgery
   AND
4. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal [DOCUMENTATION REQUIRED]
AND
5. FOR SQ REQUESTS FOR ADULTS ONLY: Member has completed an intravenous infliximab induction regimen and request is for maintenance treatment starting week 10 or later

G. BEHCET'S SYNDROME (IV ONLY):
1. Documented diagnosis of Behcet's Syndrome
AND
2. Documentation of recurrent oral aphthae (at least three times in one year) plus two of the following clinical features: (a) Recurrent genital aphthae (aphthous ulceration or scarring) (b) Eye lesions (including anterior or posterior uveitis, cells in vitreous on slit lamp examination, or retinal vasculitis observed by an ophthalmologist), (c) Skin lesions (including erythema nodosum, pseudo folliculitis, papulopustular lesions, or acneiform nodules consistent with Behçet syndrome) or (d) A positive pathergy test.
AND
3. (a) The member has tried at least ONE conventional therapy (e.g., systemic corticosteroids [for example, methylprednisolone], immunosuppressants [azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, tacrolimus, Leukeran® (chlorambucil), cyclophosphamide], interferon alfa, colchicine, sucralfate suspension or triamcinolone in Orabase).
NOTE: An exception to the requirement for a trial of one conventional therapy can be made if the member has already had a trial of at least one tumor necrosis factor inhibitor (e.g., an adalimumab product [e.g., Humira], an etanercept product [e.g., Enbrel]). These members who have already tried a biologic for Behcet's disease are not required to "step back" and try a conventional therapy.
OR
(b) The member has ophthalmic manifestations of Behcet's disease
AND
4. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal [DOCUMENTATION REQUIRED]

H. HIDRADENITIS SUPPURATIVA (IV ONLY):
1. Documentation of diagnosis of Hidradenitis suppurativa Hurley stage II (moderate recurrent) or stage III (severe diffuse) disease
AND
2. Prescriber attestation that IF member is a smoker, the member has been counseled regarding the benefits of smoking cessation and/or connected with a program to support smoking cessation
AND
3. Documentation indicating the member has been counseled on the use of general supportive measures (e.g., education and support, avoidance of skin trauma, hygiene, dressings, smoking cessation, weight management, diet)
AND
4. (a) Documentation of treatment failure with or a clinical contraindication to a 3-month trial of the following:
(i) Oral antibiotic (e.g., minocycline, doxycycline, clindamycin/rifampin) AND
(ii) Antiandrogen (e.g., finasteride)
AND
(b) Documentation of treatment failure with or a clinical contraindication to intralesional corticosteroids
AND
5. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal [DOCUMENTATION REQUIRED]

I. ACTIVE STILL'S DISEASE (IV ONLY):
1. Documented diagnosis of adult onset still's disease
AND
2. Documentation of treatment failure or labeled contraindication to: (i) TWO formulary non-steroidal anti-inflammatory drugs (after 14 days of treatment) AND (ii) methotrexate (after 2 months of treatment at maximally tolerated dose)
AND

3. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal [DOCUMENTATION REQUIRED]

J. JUVENILE IDIOPATHIC ARTHRITIS (ACTIVE SYSTEMIC AND POLYARTICULAR) (IV ONLY):
1. Documented diagnosis of systemic juvenile idiopathic arthritis (SJIA) or polyarticular juvenile idiopathic arthritis (PJIA) in a pediatric member
AND
2. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal [DOCUMENTATION REQUIRED]
AND
3. (a) FOR ACTIVE SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS:
   i. Documentation of treatment failure, serious side effects or clinical contraindication to an adequate trial (12 weeks) of one NSAID or glucocorticoid
   AND
   ii. Documentation of treatment failure, serious side effects or clinical contraindication to an adequate trial (12 weeks) of one of the following: methotrexate, leflunomide, anakinra (Kineret), canakinumab (Ilaris), or tocilizumab (Actemra)

OR

(b) FOR POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS: Documentation of treatment failure, serious side effects or clinical contraindication to an adequate trial (generally ≥12 weeks) of one or more of the following: Methotrexate, hydroxychloroquine, sulfasalazine, leflunomide

K. KAWASAKI DISEASE (IV ONLY):
1. Documented diagnosis of Kawasaki disease
AND
2. Documentation member has failed respond to IVIG therapy AND 1-3 doses of glucocorticoid therapy (failure defined as: member has persistent and recurrent fever 24 hours after completion of therapy) [DOCUMENTATION REQUIRED]

L. TAKAYASU'S DISEASE (IV ONLY):
1. Documented diagnosis of Takayasu arteritis
AND
2. Documentation member has had a trial and failure (3 months) or contraindication to glucocorticoids AND any ONE of the following at maximally tolerated doses: methotrexate, azathioprine, mycophenolate or leflunomide
AND
3. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal [DOCUMENTATION REQUIRED]

M. NON-INFECTIOUS UVEITIS (IV ONLY):
1. Documentation of diagnosis of non-infectious intermediate, posterior, or pan- uveitis
AND
2. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal [DOCUMENTATION REQUIRED]
AND
3. (a) Documentation of treatment failure, serious side effects, or clinical contraindication to ONE of the following: (i) an intravitreal steroid (e.g., triamcinolone, dexamethasone) OR (ii) a systemic corticosteroid (e.g., prednisone, methylprednisolone) OR (iii) an anti-metabolite (e.g., methotrexate, azathioprine, mycophenolate) OR (iv) a calcineurin inhibitor (e.g., Cyclosporine, tacrolimus)
OR
(b) Documentation of severe uveitis associated with Behcet's syndrome

CONTINUATION OF THERAPY:

Drug and Biologic Coverage Criteria

A. ALL INDICATIONS (except KAWASAKI DISEASE):
   1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
      AND
   2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
      AND
   3. Documentation of positive clinical response as demonstrated by low disease activity and/or improvements in the condition's signs and symptoms [DOCUMENTATION REQUIRED]
      AND
   4. Prescriber attests to ongoing monitoring for development of infection (e.g., tuberculosis, Hepatitis B reactivation, etc.) according to the FDA label
      AND
   5. FOR INITIAL SQ REQUESTS FOR UC OR CROHN'S DISEASE FOR ADULTS ONLY: Member has completed an intravenous infliximab induction regimen and request is for maintenance treatment starting week 10 or later
      AND
   6. (a) IF THIS IS A PHARMACY BENEFIT REQUEST FOR A NON-FORMULARY/NON-PREFERRED PRODUCT: Documentation of trial/failure of or serious side effects to a majority (not more than 3) of the preferred formulary/PDL alternatives for the given diagnosis. Documentation of medication(s) tried, dates of trial(s) and reason for treatment failure(s) is required.
      AND
      (b) If request is for reference product with a biosimilar available for initial or continuation of therapy requests: Documentation of a trial and failure, serious side effects or contraindication to a majority (not more than 3) biosimilar product(s) is required (unless otherwise specified per applicable state regulations and/or there is data demonstrating clinical superiority of reference drugs over the FDA approved biosimilar drugs).
      [DOCUMENTATION REQUIRED: Document when the preferred biologic product or biosimilar was tried and the length of the trial period. Provide specific clinical documentation of therapeutic failure on the preferred biologic product or biosimilar whenever possible. Describe the medical problem caused by the preferred referenced biologic. Vague and non-descriptive symptoms are not adequate rationale (e.g., stomachache).]
      OR
   7. FOR INITIAL OR CONTINUATION OF THERAPY REQUESTS OF A PHYSICIAN ADMINISTERED MEDICATION: BIOSIMILAR DRUGS are preferred when requested as a physician administered drug per applicable state regulations and/or there is a lack of data demonstrating clinical superiority of reference drugs over the FDA approved biosimilar drugs. A reference medication is approved under the following conditions:
      a. Treatment with at least two associated biosimilar drug(s) has been ineffective, resulted in serious side effects, or is contraindicated (i.e. an allergic reaction to a specific inactive ingredient in the preferred biologic product or biosimilar OR an adverse reaction to a specific inactive ingredient in the preferred biologic product or biosimilar OR therapeutic success while taking a non-preferred biologic product or biosimilar and therapeutic failure while taking the preferred biologic product or biosimilar documented by patient diary or medical charted notes)

      [DOCUMENTATION REQUIRED: Document when the preferred biologic product or biosimilar was tried and the length of the trial period. Provide specific clinical documentation of therapeutic failure on the preferred biologic product or biosimilar whenever possible. Describe the medical problem caused by the preferred referenced biologic. Vague and non-descriptive symptoms are not adequate rationale (e.g., stomachache).]

DURATION OF APPROVAL:

KAWASAKI DISEASE: 1 month

ALL OTHER INDICATIONS: Initial authorization: 6 months, Continuation of therapy: 12 months

PRESCRIBER REQUIREMENTS:

CROHN'S DISEASE AND ULCERATIVE COLITIS: Prescribed by or in consultation with a board-certified gastroenterologist, colorectal surgeon

MODERATE TO SEVERE ANKYLOSING SPONDYLITIS, RHEUMATOID ARTHRITIS, JUVENILE IDIOPATHIC ARTHRITIS: Prescribed by or in consultation with a board-certified rheumatologist

PSORIATIC ARTHRITIS (PsA): Prescribed by or in consultation with a board-certified rheumatologist or dermatologist

CHRONIC PLAQUE PSORIASIS, HIDRADENITIS SUPPURATIVA: Prescribed by or in consultation with a board-certified dermatologist

BEHCET'S SYNDROME, STILLS DISEASE, KAWASAKI DISEASE, OR TAKAYASU DISEASE: Prescribed by or in consultation with a rheumatologist, dermatologist, ophthalmologist, gastroenterologist, or neurologist.

UVEITIS: Prescribed by or in consultation with a board-certified ophthalmologist
[If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

RHEUMATOID ARTHRITIS, PLAQUE PSORIASIS, PSORIATIC ARTHRITIS, ANKYLOSING SPONDYLITIS, HIDRADENITIS SUPPURATIVA, STILLS DISEASE, UVEITIS, TAKAYASU DISEASE, BEHCET'S SYNDROME: 18 years of age and older
CROHN'S DISEASE, ULCERATIVE COLITIS IV ONLY: 6 years of age and older
CROHN'S DISEASE, ULCERATIVE COLITIS SQ ONLY: 18 years of age and older
JUVENILE IDIOPATHIC ARTHRITIS: 4 years of age and older
KAWASAKI DISEASE: No restriction

QUANTITY[1,2]:

Dosing in Crohn's Disease or Ulcerative Colitis:
Initial dose is 5 mg per kg IV infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then every 8 weeks thereafter.
If the Member has an inadequate response to the initial dosage, the dose may be adjusted:
i. The dose can be increased up to a maximum of 10 mg/kg.
ii. In patients who lose response before the next dose is scheduled, the interval can be decreased to every 7, 6, 5, or 4 weeks or the dose per infusion can be increased.
iii. The maximum dose is 10 mg/kg, and the shortest interval is every 4 weeks

Maintenance SQ dosing in adults only: 120 mg subcutaneously once every two weeks starting at week 10 or later of treatment after member has completed an intravenous induction regimen with an infliximab product

Dosing in Rheumatoid Arthritis:
Initial dose is 3 mg per kg IV infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then every 8 weeks thereafter.
If the Member has an inadequate response after ≥ 2 months of therapy, the dose may be adjusted:
i. The dose can be increased up to a maximum of 10 mg/kg.
ii. In patients who lose response before the next dose is scheduled, the interval can be decreased to every 7, 6, 5, or 4 weeks or the dose per infusion can be increased.
iii. The maximum dose is 10 mg/kg, and the shortest interval is every 4 weeks.
It has been shown that increasing the dose or shortening the dosing interval of Infliximab may be beneficial in patients with RA.[1, 40] The criteria for an inadequate response after ≥ 2 months of therapy are recommended based on the professional opinion of specialized physicians.

Dosing in ankylosing spondylitis[1,2]

Initial dose is 5 mg per kg IV infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then every 6 weeks thereafter.

If the Member has an inadequate response after ≥ 2 months of therapy, the dose may be adjusted:

i. The dose can be increased up to a maximum of 10mg/kg.
ii. In patients who lose response before the next dose is scheduled, the interval can be decreased to every 5 or 4 weeks or the dose per infusion can be increased.
iii. The maximum dose is 10 mg/kg, and the shortest interval is every 4 weeks.

In certain cases, changes in infliximab dosage or dosing interval are recommended for patients with AS who initially respond and then lose that response. The criteria for dosing ranges and an inadequate response after ≥ 2 months of therapy are recommended based on the professional opinion of specialized physicians.

Dosing in Plaque or Psoriatic Arthritis

Initial dose is 5 mg per kg IV infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, and then every 8 weeks thereafter.

If the Member has an inadequate response to ≥ 2 months of therapy, the dose may be adjusted:

i. The dose can be increased up to a maximum of 10 mg/kg.
ii. In patients who lose response before the next dose is scheduled, the interval can be decreased to every 7, 6, 5, or 4 weeks or the dose per infusion can be increased.
iii. The maximum dose is 10 mg/kg and the shortest interval is every 4 weeks.

Dosing in Behcet's Disease: [36,37]

Initial dose is 3 to 5 mg per kg IV infusion followed by additional similar doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks thereafter.

If the Member has an inadequate response after
≥ 2 months of therapy, the dose may be adjusted

i. The dose can be increased up to a maximum of 10 mg/kg with the same treatment interval (every 6 to 8 weeks) OR
ii. The dose may remain the same (3 to 5 mg/kg) and the interval can be decreased to every 7, 6, 5, or 4 weeks. OR
iii. In selected case, patients may be titrated to the maximum dose (10 mg/kg) and the shortest dosing interval (every 4 weeks).

Dosing in Hidradenitis Suppurativa. Dosing must meet the following: The initial dose is 5 mg per kg IV infusion followed by additional similar doses 2 and 6 weeks after the first infusion, and then every 8 weeks thereafter.

Dosing in juvenile idiopathic arthritis: Children ≥4 years and Adolescents: IV: Initial: 3 mg/kg at 0, 2, and 6 weeks; then 3 to 6 mg/kg/dose every 8 weeks thereafter, in combination with methotrexate during induction and maintenance

Dosing in noninfectious uveitis: For induction, give 5 mg/kg IV infusion at weeks 0, 2, 6. Give a maintenance dose of 5 mg/kg IV infusion every 8 weeks thereafter.

Dosing in Takayasu disease: 3 mg/kg or 5 mg/kg IV every 4 to 8 weeks

Dosing in Still's Disease: 3 mg/kg at weeks 0, 2, and 6, and then every 8 weeks thereafter

When requests for off-label dosing, dose escalation, or dose intensification are received, requests will be reviewed for evidence that current or standard dosing is not adequate to produce a therapeutic level of drug (e.g., pharmacokinetic failure), clinical failure or significant loss of response is present, and the requested dosing is established as safe and effective for the condition. There are certain situations where no additional amount of drug is likely to produce or recapture clinical effect because the condition is no longer responsive to the drug (e.g., pharmacodynamic failure) or the drug cannot reach the site of activity at sufficient levels. Review the

following items to determine if the requested dosing is medically necessary:

1. *FDA or compendium-supported dosing and therapeutic monitoring recommendations for the drug*
   AND
2. *Member claims/adherence history*
   AND
3. *Clinical documentation of the member's response to current or standard dosing regimens (disease activity indices if commonly used in clinical practice or documentation to approximate them may be necessary to demonstrate the response)*
   AND
4. *In conjunction with documented clinical failure or loss of response or wearing off of effect, test results that demonstrate failure of current or standard dosing to reach established treatment thresholds (eg, established therapeutic monitoring recommendations)*
   AND
5. *If applicable, documentation showing the member does not have conditions which make achieving a therapeutic level of drug unlikely even with dose intensification (e.g., dose intensification may be futile due to the presence of anti-drug antibodies, protein losing enteropathy, nephrotic syndrome, severe drug excretion or malabsorption issues, etc.)*
   AND
6. *In certain situations, documentation or peer-to-peer determination that re-induction cannot be tried to recapture response as an alternative to long term dose escalation or intensification*

Dosing in Kawasaki disease: 5 mg/kg/dose as a single infusion

PLACE OF ADMINISTRATION:
The recommendation is that subcutaneous injectable medications in this policy will be for pharmacy benefit coverage and patient self-administered.

The recommendation is that infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.

Note: Site of Care Utilization Management Policy applies for Remicade (infliximab), Inflectra (infliximab-dyyb), Renflexis (infliximab-abda), Avsola (infliximab-axxq) and infliximab. For information on site of care, see Specialty Medication Administration Site of Care Coverage Criteria (molinamarketplace.com)

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intravenous, Subcutaneous

DRUG CLASS:
Tumor Necrosis Factor Alpha Blockers

FDA-APPROVED USES:
Infliximab (Avsola, Inflectra, Remicade, Renflexis) is indicated for the following conditions:
Crohn's Disease:
•reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.
• reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease.

Pediatric Crohn's Disease: reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy.

Ulcerative Colitis: reducing signs and symptoms, inducing, and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.

Pediatric Ulcerative Colitis: reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy.

Rheumatoid Arthritis in combination with methotrexate: reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active disease.

Ankylosing Spondylitis: reducing signs and symptoms in adult patients with active disease.

Psoriatic Arthritis: reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in adult patients.

Plaque Psoriasis: treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate

Zymfentra (infliximab-dyyb) subcutaneous is indicated in adults for maintenance treatment of:

- moderately to severely active ulcerative colitis following treatment with an infliximab product administered intravenously
- moderately to severely active Crohn's disease following treatment with an infliximab product administered intravenously

COMPENDIAL APPROVED OFF-LABELED USES:

Hidradenitis Suppurativa, Behcet's Syndrome, Adult-onset Still's Disease, granulomatosis with polyangiitis, severe refractory juvenile idiopathic arthritis, refractory Kawasaki disease, refractory Takayasu's disease, refractory uveitis as adjunctive therapy

NOTE TO REVIEWER: *Requests for the following indications should be reviewed for approval through Molina Off-Label policy (see Background for additional information): Immunotherapy related diarrhea or colitis, Multisystem inflammatory syndrome in children, Refractory; associated with SARS-CoV-2 (COVID-19)*

APPENDIX

APPENDIX:

A biosimilar is highly similar version of a brand name biological drug that meets strict controls for structural, pharmaceutical, and clinical consistency. A biosimilar manufacturer must demonstrate that there are no meaningful clinical differences (i.e., safety and efficacy) between the biosimilar and the reference product. Clinical performance is demonstrated through human pharmacokinetic (exposure) and pharmacodynamic (response) studies, an assessment of clinical immunogenicity, and, if needed, additional clinical studies.1
As costs for biological specialty drugs continue to rise, the growing biosimilar market will benefit providers and patients by broadening biological treatment options and expanding access to these medications at lower costs.
Molina Healthcare, Inc. continues to be committed to continually reevaluating Preferred strategies and applying innovative cost-controls to ensure patients receive safe, effective, and quality healthcare.
This commitment includes potentially creating a preference for biosimilars when value can be added without compromising Member satisfaction and safety.

1. Food and Drug Administration. Biosimilar and Interchangeable Products. Retrieved from https://www.fda.gov/drugs/biosimilars/biosimilar- and-interchangeable- products. Accessed October8,2019.

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Infliximab is a chimeric (murine-human) Immunoglobulin (Ig) G1κ monoclonal antibody produced by recombinant DNA technology that binds specifically with human tumor necrosis factor-alpha (TNF- α). The recommended dose of intravenous infliximab is weight-based and varies slightly by indication. Dosing increase, interval shortening, or changing to another therapy is generally recommended for attenuation of response. Avsola, Inflectra and Renflexis were approved as biosimilar to Remicade, indicating no clinically meaningful differences in safety and effectiveness and the same mechanism of action, route of administration, dosage form, and strength as Remicade.
However, minor differences in clinically inactive components are allowed. At this time, Avsola, Inflectra and Renflexis have only demonstrated biosimilarity, not interchangeability.
The subcutaneous infliximab product is a self-administered form of Inflectra (infliximab-dyyb), and was approved as a novel product and not as a biosimilar to Remicade due to the dosage form difference.

Disease Overview

Increased levels of TNF are found in the joints of patients with rheumatoid arthritis (RA) and the stools of patients with Crohn's disease and correlate with elevated disease activity. TNF has an important role in both the pathologic inflammation and the joint destruction that are characteristic of RA. TNF is a naturally occurring cytokine that mediates inflammation and modulates cellular immune responses. Increased levels of TNF have been implicated in the pathology of inflammatory conditions such as psoriasis, psoriatic arthritis, inflammatory bowel disease, and rheumatoid arthritis (RA). Increased levels of TNF are found in the synovial fluid of patients with RA, JIA, AS, and PsA;TNF has an important role in both the pathologic inflammation and the joint destruction that are characteristic of this disease. In psoriasis, increased levels of TNF are found in the blood and skin lesions. Infliximab products binds to TNFα and inhibits binding of TNFα with its receptors.

Risk of tuberculosis during infliximab therapy for inflammatory bowel disease, rheumatoid arthritis, and spondyloarthropathy: A meta-analysis.

In conclusion, the present meta-analysis of 24 RCTs, comprising details from >6,340 patients with RA, SpA and IBD, demonstrated that the OR of tuberculosis infection was markedly increased with infliximab therapy, as compared with placebo therapy. The overall rates of tuberculosis infection were low (0.51%).

Guidelines

TNFis feature prominently in guidelines for treatment of inflammatory conditions. Guidelines from the American College of Rheumatology (ACR) [2015] have TNFis (e.g., Cimzia® [certolizumab pegol SC injection], etanercept SC products [e.g., Enbrel®], adalimumab SC products [e.g., Humira®], infliximab IV products [e.g., Remicade®, Renflexis, Inflectra], Simponi® [golimumab SC injection], Simponi Aria® [golimumab IV infusion]) and non-TNF biologics (i.e., Actemra® [tocilizumab IV infusion, tocilizumab SC injection], Orencia® [abatacept IV infusion, abatacept SC injection], rituximab IV products [e.g., Rituxan®]), administered with or without MTX, equally positioned as a recommended therapy following a trial of a csDMARD (e.g., MTX, leflunomide, hydroxychloroquine, sulfasalazine).18 Other guidelines for inflammatory conditions (e.g., PsA [European Union Against Rheumatism; Group for Research and Assessment of Psoriasis and Psoriatic Arthritis {GRAPPA}] and spondylitis [AS and non- radiographic axial {nr-ax}SpA] {ACR and Spondylitis Association of America/Spondyloarthritis Research and Treatment Network}, inflammatory bowel disease [Crohn'sdisease, UC] {American Gastroenterological Association} also note the significant place in therapy for TNFis.

Safety

Infliximab has Boxed Warnings concerning risks of serious infection and the risk of malignancy. Prior to initiating therapy with infliximab, patients should be evaluated for active tuberculosis (TB) infection, and periodically during therapy patients should be assessed for latent TB infection. Patients should also be monitored for signs and symptoms of infection during and after treatment with infliximab, and if a serious

infection or sepsis develops, infliximab should be discontinued. It is also recommended that patients treated with any TNF antagonist should be monitored for malignancies.

Infliximab is indicated for ankylosing spondylitis. Guidelines for axial spondyloarthritis are available from the Assessment of Spondyloarthritis International Society (ASAS)/EULAR (2016). The guidelines state that biologics (e.g., TNFis, Cosentyx) should be considered in patients with persistently high disease activity despite traditional conventional treatments (e.g., nonpharmacological management, NSAIDs). For patients with primarily peripheral manifestations of axial spondylitis, local steroid injections and sulfasalazine may be considered as conventional treatment; however, these are not considered for patients who present primarily with axial disease. Furthermore, the guidelines state that patients with purely axial disease should not be treated with conventional synthetic DMARDs. Guidelines from the American College of Rheumatology (ACR) and the Spondyloarthritis Research and Treatment Network (SPARTAN) [2015] make recommendations for treatment of AS.19 TNF inhibitors (e.g., Cimzia, Enbrel, Humira, infliximab, Simponi SC) are recommended for patients who have active disease despite treatment with an NSAID. There is not a preference for TNF inhibitor, except for in the cases of concomitant inflammatory bowel disease or recurrent iritis, when a monoclonal antibody (Humira, infliximab) is recommended over Enbrel. According to Assessments in Ankylosing Spondylitis/European League Against Rheumatism (ASAS/EULAR) 2010 recommendations for ankylosing spondylitis, all patients should have an adequate trial of at least two nonsteroidal anti-inflammatory drugs (NSAIDs) for pain and stiffness, unless contraindicated. Recommendations for other therapies before receiving a TNF blocker vary according to the manifestations of the disease, level of current symptoms, clinical findings, etc. According to these recommendations, patients with pure axial manifestations do not have to try traditional DMARDs before anti-TNF agents such as Infliximab; patients with symptomatic peripheral arthritis should have an insufficient response to at least one local corticosteroid injection, if appropriate; patients with peripheral arthritis should normally have a trial of a DMARD, preferably sulfasalazine; and patients with enthesitis should try appropriate local therapy(e.g., corticosteroid injection in selected cases). In patients with AS, concomitant treatment with a nonbiologic DMARD does not add to the safety or efficacy with an anti-TNF inhibitor.

Infliximab has been shown to reduce the chance of recurrence of symptoms after surgery in patients with Crohn’s disease. In one study, patients treated with infliximab following ileocolonic resection of Crohn’s disease noticed a significant decrease in Crohn's Disease Activity Index (CDAI) score at Month 2 ($P < 0.01$ compared to baseline); this decrease in CDAI was not found in study patients treated post- resection with mesalamine or azathioprine. The American College of Gastroenterology (ACG) has guidelines for Crohn’s disease (2018). Infliximab is listed as an option for severely active disease, fulminant Crohn’s disease, enterocutaneous and rectovaginal fistulas, and maintenance of remission. In post-operative Crohn’s disease, a TNFi should be started within 4 weeks of surgery to prevent recurrence.
Infliximab is indicated for plaque psoriasis. Guidelines for treatment of plaque psoriasis recommend topical therapy for limited disease. However, for patients with chronic plaque psoriasis that does not respond to topical therapies or patients with more extensive disease, systemic therapy may be used. The traditional systemic agents for plaque psoriasis are MTX, Soriatane, and cyclosporine. A biologic agent such as infliximab is an option for patients who are candidates for phototherapy or systemic therapy, especially those who are intolerant of or unresponsive to traditional systemic agents. The guidelines for the management of psoriasis from the American Academy of Dermatology (2010) note that there is no specific sequence in which the available TNF blockers should be used. However, guidelines from the National Psoriasis Foundation for management of plaque psoriasis (2012) note that infliximab is commonly used as a second- or third-line agent whereas Enbrel and Humira are listed as drugs which may be used as first-line systemic agents. In the professional opinion of specialist physicians reviewing the data, we have adopted the criteria requirements for previous therapy.

Infliximab is indicated for PsA. In clinical trials, infliximab was effective in patients with active PsA despite therapy with a DMARD or NSAID. There are few well-controlled, prospective studies with adequate duration that have evaluated the efficacy of the oral DMARDs. Recommendations for the management of PsA have been developed by European League Against Rheumatism (EULAR) [2015] and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) [2015]. According to EULAR, treatment is recommended based on clinical presentation. In peripheral arthritis, a biologic (usually a TNF blocker) should be started if there is an inadequate response to at least one conventional synthetic

DMARD. This recommendation is supported by the long-term experience and established safety/efficacy balance of TNF blockers vs. other biologics. In patients with enthesitis, dactylitis, or axial disease, the initial DMARD recommended are biologics; according to current practice a TNF blocker would be used. The guidelines note that comparison across trials is difficult because different outcomes were used. For enthesitis/dactylitis, the longest clinical experience is with TNF blockers. For axial disease, limited data exist for IL blockers. In patients who fail to respond to a biologic, switching to another biologic should be considered, including switching between TNF blockers. GRAPPA recommends TNF blockers for patients presenting with various manifestations of PsA (i.e., peripheral arthritis, axial disease, enthesitis, dactylitis, skin, and nail disease).

Infliximab is indicated for adults with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. Remicade is also approved in pediatric patients ≥ 6 years of age with ulcerative colitis; although Inflectra and Renflexis do not share this indication, the prescribing information notes that pediatric assessment demonstrated safety and efficacy in this indication. Infliximab has been effective in cases of refractory pouchitis.34 Clinical guidelines for the management of pouchitis, published in 2009, and ulcerative colitis practice guidelines from the ACG (2010) indicate that first-line therapy for pouchitis is antibiotic therapy (e.g. metronidazole, ciprofloxacin). Other treatment options include maintenance probiotics, oral or topical budesonide, anti-inflammatory drugs (e.g., mesalamine), or immunosuppressive drugs (e.g., infliximab).
Numerous case series have reported that infliximab is effective in producing short-term remission of Behcet's disease, especially uveitis, in patients who were refractory to corticosteroids and conventional immunosuppressive therapy. EULAR recommendations for the management of Behcet's disease (2018) include infliximab for initial or recurrent episodes of acute sight-threatening uveitis. For patient's refractory to first-line treatments (e.g., corticosteroids), infliximab is among the treatment options for mucocutaneous manifestations, venous thrombosis, severe or refractory gastrointestinal disease, and recurrent/chronic joint involvement. Recommendations for the use of TNF blockers in ocular inflammatory disorders from the American Academy of Ophthalmology (AAO) [2014] notes that infliximab may be used first line in patients with ophthalmic manifestations of Behcet's disease and for acute exacerbations of preexisting Behcet's disease.

Psoriatic Arthritis

An estimated 1% of the U.S. adult population harbors cutaneous evidence of psoriasis, characterized by well demarcated erythematous scaly plaques, some of whom develop a related arthritis. In fact, there are several distinct subsets of psoriatic arthritis, including (a) an asymmetric oligoarthritis affecting lower extremity joints; (b) a symmetric polyarthritis affecting upper and lower extremity joints; (c) monoarticular involvement of a distal interphalangeal joint alone; (d) a destructive finger joint arthritis that produces "telescoping," a shortening of the digit as a consequence of aggressive bone destruction and resorption (arthritis mutilans); and (e) axial skeleton involvement (spondylitis, sacroiliitis).

HIDRADENITIS SUPPURATIVA: In a Phase II double-blind, placebo-controlled crossover trial, adult patients with moderate to severe hidradenitis suppurativa were randomized to placebo (n = 23) or infliximab5 mg/kg (n = 15) at Weeks 0, 2, and 6.47 After Week 8, patients were unblinded, and placebo patients were offered induction with placebo. Maintenance was continued through 22 weeks of treatment. Following Week 8, more patients in the infliximab-treatment group experienced a 50% or greater decrease in the Hidradenitis Suppurativa Severity Index (HSSI) score (approximately 26% and 5% of patients receiving infliximab and placebo, respectively [data presented graphically]; P = 0.092). In post-hoc analysis, significantly more patients treated with infliximab responded with a 25% to < 50% response (60% and 5.6% for infliximab and placebo, respectively; P < 0.001). Improvement was noted through Week 30. In case series, infliximab has been effective in treating hidradenitis suppurativa that was refractory to other therapies.

Subcutaneous use in adults with Ulcerative Colitis and Crohn's Disease

The approval of Zymfentra (infliximab-dyyb) subcutaneous was based on two Phase-3, randomized, placebo controlled trials, LIBERTY-CD and LIBERTY-UC.

In the UC trial, subjects had moderately to severely active UC and had demonstrated an inadequate response or intolerance to treatment with corticosteroids alone or in combination with 6-mercaptopurine or azathioprine. Subjects were permitted to use stable doses of oral aminosalicylates, oral corticosteroids (prednisone ≤20 mg/day or equivalent, budesonide ≤9 mg/day), UC-related antibiotics, and/or immunomodulatory agents (azathioprine, 6-mercaptopurine, or methotrexate). Corticosteroid tapering was permitted after Week 10. All subjects received three intravenous induction doses of 5 mg/kg of infliximab-dyyb at Weeks 0, 2 and 6. In order to be randomized to treatment in UC Trial I, subjects had to be in clinical response at Week 10. Clinical response was defined as a decrease from baseline in the mMS of at least 2 points and at least 30%, with an accompanying decrease in rectal bleeding (RBS) of at least 1 point or an absolute RBS of 0 or 1 point. A total of 438 subjects were randomized at Week 10 in a double-blind fashion (2:1) to Zymfentra 120 mg as a subcutaneous injection or placebo every two weeks. The primary endpoint was proportion of subjects in clinical remission at week 54. The rate of clinical remission was greater in patients receiving Zymfentra (43.2%) compared to placebo (20.8%) (P <0.0001).

In the CD trial, subjects had moderately to severely active CD and had demonstrated an inadequate response or intolerance to treatment with corticosteroids and/or immunosuppressants. Subjects were permitted to use stable doses of oral aminosalicylates, oral corticosteroids (prednisone ≤ 20 mg/day or equivalent, budesonide ≤9 mg/day), CD-related antibiotics and/or immunomodulatory agents (azathioprine, 6-mercaptopurine, or methotrexate). Corticosteroid dose was tapered after Week 10. All subjects received three intravenous induction doses of 5 mg/kg infliximab-dyyb at Weeks 0, 2 and 6. In order to be randomized to treatment in CD Trial I, subjects had to be in clinical response at Week 10. Clinical response was defined as a decrease from baseline in CDAI of at least 100 points (i.e., CDAI-100 responders). A total of 323 subjects were randomized at Week 10 in a double-blind fashion (2:1) to Zymfentra 120 mg as a subcutaneous injection or placebo every 2 weeks. The co-primary endpoints were clinical remission (based on CDAI) and endoscopic response at Week 54. At Week 54, clinical remission was 62.3% in the Zymfentra arm versus 32.1% in the placebo arm (*P* <0.0001). A statistically significant greater proportion of patients in the Zymfentra arm had an endoscopic response compared to placebo (51.1% vs. 17.9%, respectively; *P* <0.0001).

Infliximab SQ was studied against and found to be non-inferior to Infliximab IV in a phase 1 study in patients with active inflammatory bowel disease.

AGA Guidelines Moderate to Severe Ulcerative Colitis

Recommendations from the recent 2020 guideline update include:

- In adult outpatients with moderate to severe UC who are naïve to biologic agents, the AGA suggests using infliximab or vedolizumab rather than adalimumab, for induction of remission.
- Updated FDA recommendations (July 26, 2019) on indications for use of tofacitinib in UC recommends its use only after failure of or intolerance to TNF-a antagonists.
- In adult outpatients with moderate to severe UC who have previously been exposed to infliximab, particularly those with primary nonresponse, the AGA suggests using ustekinumab or tofacitinib rather than vedolizumab or adalimumab for induction of remission.
- In adult outpatients with moderate to severe UC, the AGA suggests against using methotrexate monotherapy for induction or maintenance of remission
- In adult outpatients with active moderate to severe UC, the AGA suggests using biologic monotherapy (TNF-a antagonists, vedolizumab, or ustekinumab) or tofacitinib rather than thiopurine monotherapy for induction of remission.
- In adult outpatients with moderate to severe UC, the AGA suggests combining TNF-a antagonists, vedolizumab or ustekinumab with thiopurines or methotrexate rather than biologic monotherapy.
- In adult outpatients with moderate to severe UC who have achieved remission with biologic agents and/or immunomodulators or tofacitinib, the AGA suggests against continuing 5-ASA for induction and maintenance of remission.

Immunotherapy related diarrhea or colitis

Recent NCCN guidelines include use of infliximab for moderate and severe diarrhea and colitis (grade 2 and above) related to immune checkpoint inhibitor therapy. If no response to treatment with steroids, consider adding infliximab or vedolizumab. For infliximab and/or vedolizumab refractory colitis, consider tofacitinib or ustekinumab. Refer to NCCN guidelines for management of immunotherapy related

toxicities.

Multisystem inflammatory syndrome in children, Refractory; associated with SARS-CoV-2 (COVID-19)
Children with MIS-C typically respond briskly to immunomodulatory therapy and show clinical improvements within the first 24 hours of treatment. Treatment response is characterized by resolution of fever, improvement of organ function, and reduced levels of inflammatory markers, particularly C-reactive protein. By contrast, refractory disease is often accompanied by persistent fever, worsening organ dysfunction, and increasing levels of inflammatory markers. Intensification therapy is recommended for children with refractory MIS-C who do not improve within 24 hours of initial immunomodulatory therapy (AIII). Children with uncontrolled MIS-C despite treatment with IVIG and low-to-moderate-dose glucocorticoids will often continue to deteriorate without further intervention, and this decline in clinical status can be quite rapid.
There are no comparative studies evaluating intensification therapies for MIS-C. Available data on this topic are limited to results from cohort studies in patients with MIS-C, expert opinion, and experience in treating other hyperinflammatory syndromes in children, such as Kawasaki disease and macrophage activation syndrome. For children with refractory MIS-C, the Panel recommends additional immunomodulatory therapy (in alphabetical order) with anakinra (BIIb), higher-dose glucocorticoids (BIIb), or infliximab (BIIb). Currently, there is insufficient evidence to determine which of these agents is most effective for intensification therapy in patients with refractory MIS-C. In certain patients with severe illness, intensification therapy may include dual therapy with higher-dose glucocorticoids and anakinra (BIII) or higher-dose glucocorticoids and infliximab (BIII). Anakinra and infliximab should not be used in combination.
Patients with MIS-C who receive multiple immunomodulatory agents are at risk for infection and need to be monitored carefully. Most children with MIS-C were previously healthy. In patients who have an immune disorder or are taking immunosuppression therapy, the risk of infection is greater. The risks and benefits of treating immunocompromised MIS-C patients with immunomodulatory agents need to be evaluated on a case-by-case basis.
The Panel recommends a single dose of infliximab 5 to 10 mg/kg IV as an option for intensification therapy.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of infliximab, Remicade (infliximab), Avsola (infliximab-axxq), Inflectra (infliximab-dyyb), Renflexis (infliximab-abda), Ixifi (infliximab-qbtx), Zymfentra (infliximab-dyyb) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to infliximab include: previous severe hypersensitivity reaction to infliximab or any inactive ingredients or to any murine proteins, the use of infliximab at doses >5 mg/kg is contraindicated in patients with moderate or severe heart failure. Do not give Remicade during an active infection. Live vaccines or therapeutic infectious agents should not be given with Remicade. The concomitant use of tocilizumab with biological DMARDs such as TNF antagonists, including Remicade, should be avoided because of the possibility of increased immunosuppression and increased risk of infection.

OTHER SPECIAL CONSIDERATIONS:
Infliximab has a Black Boxed warning for serious infections and malignancy. Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis) and infections due to other opportunistic pathogens. Discontinue Remicade if a patient develops a serious infection. Perform test for latent TB; if positive, start treatment for TB prior to starting Remicade. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor (TNF) blockers, including Remicade. Post marketing cases of fatal hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF blockers including Remicade. Almost all had received azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. The majority of Remicade cases were reported in patients with Crohn's disease or ulcerative colitis, most of whom were adolescent or young adult males.

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective*

at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.

HCPCS CODE	DESCRIPTION
J1745	Injection, infliximab, excludes biosimilar, (Remicade), 10mg
J1748	Injection, infliximab-dyyb (Zymfentra), 10 mg
Q5103	Injection, infliximab-dyyb, biosimilar, (Inflectra),10mg
Q5104	Injection, infliximab-abda, biosimilar, (Renflexis)10mg
Q5121	Injection, infliximab-axxq, biosimilar, (Avsola), 10 mg

AVAILABLE DOSAGE FORMS:
Avsola SOLR 100MG
Inflectra SOLR 100MG
inFLIXimab SOLR 100MG
Remicade SOLR 100MG
Renflexis SOLR 100MG
Zymfentra (1 Pen) AJKT 120MG/ML auto-injector
Zymfentra (2 Pen) AJKT120MG/ML auto-injector
Zymfentra (2 Syringe) PSKT120MG/ML prefilled syringe

REFERENCES

1. Remicade® injection [prescribing information]. Horsham, PA: Janssen Biotech; October 2021.
2. Avsola (infliximab-axxq) [prescribing information]. Thousand Oaks, CA: Amgen Inc; September 2021.
3. Zymfentra (infliximab-dyyb) injection, for subcutaneous use [prescribing information]. Jersey City, NJ: Celltrion USA, Inc.; February 2024.
4. de Vries HS, van Oijen MG, Driessen RJ, et al. Appropriate infliximab infusion dosage and monitoring: results of a panel meeting of rheumatologists, dermatologists and gastroenterologists.
5. Br J Clin Pharmacol. 2011;71(1):7-19. 3. Lipsky PE, van der Heijde DM, St Clair EW, et al; for the Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med. 2000;343:1594- 1602.
6. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet. 1999;354:1932- 1939.
7. Maini RN, Breedveld FC, Kalden JR, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. Arthritis Rheum. 2004;50:1051-1065.
8. St Clair EW van der Heijde DM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum. 2004;50:3432- 3443.
9. Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J

Med.1997;337:1029-1035.
10. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the Accent I randomized trial. Lancet.2002;359:1541-1549.
11. Hyams J, Crandall W, Kugathasan S, et al; REACH Study Group. Induction and maintenance infliximab therapy for the treatment of moderate to-severe Crohn's disease in children. Gastroenterology. 2007;132:863-873.
12. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med. 1999;340:1398- 1405.
13. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med. 2004;350:876-885.
14. van der Heijde D, Dijkmans B, Geusens P, et al; Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy Study Group. Efficacy and safety of infliximab inpatients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum. 2005;52:582-591.
15. Antoni C, Krueger GG, de Vlam K, et al; IMPACT 2 Trial Investigators. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis. 2005;64:1150- 1157.
16. Reich K, Nestle FO, Papp K, et al; EXPRESS study investigators. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double- blind trial. Lancet. 2005;366:1367-1374.
17. Reich K, Nestle FO, Papp K, et al. Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate to-severe psoriasis: a randomized controlled trial. Br J Dermatol. 2006;154:1161-1168.
18. Menter A, Feldman SR, Weinstein GD, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate- to- severe plaque psoriasis. J Am Acad Dermatol.2007;56:31.e1-15.
19. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med.2005;353:2462-2476.
20. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2016;68(1):1-26.
21. Ward MM, Deodhar A, Akl EA, et al. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 Recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. Arthritis Rheumatol. Braun J, van den Berg R, Baraliakos X, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis. 2011;70(6):896-904.
22. van den Berg R, Baraliakos X, Braun J, van der Heijde D. First update of the current evidence for the management of ankylosing spondylitis with non-pharmacological treatment and non- biologic drugs: a systematic literature review for the ASAS/EULAR management recommendations in ankylosing spondylitis. Rheumatology(Oxford).2012;51(8):1388-1396.
23. van der Heijde D, Sieper J, Maksymowych WP, et al. 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. Ann Rheum Dis. 2011;70(6):905-908.
24. Baraliakos X, van den Berg R, Braun J, van der Heijde D. Update of the literature review on treatment with biologics as a basis for the first update of the ASAS/EULAR management recommendations of ankylosing spondylitis. Rheumatology (Oxford). 2012;51(8):1378-1387.
25. Regueiro M, Schraut W, Baidoo L, et al. Infliximab prevents Crohn's disease recurrence after ileal resection. Gastroenterology. 2009;136(2):441- 450.
26. Yamamoto T, Umegae S, Matsumoto K. Impact of infliximab therapy after early endoscopic recurrence following ileocolonic resection of Crohn's disease: a prospective pilot study. Inflamm Bowel Dis.2009;15(10):1460-1466.
27. Sakuraba A, Sato T, Matsukawa H, et al. The use of infliximab in the prevention of postsurgical recurrence in polysurgery Crohn's disease patients: a pilot open- labeled prospective study. Int J Colorectal Dis. 2012;27(7):947-952
28. Sorrentino D, Terrosu G, Paviotti A, et al. Early diagnosis and treatment of postoperative endoscopic recurrence of Crohn's disease: partial benefit by infliximab--a pilot study. DigDis Sci. 2012;57(5):1341-1348.
29. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease

in Adults. Am J Gastroenterol. 2018;113(4):481- 517.
30. Hsu S, Papp KA, Lebwohl MG, et al. Consensus guidelines for the management of plaque psoriasis. Arch Dermatol. 2012;148(1):95-102.
31. American Academy of Dermatology Work Group, Menter A, Korman NJ, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence- based conclusions. J Am Acad Dermatol. 2011;65(1):137- 174.
32. Gossec L, Smolen JS, Ramiro S, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 015 update. Ann RheumDis.2016;75(3):499-510.
33. Coates LC, Kavanaugh A, Mease PJ, et al. Group for research and assessment of psoriasis and psoriatic arthritis: treatment recommendations for psoriatic arthritis 2015. Arthritis Rheumatol. 2016;68(5):1060-1071.
34. Nattiv R, Wojcicki JM, Garnett EA, et al. High-dose infliximab for treatment of pediatric ulcerative colitis: a survey of clinical practice. World J Gastroenterol. 2012;18(11):1229- 1234.
35. Ferrante M, D'Haens G, Dewit O, et al. Efficacy of infliximab in refractory pouchitis and Crohn's disease-related complications of the pouch: a Belgian case series. Inflamm Bowel Dis. 2010;16(2):243-249.
36. Pardi DS, D'Haens G, Shen B, et al. Clinical guidelines for the management of pouchitis. Inflamm Bowel Dis. 2009;15(9):1424-1431.
37. Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2010;105(3):501-523.
38. Sfikakis PP, Markomichelakis N, Alpsoy E, et al. Anti-TNF therapy in the management of Behcet's disease--review and basis for recommendations. Rheumatology (Oxford). 2007;46:736-741. 2016;68(2):282-298.
39. Calvo-Río V, Blanco R, Beltrán E, et al. Anti-TNF-α therapy in patients with refractory uveitis due to Behçet's disease: a 1-year follow-up study of 124 patients. Rheumatology (Oxford). 2014;53(12):2223-2231.
40. Hatemi G, Christensen R, Bang D, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. Ann Rheum Dis.2018;77(6):808-818.
41. Levy-Clarke G, Jabs DA, Read RW, et al. Expert panel recommendations for the use of anti- tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. Ophthalmology. 2014;121(3):785-796.
42. Furst DE, Keystone EC, Braun J, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2010. Ann Rheum Dis. 2011;70Suppl1:i2-36.
43. Wang, Q., Wen, Z., & Cao, Q. (2016). Risk of tuberculosis during infliximab therapy for inflammatory bowel disease, rheumatoid arthritis, and spondyloarthropathy: Ameta-analysis. Experimental and Therapeutic Medicine, 12(3), 1693-1704. doi: 10.3892/etm.2016.3548
44. Mekinian A, Neel A, Sibilia J, et al: Efficacy and tolerance of infliximab in refractory Takayasu arteritis: French multicentre study. Rheumatology (Oxford) 2012; 51(5):882-886
45. Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti- tumor necrosis factor agents infliximab and etanercept. AU Braun J, Baraliakos X, Listing J, Sieper J SO Arthritis Rheum. 2005;52(8):2447.
46. Ringold, S., Angeles-Han, S., Beukelman, T., Lovell, D., Cuello, C., Becker, M., Colbert, R., Feldman, B., Ferguson, P., Gewanter, H., Guzman, J., Horonjeff, J., Nigrovic, P., Ombrello, M., Passo, M., Stoll, M., Rabinovich, C., Schneider, R., Halyabar, O., Hays, K., Shah, A., Sullivan, N., Szymanski, A., Turgunbaev, M., Turner, A. and Reston, J., 2019. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. Arthritis Care & Research, 71(6), pp.717-734.
47. Ringold S, Weiss PF, Beukelman T, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. Arthritis Rheum. 2013;65(10):2499-2512.
48. Onel, K., Horton, D., Lovell, D., Shenoi, S., Cuello, C., & Angeles-Han, S. et al. (2022). 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic

Approaches for Oligoarthritis, Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis. Arthritis & Rheumatology, 74(4), 553-569. doi: 10.1002/art.42037
49. Ringold, S., Angeles-Han, S., Beukelman, T., Lovell, D., Cuello, C., & Becker, M. et al. (2019). 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. Arthritis Care & Research, 71(6), 717-734. doi: 10.1002/acr.23870
50. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed [August 18, 2022].
51. Fraenkel, L., Bathon, J., England, B., St. Clair, E., Arayssi, T., & Carandang, K. et al. (2021). 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care & Research, 73(7), 924-939. Doi: 10.1002/acr.24596
52. Singh, J., Guyatt, G., Ogdie, A., Gladman, D., Deal, C., & Deodhar, A. et al. (2018). 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. Arthritis & Rheumatology, 71(1), 5-32. doi: 10.1002/art.40726
53. Feuerstein, J., Isaacs, K., Schneider, Y., Siddique, S., Falck-Ytter, Y., & Singh, S. et al. (2020). AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. Gastroenterology, 158(5), 1450-1461. doi: 10.1053/j.gastro.2020.01.006
54. Menter, A., Strober, B., Kaplan, D., Kivelevitch, D., Prater, E., & Stoff, B. et al. (2019). Joint AAD- NPF guidelines of care for the management and treatment of psoriasis with biologics. Journal Of The American Academy Of Dermatology, 80(4), 1029-1072. doi: 10.1016/j.jaad.2018.11.057
55. Menter, A., Gelfand, J., Connor, C., Armstrong, A., Cordoro, K., & Davis, D. et al. (2020). Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. Journal Of The American Academy Of Dermatology, 82(6), 1445-1486. doi: 10.1016/j.jaad.2020.02.044
56. Elmets, C., Lim, H., Stoff, B., Connor, C., Cordoro, K., & Lebwohl, M. et al. (2019). Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis with phototherapy. Journal Of The American Academy Of Dermatology, 81(3), 775-804. doi: 10.1016/j.jaad.2019.04.042
57. Ward, M., Deodhar, A., Gensler, L., Dubreuil, M., Yu, D., & Khan, M. et al. (2019). 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis & Rheumatology, 71(10), 1599-1613. doi: 10.1002/art.41042
58. Feuerstein, J. D., Ho, E. Y., Shmidt, E., Singh, H., Falck-Ytter, Y., Sultan, S., … Spechler, S. J. (2021). AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. Gastroenterology, 160(7), 2496–2508. https://doi.org/10.1053/j.gastro.2021.04.02
59. Schreiber, S., Ben-Horin, S., Leszczyszyn, J., Dudkowiak, R., Lahat, A., Gawdis-Wojnarska, B., … Reinisch, W. (2021). Randomized Controlled Trial: Subcutaneous vs Intravenous Infliximab CT-P13 Maintenance in Inflammatory Bowel Disease. Gastroenterology, 160(7), 2340–2353. https://doi.org/10.1053/j.gastro.2021.02.068
60. Gossec, L., Kerschbaumer, A., Ferreira, R. J. O., Aletaha, D., Xenofon Baraliakos, Bertheussen, H., … Lars Erik Kristensen. (2024). EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2023 update. Annals of the Rheumatic Diseases, 0, 1–14. https://doi.org/10.1136/ard-2024-225531
61. Alikhan, A., Sayed, C., Alavi, A., Alhusayen, R., Brassard, A., Burkhart, C., … Poulin, Y. (2019). North American clinical management guidelines for hidradenitis suppurativa: A publication from the United States and Canadian Hidradenitis Suppurativa Foundations. Journal of the American Academy of Dermatology, 81(1), 91–101. https://doi.org/10.1016/j.jaad.2019.02.068

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Coding/Billing Information Template Update Products Affected Required Medical Information Continuation of Therapy Place of Administration Route of Administration Contraindications/Exclusions/Discontinuation Coding/Billing Information References	Q4 2024
REVISION- Notable revisions: Name Change Products Affected Required Medical Information Continuation of Therapy Age Restrictions Quantity Place of Administration Route of Administration FDA-Approved Uses Background Available Dosage Forms References	Q2 2024
REVISION- Notable revisions: Compendial Approved Off-Labeled Uses	Q1 2024
REVISION- Notable revisions: Name Change Required Medical Information Continuation of Therapy FDA-Approved Uses Background Contraindications/Exclusions/Discontinuation Other Special Considerations Available Dosage Forms References	Q4 2023
REVISION- Notable revisions: Products Affected Diagnosis Required Medical Information Continuation of Therapy Prescriber Requirements Age Restrictions Quantity Compendial Approved Off-Labeled Uses Background Contraindications/Exclusions/Discontinuation Available Dosage Forms References	Q4 2022
Q2 2022 Established tracking in new format	Historical changes on file