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 Policy Number: C10421-A

## Infliximab (Remicade\_Renflexis\_Ixifi\_Avsola\_Infliximab)

### PRODUCTS AFFECTED

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

### 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 Syndrome, Graft V Host Disease, 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*

#### **FOR ALL INDICATIONS:**

1. (a) Prescriber attests member has had (a) negative TB screening or TB test result within the last 12 months for initial and continuation of therapy requests  
 OR  
 (b) For members who have a positive test for latent TB, provider documents member has

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completed a treatment course (a negative chest x-ray is also required every 12 months) OR that member has been cleared by an infectious disease specialist to begin treatment

AND

2. Prescriber attests member has been evaluated and screened for the presence of hepatitis B virus (HBV) prior to initiating treatment  
AND
3. Member is not on concurrent treatment or will 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
4. Prescriber attests member does not have an active infection, including clinically important localized infections  
AND
5. 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]  
AND
6. (a) IF THIS IS A PHARMACY BENEFIT REQUEST FOR A NON-FORMULARY/NON-PREFERRED PRODUCT: Documentation of trial/failure of or intolerance to a majority (not more than 3) of the preferred formulary 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, intolerance 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:
  1. Treatment with at least two (2) associated biosimilar drug(s) has been ineffective, not tolerated, 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:

1. Documentation of moderate to severe rheumatoid arthritis diagnosis

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AND

2. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal -

AND

3. (a) Member is concurrently receiving methotrexate

OR

(b) Member tried, failed, or has an FDA labeled contraindication or intolerance 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 at least one biologic. These patients who have already tried a biologic for RA are not required to “step back” and try a conventional synthetic DMARD).

OR

(c) Member has early RA (defined as disease duration of < 6 months) with at least one of the following features of poor prognosis: functional limitation (e.g., based on Health Assessment Questionnaire Disability Index [HAQ-DI] score); extra articular disease such as rheumatoid nodules, RA vasculitis, or Felty’s syndrome; positive rheumatoid factor or anti-cyclic citrullinated protein (anti-CCP) antibodies; or bony erosions by radiograph

### B. PSORIATIC ARTHRITIS (PsA):

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

AND

3. (a) Documented treatment failure with or FDA labeled 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  $\geq$ 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) Member has had a 2-month trial of one systemic agent (e.g., 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone, methylprednisolone) or was intolerant to one of these agents 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 Rowasa® (mesalamine) enema

AND

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

### D. CHRONIC PLAQUE PSORIASIS:

1. Documented diagnosis of moderate to severe psoriasis (BSA 3%-10%-moderate, >10%-

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severe) OR  $\leq 10\%$  body surface area with plaque psoriasis that involves sensitive areas of the body or areas that would significantly impact daily function (ex. face, neck, hands, feet, genitals)

AND

2. (a) Documentation of treatment failure with or a clinical contraindication to TWO of the following systemic therapies for  $\geq 3$  months: Methotrexate (oral or IM at a minimum dose of 15 mg/week), cyclosporine, acitretin, azathioprine, hydroxyurea, leflunomide, mycophenolate mofetil, sulfasalazine, or tacrolimus  
OR  
(b) Documentation of treatment failure to Phototherapy for  $\geq 3$  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 type 1 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

### E. MODERATE TO SEVERE ANKYLOSING SPONDYLITIS:

1. Documentation of ankylosing spondylitis diagnosis  
AND
2. Prescriber attestation of member having an inadequate response or FDA labeled contraindication to TWO NSAIDs (e.g., ibuprofen, naproxen, etodolac, meloxicam, indomethacin) for  $\geq 3$  consecutive months at maximal recommended or tolerated anti-inflammatory doses  
AND
3. FOR THOSE MEMBERS WITH PROMINENT PERIPHERAL ARTHRITIS: Documentation of trial ( $\geq 3$  consecutive months) or FDA labeled contraindication to 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

### F. MODERATE TO SEVERE ACTIVE CROHN'S DISEASE:

1. Documentation of a diagnosis of currently ACTIVE moderate to severely active Crohn's Disease (Crohn's disease activity index-CDAI score of 221-450)  
AND
2. (a) Member has had a trial ( $>3$  months) and inadequate response to ONE immunomodulator (e.g., azathioprine, 6-mercaptopurine, methotrexate) up to maximally indicated doses unless contraindicated or significant adverse reactions are experienced  
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

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

### G. BEHCETSYNDROME:

1. Documented diagnosis of Behcet 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{MTX}, mycophenolate mofetil, cyclosporine, tacrolimus, Leukeran® [chlorambucil, cyclophosphamide], interferon alfa, colchicine, sucralfate suspension or triamcinolone in or a base).  
OR  
b) The member has ophthalmic manifestations of Behcet's disease.  
*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 patients who have already tried a biologic for Behcet's disease are not required to "step back" and try a conventional therapy*  
AND
4. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal

### H. HIDRADENITIS SUPPURATIVA:

1. Documentation of 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. Documentation of treatment failure with or a clinical contraindication:  
(a) to a 3-month trial of the following treatment options: (i) Oral tetracycline (e.g., minocycline, doxycycline) AND (ii) Topical antibiotic AND (iii) Antiandrogen (e.g., finasteride)  
OR clindamycin/rifampin  
AND  
(b) Documentation of treatment failure with or a clinical contraindication to intralesional corticosteroids  
*Note to reviewer- guideline recommended first line agents are as follows:  
Hurley stage I disease: topical clindamycin, oral tetracycline, metformin and antiandrogenic agents  
Hurley stage II or III disease: oral tetracycline, oral clindamycin, rifampin, metformin*  
AND
5. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal

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### I. ACTIVE STILL'S DISEASE:

1. Documented diagnosis of adult 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

### J. JUVENILE IDIOPATHIC ARTHRITIS (ACTIVE SYSTEMIC AND ACTIVE POLYARTICULAR):

1. Member must have a diagnosis of juvenile idiopathic arthritis (JIA)  
AND
2. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy  
AND
3. (a) FOR SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS: Documentation of drug failure or serious side effects to an adequate trial (up to 12 weeks) of TWO of the following: NSAIDs, glucocorticoids, methotrexate, leflunomide, anakinra (Kineret), Ilaris (canakinumab), or Actemra (tocilizumab)  
OR  
(b) FOR POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS: Documentation of treatment failure, serious side effects or clinical contraindication to an adequate trial (generally  $\geq 12$  weeks) of  $\geq 1$  of the following: Methotrexate, hydroxychloroquine, sulfasalazine, azathioprine, leflunomide  
OR  
(c) FOR JUVENILE IDIOPATHIC ARTHRITIS WITH SACROLITIS OR ENTHESTITIS: Documentation of drug failure or serious side effects, clinical contraindication, or treatment failure to an adequate trial to at least one NSAID, unless contraindicated or significant adverse reactions are experienced.

### K. KAWASAKI DISEASE:

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)

### L. TAKAYASU'S DISEASE:

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

### M. NON-INFECTIOUS UVEITIS:

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

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AND

3. (a) Documentation of treatment failure with or a 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 Bechet syndrome

### CONTINUATION OF THERAPY:

#### 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 (documentation required)  
AND
2. Documentation of no intolerable adverse effects or drug toxicity  
AND
3. Documentation of clinical response as demonstrated by low disease activity and/or improvements in the condition's signs and symptoms.  
AND
4. (a) Prescriber attests member has had a negative TB screening or TB test result within the last 12 months for initial and continuation of therapy requests  
OR  
(b) For members who have a positive test for latent TB, provider documents member has completed a treatment course (a negative chest x-ray is also required every 12 months) OR that member has been cleared by an infectious disease specialist to begin treatment  
AND
5. IF REQUEST IS FOR REFERENCE PRODUCT WITH A BIOSIMILAR AVAILABLE FOR INITIAL OR CONTINUATION OF THERAPY REQUESTS AS A PHARMACY BENEFIT: Documentation of a trial and failure, intolerance, 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
6. 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:  
Treatment with at least two (2) associated biosimilar drug(s) has been ineffective, not tolerated, 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

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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:**

CROHNS DISEASE AND ULCERATIVE COLITIS: Prescribed by or in consultation with a board-certified gastroenterologist, colorectal surgeon or specialist who is consulting with a board-certified gastroenterologist or colorectal surgeon (consultation notes to be submitted)

MODERATE TO SEVERE ANKYLOSING SPONDYLITIS, RHEUMATOID ARTHRITIS, JUVENILE IDOPATHIC 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 within initial request and reauthorization requests]

### **AGE RESTRICTIONS:**

CROHNS DISEASE, ULCERATIVE COLITIS: 6 years of age and older

RHEUMATOID ARTHRITIS, ANKYLOSING SPONDYLITIS, PLAQUE PSORIASIS, PSORIATIC ARTHRITIS, ANKYLOSING SPONDYLITIS, HIDRADENITIS SUPPURATIVA, STILLS DISEASE, UVEITIS, TAKAYASU DISEASE, BEHCET'S SYNDROME: 18 years and older

KAWASAKI DISEASE- no age requirement

JUVENILE IDOPATHIC ARTHRITIS: 4 years of age and older

### **QUANTITY<sup>1,2</sup>:**

#### *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

#### *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  $\geq$  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.

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- 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.<sup>1, 40</sup> The criteria for an inadequate response after  $\geq 2$  months of therapy are recommended based on the professional opinion of specialized physicians.

### *Dosing in ankylosing spondylitis<sup>1,2</sup>*

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  $\geq 2$  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  $\geq 2$  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  $\geq 2$  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:*<sup>36,37</sup>

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  $\geq 2$  months of therapy, the dose may be adjusted (i, ii, or iii):

- 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  $\geq 4$  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 Kawasaki disease:* 5 mg/kg/dose as a single infusion

*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

## Drug and Biologic Coverage Criteria

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. The following items will assist reviewers in determining if the requested dosing is medically necessary:

- FDA or compendium-supported dosing and therapeutic monitoring recommendations for the drug
- Member claims/adherence history
- 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)
- 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)
- If applicable, documentation showing the member does not have conditions which make achieving a therapeutic level of drug unlikely even with dose intensification (eg, 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.)

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

### PLACE OF ADMINISTRATION:

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) and Avsola (infliximab-axxq). For information on site of care, see [Specialty Medication Administration Site of Care Coverage Criteria \(molinamarketplace.com\)](https://www.molinamarketplace.com)

The recommendation is that Ixifi (infliximab-qbtx) will be for pharmacy or medical benefit coverage administered in a place of service that is a non-inpatient hospital facility-based location.

## DRUG INFORMATION

### ROUTE OF ADMINISTRATION:

Intravenous

### DRUG CLASS:

Tumor Necrosis Factor Alpha Blockers

### FDA-APPROVED USES:

*Infliximab (Inflectra, Remicade, Renflexis and Avsola)* 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.

## Drug and Biologic Coverage Criteria

**Pediatric Crohn's Disease:** reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 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 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 patients with moderately to severely active disease.

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

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

**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

### COMPENDIAL APPROVED OFF-LABELED USES:

Graft V Host Disease, Hidradenitis Suppurativa, Behcet 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

## 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.<sup>1</sup>

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 October 8, 2019.

## BACKGROUND AND OTHER CONSIDERATIONS

### BACKGROUND:

Infliximab is a chimeric (murine-human) Immunoglobulin (Ig) G1k monoclonal antibody produced by

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## Drug and Biologic Coverage Criteria

recombinant DNA technology that binds specifically with human tumor necrosis factor-alpha (TNF-  $\alpha$ ). The recommended dose of 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. 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, Inflectra and Renflexis have only demonstrated biosimilarity, not interchangeability

### *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 TNF $\alpha$  and inhibits binding of TNF $\alpha$  with its receptors.

### *Risk of tuberculosis during infliximab therapy for inflammatory bowel disease, rheumatoid arthritis, and spondyloarthritis: 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).<sup>18</sup> 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's disease, 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.<sup>1</sup> Guidelines for axial spondyloarthritis are available from the Assessment of Spondyloarthritis International Society (ASAS)/EULAR (2016).<sup>116</sup> 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.20-22 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 nonbiologicDMARD 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.24-27 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.25 The American College of Gastroenterology (ACG) has guidelines for Crohn's disease (2018).27 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.1 Guidelines for treatment of plaque psoriasis recommend topical therapy for limited disease.28-29 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.29 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.1 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].30- 31 According to EULAR, treatment is recommended based on clinical presentation.<sup>31</sup> 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  $\geq 6$  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.<sup>117</sup> Infliximab has been effective in cases of refractory pouchitis.<sup>34</sup> 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).<sup>35-36</sup> 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.<sup>37-38</sup> 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. <sup>39</sup> 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 infliximab 5 mg/kg (n = 15) at Weeks 0, 2, and 6.<sup>47</sup> 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.

**CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:**

The use of infliximab at doses >5 mg/kg is contraindicated in patients with moderate or severe heart failure. All other uses of Remicade (infliximab), Inflectra (infliximab-dyyb), Renflexis (infliximab-abda), Ixifi (infliximab-qbtx) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy is considered not medically necessary. This is subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

**OTHER SPECIAL CONSIDERATIONS:**

Boxed warning for serious infections and malignancy

**CODING/BILLING INFORMATION**

*Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement*

HCPCS CODE	DESCRIPTION
J1745	Injection, infliximab,excludes biosimilar, (Remicade), 10mg
Q5103	Injection, infliximab-dyyb, biosimilar,(Inflectra),10mg
Q5104	Injection, infliximab-abda, biosimilar,(Renflexis)10mg
Q5109	Injection, infliximab- qbtx, biosimilar, (Ixifi) 10mg
Q5121	Injection, infliximab-axxq, biosimilar,(Avsola), 10 mg

**AVAILABLE DOSAGE FORMS:**

Remicade 100MG (infliximab) single vial  
 Renflexis 100mg (infliximab-abda)  
 Inflectra 100mg(infliximab-dyyb)  
 Avsola (infliximab-axxq)

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