BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

ZYMFENTRA™ (infliximab-dyyb) injection

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864 3126 or email it to Pharmacyprecert@azblue.com.

Medical Necessity Requirements for ZYMFENTRA (infliximab dyyb)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a physician specializing in the diagnosis or in consultation with a Gastroenterologist

Indication
- Moderately to severely active Crohn's disease
- Moderately to severely active ulcerative colitis
- Must have received prior treatment with an infliximab product administered intravenously

ORIGINAL EFFECTIVE DATE: 05/16/2024 | ARCHIVE DATE: | LAST REVIEW DATE: 05/21/2026 | LAST CRITERIA REVISION DATE: 05/21/2026

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ZYMFENTRA™ (infliximab-dyyb) injection

Age Requirement

- 18 years or older

Baseline Clinical Evaluation

- **Crohn's Disease**
  - Diagnosis confirmed by **ONE** of the following:
    1. **At least five** of the following signs and symptoms:
       a. Crampy abdominal pain
       b. Chronic intermittent diarrhea (with or without blood)
       c. Fatigue
       d. Weight loss
       e. Anemia
       f. Perianal disease (e.g., anal fissures, anorectal abscess)
       g. Fistulas
       h. Elevated serum C reactive protein and/or fecal calprotectin
       i. Extraintestinal manifestations (arthritis, arthropathy, eye/skin disorders, biliary tract involvement, kidney stones)
    2. Crohn's Disease Activity Index greater than 220
- **Ulcerative Colitis**
  - Diagnosis confirmed by **ONE** of the following:
    1. **At least five** of the following signs and symptoms:
       a. Bloody diarrhea
       b. Bowel movements 4 to 6 or more times per day
       c. Colicky abdominal pain
       d. Urgency
       e. Tenesmus
       f. Fever
       g. Fatigue
       h. Weight loss
       i. Anemia
       j. Elevated serum C reactive protein or erythrocyte sedimentation rate
       k. Elevated fecal calprotectin
    2. American College of Gastroenterology Ulcerative Colitis activity index rating of moderate to severe disease

Alternative Therapies

- **Crohn's Disease**
  - Failure (trial for at least three months duration), contraindication, intolerance to **ONE** or more of the following: [**Note:** This criterion is waived if already tried an FDA approved Crohn's disease biologic]
    1. Azathioprine
    2. 6 mercaptopurine
    3. Methotrexate
    4. Oral corticosteroids

- Failure (trial for at least three months duration), contraindication, intolerance to **TWO** or more of the following preferred agents:
  1. Adalimumab product
  2. Cimzia
  3. Rinvoq
  4. Skyrizi
  5. Tremfya
  6. Ustekinumab product
- Individual is switching to Zymfentra after **ONE** of the following:
  1. Currently established on maintenance infliximab IV infusion
  2. Zymfentra will be started on week 10 after completing an IV infliximab induction regimen

- **Ulcerative Colitis**
  - Failure (trial for at least three months duration), contraindication, intolerance to **ONE** or more of the following: [**Note:** This criterion is waived if already tried an FDA approved Ulcerative Colitis biologic]
    1. Azathioprine
    2. 6 mercaptopurine
    3. Oral corticosteroids
  - Failure (trial for at least three months duration), contraindication, intolerance to **TWO** or more of the following preferred agents:
    1. Adalimumab product
    2. Rinvoq
    3. Simponi
    4. Skyrizi
    5. Ustekinumab product
    6. Tremfya
    7. Xeljanz or Xeljanz XR
  - Individual is switching to Zymfentra after **ONE** of the following:
    1. Currently established on maintenance infliximab IV infusion
    2. Zymfentra will be started on week 10 after completing an IV infliximab induction regimen

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No evidence of active serious infections including opportunistic infections, fungal infections, tuberculosis, localized infections, sepsis, Hepatitis B, or Hepatitis C
  - Serologic tests for Hepatitis B and C (HB surface antigen, anti HB surface antibody, anti HB core antibody, and hepatitis C antibody tests) completed within previous 12 months
  - Screening for latent tuberculosis infection completed and treatment initiated if positive
- No concurrent use of live vaccines

- No concomitant use with another biologic immunomodulator or potent immunosuppressants (e.g., adalimumab, Adbry, cyclosporine, Dupixent, rituximab, infliximab, Enbrel, Otezla, Vtama, Sotyktu, Xolair, or JAK inhibitors such as Cibinqo, Olumiant, Opzelura, Rinvoq, Rinvoq LQ, Xeljanz IR/XR/solution, etc.)

Documentation Requirements

- A completed request form must be submitted including:
  - Chart notes
  - Lab results (e.g., C reactive protein, fecal calprotectin, hepatitis serologies, tuberculosis screening)
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration

- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualification

- Continues to be seen by a physician specializing in or is in consultation with a Gastroenterologist

Clinical Response

- **Crohn's Disease, ONE** of the following:
  - **AT LEAST** a 20 percent improvement in signs and symptoms
  - Decrease in Crohn's Disease Activity Index of more than 70 from baseline or index less than 150 (in remission)
- **Ulcerative Colitis, ONE** of the following:
  - **AT LEAST** a 20 percent improvement in signs and symptoms
  - American College of Gastroenterology Ulcerative Colitis activity index rating of mild disease or disease in remission

Adherence

- Adherence to the prescribed therapy regimen has been documented

Safety

- No development of contraindications or significant adverse drug effects including:
  - Hypersensitivity (including anaphylaxis)
  - New onset or worsening heart failure
  - New onset or exacerbation of central nervous system demyelinating disorders
  - Cytopenia
  - Hepatotoxicity
  - Lupus like syndrome
- No evidence of active serious infections, including opportunistic infections, fungal infections, tuberculosis, clinically important infections, sepsis, Hepatitis B, or Hepatitis C
- No concurrent use of live vaccines

- No concomitant use with another biologic immunomodulator or potent immunosuppressants (e.g., adalimumab, Adbry, cyclosporine, Dupixent, rituximab, infliximab, Enbrel, Otezla, Vtama, Sotyktu, Xolair, or JAK inhibitors such as Cibinqo, Olumiant, Opzelura, Rinvoq, Rinvoq LQ, Xeljanz IR/XR/solution, etc.)

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement in given indication
- Lab values that confirm safe use

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Off Label Use Requests:

Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. Off Label Use of Non Cancer Medications
2. Off Label Use of Cancer Medications

Description:

Zymfentra (infliximab dyyb) is a tumor necrosis factor (TNF) blocker 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 with an infliximab products administered intravenously.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Adult: Age 18 years and older.

Crohn's Disease Activity Index:

Sum each factor after adjustment with a weighting factor

Clinical or laboratory variable	Weighting factor	Factor Sum
Number of liquid or soft stools each day for seven days	x 2	

Abdominal pain (graded 0 = none, 1 = mild, 2 = moderate, 3 = severe) each day for 7 days	x 5	
General well being (assessed from 0 = well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible) each day for 7 days	x 7	
Presence of complications†	x 20	
Taking Lomotil (diphenoxylate/atropine) or opiates for diarrhea (0 = No, 1 = Yes)	x 30	
Presence of an abdominal mass (0 = none, 2 = questionable, 5 = definite)	x 10	
Hematocrit of < 0.47 in men and < 0.42 in women	x 6	
Percentage deviation from standard weight [1 – (ideal/observed)] x 100	x 1	
† **Complications**: one point each is added for each: • the presence of joint pains (arthralgia) or frank arthritis • inflammation of the iris or uveitis • presence of erythema nodosum, pyoderma gangrenosum, or aphthous ulcers • anal fissures, fistulae or abscesses • other fistulae • fever during the previous week		
Total CDAI		
Remission of CD: CDAI < 150 Moderate CD: CDAI 220 450 Severe CD: CDAI > 450 CD response: decrease in CDAI of > 70		

Ulcerative Colitis Activity:

American College of Gastroenterology Ulcerative Colitis Activity Index				
	Remission	Mild	Moderate severe	Fulminant
Stools (no./d)	Formed	< 4	> 6	> 10
Blood in stools	None	Intermittent	Frequent	Continuous
Urgency	None	Mild, occasional	Often	Continuous
Hemoglobin	Normal	Normal	< 75% of normal	Transfusion needed
ESR	< 30	< 30	> 30	> 30
CRP (mg/L)	Normal	Elevated	Elevated	Elevated
Fecal calprotectin (mg/g)	< 150 200	> 150 200	> 150 200	> 150 200
Endoscopy (Mayo sub score)	0 1	1	2 3	3
UCEIS	0 1	2 4	5 8	7 8
The above factors are general guides for disease activity. With the exception of remission, a patient does not need to have all the factors to be considered in a specific category. CRP, C reactive protein; ESR, erythrocyte sedimentation rate; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.				

Endoscopic Assessment of Disease Activity		
Endoscopic Features	UCEIS Score	Mayo Score
Normal	0	0

Erythema, decreased vascular pattern, mild friability	1 3	1
Marked erythema, absent vascular pattern, friability, erosions	4 6	2
Spontaneous bleeding, ulceration	7 8	3

Immunomodulator therapies:

- Azathioprine
- 6 mercaptopurine
- Methotrexate

Resources:

Al Hashash J, Reguerio M. Medical management of moderate to severe Crohn disease in adults. In: UpToDate, Kane SV, Robson KM (Eds), UpToDate, Waltham, MA.: UpToDate Inc. Available at http://uptodate.com. Literature review through February 2026. Topic last updated October 31, 2025. Accessed March 27, 2026.

Cohen RD, Stein AC. Management of moderate to severe ulcerative colitis in adults. In: UpToDate, Kane SV, Meyer C (Eds), UpToDate, Waltham, MA.: UpToDate Inc. Available at http://uptodate.com. Literature review through February 2026. Topic last updated March 10, 2026. Accessed March 27, 2026.

Off Label Use of Cancer Medications: A.R.S. §§ 20 826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20 1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.

Peppercorn MA, Kane SV. Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults. In: UpToDate, Al Hashash J, Jaffe T, Robson KM (Eds), UpToDate, Waltham, MA.: UpToDate Inc. Available at http://uptodate.com. Literature review through February 2026. Topic last updated November 24, 2025. Accessed March 27, 2026.

Peppercorn MA, Kane SV. Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults. In: UpToDate, Al Hashash J, Meyer C (Eds), UpToDate, Waltham, MA.: UpToDate Inc. Available at http://uptodate.com. Literature review through February 2026. Topic last updated October 16, 2025. Accessed March 27, 2026.

Zymfentra (infliximab dyyb) injection product information, revised by Celltrion USA Inc. 05/2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 12, 2026.