

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 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.

Criteria:

- **Criteria for initial therapy:** Zymfentra (infliximab-dyyb) is considered **medically necessary** and will be approved when **ALL** the following criteria are met:
1. Prescriber is a physician specializing in the patient’s diagnosis or is in consultation with a Gastroenterologist
 2. Individual is 18 years of age or older
 3. Individual has a confirmed diagnosis of moderately to severely active Crohn’s disease or moderately to severely active ulcerative colitis following treatment with an infliximab product administered intravenously
 4. **For Crohn’s disease:** Individual meets **ALL** of the following:

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- a. Diagnosis of moderate to severe active Crohn disease is confirmed with **ONE** of the following:
 - i. **At least 5** of the following signs and symptoms:
 1. Crampy abdominal pain
 2. Chronic intermittent diarrhea (with or without blood)
 3. Fatigue
 4. Weight loss
 5. Anemia
 6. Perianal disease (e.g., anal fissures, anorectal abscess)
 7. Fistulas
 8. Elevated serum C-reactive protein and/or fecal calprotectin
 9. Extraintestinal manifestations such as arthritis or arthropathy, eye and skin disorders, biliary tract involvement, and kidney stones
 - ii. Crohn's disease activity index > 220
 - b. Individual has documented failure (used for ≥ 3 consecutive months), contraindication or intolerance to the **ONE or more** of the following: [Note: This criterion is waived if the individual already has tried an FDA-approved Crohn's disease biologic]:
 - i. Azathioprine
 - ii. 6-mercaptopurine
 - iii. Methotrexate
 - iv. Oral corticosteroids
 - c. Individual has documented failure (used for ≥ 3 consecutive months), contraindication or intolerance to the **TWO or more** of the following preferred agents:
 - i. Adalimumab product
 - ii. Cimzia
 - iii. Rinvoq
 - iv. Skyrizi
 - v. Ustekinumab product
 - d. Individual is switching to Zymfentra after **ONE** of the following:
 - i. Currently established on maintenance infliximab IV infusion
 - ii. Zymfentra will be started on week 10 after completing an IV infliximab induction regimen
5. **For Ulcerative Colitis:** Individual meets **ALL** of the following:
- a. Diagnosis of moderate to severe ulcerative colitis is confirmed with **ONE** of the following:
 - i. **At least 5** of the following signs and symptoms
 1. Bloody diarrhea
 2. Bowel movements 4-6 or more times per day
 3. Colicky abdominal pain
 4. Urgency
 5. Tenesmus
 6. Fever
 7. Fatigue
 8. Weight loss
 9. Anemia
 10. Elevated serum C-reactive protein or erythrocyte sedimentation rate
 11. Elevated fecal calprotectin
 - ii. American College of Gastroenterology Ulcerative Colitis activity index rating of moderate to severe disease

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- b. Individual has documented failure (used for ≥ 3 consecutive months), contraindication or intolerance to the following **ONE or more** of the following [Note: This criterion is waived if the individual already has tried an FDA-approved Ulcerative Colitis biologic]:
 - i. Azathioprine
 - ii. 6-mercaptopurine
 - iii. Oral corticosteroids
 - c. Individual has documented failure (used for ≥ 3 consecutive months), contraindication or intolerance to the **TWO or more** of the following preferred agents:
 - i. Adalimumab product
 - ii. Rinvoq
 - iii. Simponi
 - iv. Skyrizi (risankizumab)
 - v. Ustekinumab product
 - vi. Tremfya (guselkumab)
 - vii. Xeljanz or Xeljanz XR
 - d. Individual is switching to Zymfentra after **ONE** of the following:
 - i. Currently established on maintenance infliximab IV infusion
 - ii. Zymfentra will be started on week 10 after completing an IV infliximab induction regimen
6. Individual does **NOT** have **ANY** of the following:
- a. Evidence of active serious infections including, opportunistic infections, fungal infections, tuberculosis, clinically important localized infections, sepsis, Hepatitis B, or Hepatitis C
 - i. Serologic tests for hepatitis B and C (HB surface Ag, anti-HB surface Ab, anti-HB core Ab, and hepatitis C antibody tests) have been done within the previous 12 months
 - ii. Screening for latent tuberculosis infection with a tuberculin skin test or blood test has been done and if positive, treatment has been initiated
 - b. Concurrent use of live vaccines
7. Agent will not be used in combination with another biologic immunomodulator or other potent immunosuppressants (e.g., adalimumab, Adbry, azathioprine, cyclosporine, Dupixent, rituximab, infliximab, Enbrel, Otezla, Vtama, Sotyktu, Xolair, or JAK inhibitors (Cibinqo, Olumiant, Opzelura, Rinvoq, Rinvoq LQ, Xeljanz IR, XR, solution), etc.)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Zymfentra (infliximab-dyyb) is considered **medically necessary** and will be approved when **ALL** the following criteria are met (**samples are not considered for continuation of therapy**):

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist
2. Individual's condition has responded while on therapy with response defined as the following:
 - a. **For Crohn's disease: ONE** of the following:
 - i. **AT LEAST** a 20% improvement in signs and symptoms of Crohn's disease
 - ii. Decrease in Crohn's disease activity index of more than 70 from baseline or a Crohn's disease activity index of < 150 (in remission)

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- b. **For Ulcerative Colitis: ONE** of the following:
 - i. **AT LEAST** a 20% improvement in signs and symptoms of Ulcerative Colitis
 - ii. American College of Gastroenterology Ulcerative Colitis activity index rating of mild disease or disease in remission
3. Individual has been adherent with the medication
4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use including:
 - a. Hypersensitivity, including anaphylaxis
 - b. New onset, or worsening heart failure
 - c. New onset, or exacerbation of CNS demyelinating disorders
 - d. Cytopenia
 - e. Hepatotoxicity
 - f. Lupus-like syndrome
5. Individual does **NOT** have **ANY** of the following:
 - a. Evidence of active serious infections, including opportunistic infections, fungal infections, tuberculosis, clinically important infections, sepsis, Hepatitis B, or Hepatitis C
 - b. Concurrent use of live vaccines
6. Agent will not be used in combination with another biologic immunomodulator or other potent immunosuppressants (e.g., adalimumab, Adbry, azathioprine, cyclosporine, Dupixent, rituximab, infliximab, Enbrel, Otezla, Vtama, Sotyktu, Xolair, or JAK inhibitors (Cibinqo, Olumiant, Opzelura, Rinvoq, Rinvoq LQ, Xeljanz IR, XR, solution), etc.)

Renewal duration: 12 months

- 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.

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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 $[1 - (\text{ideal}/\text{observed})] \times 100$	x 1	
† Complications: one point each is added for each: <ul style="list-style-type: none"> 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

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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 2025. Topic last updated on January 30, 2025. Accessed March 27, 2025.

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 2025. Topic last updated on February 19, 2025. Accessed March 27, 2025.

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 2025. Topic last updated on September 16, 2024. Accessed March 27, 2025.

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 2025. Topic last updated on May 17, 2024. Accessed March 27, 2025.

Zymfentra (infliximab-dyyb) injection product information, revised by Celltrion USA Inc. 02/2024. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed February 18, 2025.

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