



## PRIOR AUTHORIZATION POLICY

- POLICY:** Inflammatory Conditions – Zymfentra Prior Authorization Policy
- Zymfentra® (infliximab-dyyb subcutaneous injection – Celltrion)

**REVIEW DATE:** 12/17/2025; selected revision 02/11/2026

### **INSTRUCTIONS FOR USE**

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT WHERE APPROPRIATE AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. WHERE COVERAGE FOR CARE OR SERVICES DOES NOT DEPEND ON SPECIFIC CIRCUMSTANCES, REIMBURSEMENT WILL ONLY BE PROVIDED IF A REQUESTED SERVICE(S) IS SUBMITTED IN ACCORDANCE WITH THE RELEVANT CRITERIA OUTLINED IN THE APPLICABLE COVERAGE POLICY, INCLUDING COVERED DIAGNOSIS AND/OR PROCEDURE CODE(S). REIMBURSEMENT IS NOT ALLOWED FOR SERVICES WHEN BILLED FOR CONDITIONS OR DIAGNOSES THAT ARE NOT COVERED UNDER THIS COVERAGE POLICY (SEE "CODING INFORMATION" BELOW). WHEN BILLING, PROVIDERS MUST USE THE MOST APPROPRIATE CODES AS OF THE EFFECTIVE DATE OF THE SUBMISSION. CLAIMS SUBMITTED FOR SERVICES THAT ARE NOT ACCOMPANIED BY COVERED CODE(S) UNDER THE APPLICABLE COVERAGE POLICY WILL BE DENIED AS NOT COVERED. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

## **CIGNA NATIONAL FORMULARY COVERAGE:**

### **OVERVIEW**

Zymfentra, a subcutaneous (SC) tumor necrosis factor (TNF) inhibitor, is indicated for the following uses:<sup>1</sup>

- **Crohn's disease**, as maintenance treatment for moderately to severely active disease in adults who have received three induction doses with an infliximab intravenous product.
- **Ulcerative colitis**, as maintenance treatment for moderately to severely active disease in adults who have received three induction doses with an infliximab intravenous product.

Therapy (for either indication) begins with an infliximab intravenous (IV) product administered as an induction regimen at Weeks 0, 2, and 6.<sup>1</sup> At Week 10 or at any scheduled infliximab IV infusion in patients with a clinical response or remission, therapy can be switched to Zymfentra. The recommended dose of Zymfentra is 120 mg administered SC once every 2 weeks.

## Guidelines

Guidelines for the treatment of inflammatory conditions recommend use of infliximab.

- **Crohn's Disease (CD):** The American College of Gastroenterology (ACG) [2025] and the American Gastroenterological Association (AGA) [2025] have guidelines for the management of CD in adults.<sup>2,3</sup> Both guidelines recommend upfront use of advanced therapies, rather than step-up therapy after failure of corticosteroids and/or immunomodulators. Advanced therapies recommended include TNF inhibitors, Entyvio<sup>®</sup> (vedolizumab IV infusion, SC injection), interleukin (IL)-23 inhibitors, IL-12/23 inhibitors, and Rinvoq<sup>®</sup> (upadacitinib extended-release tablets).
- **Ulcerative Colitis (UC):** The AGA (2024) and the ACG (2025) have clinical practice guidelines on the management of moderate to severe UC.<sup>4,5</sup> In moderate to severe disease, systemic corticosteroids or advanced therapies may be utilized for induction of remission. Advanced therapies recommended include TNF inhibitors, Entyvio, IL-23 inhibitors, IL-12/23 inhibitors, sphingosine-1-phosphate (S1P) receptor modulators, and Janus kinase (JAK) inhibitors. If steroids are utilized for induction, efforts should be made to introduce steroid-sparing agents for maintenance therapy. Of note, guidelines state corticosteroids may be avoided entirely when other effective induction strategies are planned.<sup>5</sup> Both guidelines also recommend that any drug that effectively treats induction should be continued for maintenance.<sup>4,5</sup>

## POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zymfentra. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zymfentra as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Zymfentra to be prescribed by or in consultation with a physician who specializes in the condition being treated.

- **Zymfentra<sup>®</sup> (infliximab-dyyb subcutaneous injection – Celltrion) is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):**

### FDA-Approved Indications

1. **Crohn's Disease.** Approve for the duration noted if the patient meets ONE of the following (A or B):
  - A) **Initial Therapy.** Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
    - i. Patient is  $\geq$  18 years of age; AND
    - ii. According to the prescriber, the patient is currently receiving infliximab intravenous maintenance therapy or will receive induction dosing with an

- infliximab intravenous product within 3 months of initiating therapy with Zymfentra; AND
- iii. The medication is prescribed by or in consultation with a gastroenterologist; OR
- B) Patient is Currently Receiving an Infliximab Product.** Approve for 1 year if the patient meets BOTH of the following (i and ii):
- i. Patient has been established on therapy for at least 6 months; AND  
Note: A patient who has received < 6 months of therapy or who is restarting therapy with the requested drug is reviewed under criterion A (Initial Therapy).
  - ii. Patient meets at least ONE of the following (a or b):
    - a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested product); OR  
Note: Examples of objective measures include fecal markers (e.g., fecal lactoferrin, fecal calprotectin), serum markers (e.g., C-reactive protein), imaging studies (magnetic resonance enterography [MRE], computed tomography enterography [CTE]), endoscopic assessment, and/or reduced dose of corticosteroids.
    - b) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or blood in stool.
- 2. Ulcerative Colitis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
- A) Initial Therapy.** Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
- i. Patient is  $\geq$  18 years of age; AND
  - ii. According to the prescriber, the patient is currently receiving infliximab intravenous maintenance therapy or will receive induction dosing with an infliximab intravenous product within 3 months of initiating therapy with Zymfentra; AND
  - iii. The medication is prescribed by or in consultation with a gastroenterologist; OR
- B) Patient is Currently Receiving an Infliximab Product.** Approve for 1 year if the patient meets BOTH of the following (i and ii):
- i. Patient has been established on therapy for at least 6 months; AND  
Note: A patient who has received < 6 months of therapy or who is restarting therapy with an infliximab product is reviewed under criterion A (Initial Therapy).
  - ii. Patient meets at least ONE of the following (a or b):
    - a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an infliximab product); OR  
Note: Examples of objective measures include fecal markers (e.g., fecal calprotectin), serum markers (e.g., C-reactive protein), endoscopic assessment, and/or reduced dose of corticosteroids.

- b) Compared with baseline (prior to initiating an infliximab product), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or rectal bleeding.

## CONDITIONS NOT COVERED

- **Zymfentra® (infliximab-dyyb subcutaneous injection – Celltrion) is(are) considered not medically necessary for ANY other use(s) including the following (this list may not be all inclusive; criteria will be updated as new published data are available):**

- 1. Concurrent Use with a Biologic or with a Targeted Synthetic Oral Small Molecule Drug.** This medication should not be administered in combination with another biologic or with a targeted synthetic oral small molecule drug used for an inflammatory condition (see [Appendix](#) for examples). Combination therapy is generally not recommended due to a potentially higher rate of adverse events and lack of controlled clinical data supporting additive efficacy.  
Note: This does NOT exclude the use of conventional synthetic disease-modifying antirheumatic drugs (e.g., methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine) in combination with this medication.

## REFERENCES

1. Zymfentra™ subcutaneous injection [prescribing information]. Yeonsu-gu, Incheon: Celltrion; February 2024.
2. Lichtenstein, G, Loftus E, Afzali A, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol.* 2025 June;120(6):1225-1264.
3. Scott FI, Ananthakrishnan AN, Click B, et al. AGA Living Clinical Practice Guideline on the Pharmacologic Management of Moderate-to-Severe Crohn's Disease. *Gastroenterology.* 2025 Dec;169(7):1397-1448.
4. Singh S, Loftus EV Jr, Limketkai BN, et al. AGA Living Clinical Practice Guideline on Pharmacological Management of Moderate-to-Severe Ulcerative Colitis. *Gastroenterology.* 2024 Dec;167(7):1307-1343.
5. Rubin D, Ananthakrishnan A, Siegel C. ACG Clinical Guideline Update: Ulcerative Colitis in Adults. *Am J of Gastroenterol.* 2025 June;120(6):1187-1224.

## HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	-	12/06/2023
Selected Revision	<b>Conditions Not Covered:</b> Concurrent use with a Biologic or with a Targeted Synthetic Oral Small Molecule Drug was changed to as listed (previously oral small molecule drug was listed as Disease-Modifying Antirheumatic Drug).	09/11/2024
Annual Revision	No criteria changes.	12/04/2024
Selected Revision	<b>Ulcerative Colitis:</b> For initial therapy, removed the following options of approval: (1) the patient has tried one systemic therapy; (2) the patient has pouchitis and tried an antibiotic, probiotic, corticosteroid enema, or mesalamine enema.	07/23/2025

Annual Revision	No criteria changes. <b>Appendix:</b> Otezla XR (apremilast-extended release tablets) was added.	12/17/2025
Selected Revision	<b>Crohn's Disease:</b> For initial therapy, the following options of approval were removed: The patient has tried or is currently taking systemic corticosteroids, or corticosteroids are contraindicated; patient has tried one conventional systemic therapy for Crohn's disease along with the associated Note; patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas; patient had ileocolonic resection (to reduce the chance of Crohn's disease recurrence).	02/11/2026

## APPENDIX

	Mechanism of Action	Examples of Indications*
<b>Biologics</b>		
<b>Adalimumab SC Products</b> (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
<b>Cimzia®</b> (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
<b>Etanercept SC Products</b> (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA, RA
<b>Infliximab IV Products</b> (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
<b>Zymfentra®</b> (infliximab-dyyb SC injection)	Inhibition of TNF	CD, UC
<b>Simponi®, Simponi Aria®</b> (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
<b>Tocilizumab Products</b> (Actemra® IV, biosimilar; Actemra SC, biosimilar)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
<b>Kevzara®</b> (sarilumab SC injection)	Inhibition of IL-6	RA
<b>Orencia®</b> (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
<b>Rituximab IV Products</b> (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
<b>Kineret®</b> (anakinra SC injection)	Inhibition of IL-1	JIA <sup>^</sup> , RA
<b>Omvoh®</b> (mirikizumab IV infusion, SC injection)	Inhibition of IL-23	CD, UC
<b>Ustekinumab Products</b> (Stelara® IV, biosimilar; Stelara SC, biosimilar)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
<b>Siliq®</b> (brodalumab SC injection)	Inhibition of IL-17	PsO
<b>Cosentyx®</b> (secukinumab SC injection; secukinumab IV infusion)	Inhibition of IL-17A	SC formulation: AS, ERA, nr-axSpA, PsO, PsA
		IV formulation: AS, nr-axSpA, PsA
<b>Taltz®</b> (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
<b>Bimzelx®</b> (bimekizumab-bkzx SC injection)	Inhibition of IL-17A/17F	PsO, AS, nr-axSpA, PsA
<b>Ilumya®</b> (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
<b>Skyrizi®</b> (risankizumab-rzaa SC injection, risankizumab-rzaa IV infusion)	Inhibition of IL-23	SC formulation: CD, PSA, PsO, UC
		IV formulation: CD, UC
<b>Tremfya®</b> (guselkumab SC injection, guselkumab IV infusion)	Inhibition of IL-23	SC formulation: CD, PsA, PsO, UC
		IV formulation: CD, UC
<b>Entyvio®</b> (vedolizumab IV infusion, vedolizumab SC injection)	Integrin receptor antagonist	CD, UC
<b>Oral Therapies/Targeted Synthetic Oral Small Molecule Drugs</b>		
<b>Otezla®</b> (apremilast tablets)	Inhibition of PDE4	PsO, PsA
<b>Otezla® XR</b> (apremilast extended-release tablets)	Inhibition of PDE4	PsO, PsA
<b>Cibinqo™</b> (abrocitinib tablets)	Inhibition of JAK pathways	AD

<b>Olumiant</b> <sup>®</sup> (baricitinib tablets)	Inhibition of JAK pathways	RA, AA
<b>Litfulo</b> <sup>®</sup> (ritlecitinib capsules)	Inhibition of JAK pathways	AA
<b>Leqselvi</b> <sup>®</sup> (deuruxolitinib tablets)	Inhibition of JAK pathways	AA
<b>Rinvoq</b> <sup>®</sup> (upadacitinib extended-release tablets)	Inhibition of JAK pathways	AD, AS, nr-axSpA, RA, PsA, CD, UC
<b>Rinvoq</b> <sup>®</sup> LQ (upadacitinib oral solution)	Inhibition of JAK pathways	PsA, PJIA
<b>Sotyktu</b> <sup>®</sup> (deucravacitinib tablets)	Inhibition of TYK2	PsO
<b>Xeljanz</b> <sup>®</sup> (tofacitinib tablets/oral solution)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
<b>Xeljanz</b> <sup>®</sup> XR (tofacitinib extended-release tablets)	Inhibition of JAK pathways	RA, PsA, UC
<b>Zeposia</b> <sup>®</sup> (ozanimod tablets)	Sphingosine 1 phosphate receptor modulator	UC
<b>Velsipity</b> <sup>®</sup> (etrasimod tablets)	Sphingosine 1 phosphate receptor modulator	UC

\* Not an all-inclusive list of indications. Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn’s disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; AA – Alopecia areata; TYK2 – Tyrosine kinase 2.

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