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Section:	Prescription Drugs	**Effective Date:**	July 1, 2024
Subsection:	Gastrointestinal Agents	**Original Policy Date:**	March 22, 2024
Subject:	Zymfentra	**Page:**	1 of 8

Last Review Date: June 13, 2024

Zymfentra

Description

Zymfentra (infliximab-dyyb) injection, for subcutaneous use

Background
Zymfentra (infliximab-dyyb) is a tumor necrosis factor (TNF) blocker and is a chimeric IgG1κ monocloncal antibody. Zymfentra neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibit binding of TNFα with its receptors. Zymfentra has shown biological activities, such as TNFα neutralization activity and TNFα binding affinities, complement component 1q binding affinity and crystallizable fragment receptor binding affinities in a wide variety of in vitro bioassays (1).

Regulatory Status
Zymfentra is a tumor necrosis factor (TNF) blocker indicated in adults for maintenance treatment of: (1)

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

Zymfentra carries a boxed warning regarding the increased risk of serious infections and malignancies. Patients treated with Zymfentra are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or

corticosteroids. Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including infliximab products (1).

Zymfentra also has warnings regarding Hepatitis B virus reactivation, hepatotoxicity, congestive heart failure, hematologic reactions, hypersensitivity, neurologic reactions, and risk of additive immunosuppressive effects from prior biological products (1).

It is recommended that live vaccines not be given concurrently. At least a 6-month waiting period following birth is recommended before the administration of live vaccines to infants born to female patients treated with infliximab (1).

The safety and effectiveness of Zymfentra in pediatric patients less than 18 years of age have not been established (1).

Related policies
Cimzia, Humira, Infliximab, Simponi

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Zymfentra may be considered **medically necessary** if the conditions indicated below are met.

Zymfentra may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 18 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. Moderate to severely active Crohn's disease (CD)
    a. Inadequate treatment response, intolerance, or contraindication to conventional therapy for CD (See Appendix 1)

2. Moderate to severely active ulcerative colitis (UC)
    a. Inadequate treatment response, intolerance, or contraindication to conventional therapy for UC (See Appendix 1)

AND ALL of the following:

1. Patient will have completed an intravenous (IV) induction regimen with an infliximab product before starting Zymfentra
2. TB test confirming no active tuberculosis **OR** if latent tuberculosis infection is present, treatment for the infection to be started prior to use of infliximab products
3. **NO** active infections
4. **NOT** to be used in combination with any other biologic DMARD or targeted synthetic DMARD (See Appendix 2)
5. Patient is not at risk for HBV infection **OR** is at risk for HBV infection and HBV infection has been ruled out **OR** treatment for HBV infection has been initiated
6. **NOT** given concurrently with live vaccines
7. Patient **MUST** have tried the preferred product(s) (see Appendix 3) unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

Prior – Approval *Renewal* Requirements

Age 18 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. Moderate to severely active Crohn's disease (CD)
2. Moderate to severely active ulcerative colitis (UC)

AND ALL of the following:

1. Condition has improved or stabilized
2. Absence of active infection (including tuberculosis and hepatitis B virus (HBV))
3. **NOT** to be used in combination with any other biologic DMARD or targeted synthetic DMARD (See Appendix 2)
4. **NOT** given concurrently with live vaccines

5. Patient **MUST** have tried the preferred product(s) (see Appendix 3) unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

Policy Guidelines

Pre - PA Allowance
None

Prior - Approval Limits

Quantity 4 injections per 56 days

Duration 4 months

Prior – Approval *Renewal* Limits

Quantity 4 injections per 56 days

Duration 12 months

Rationale

Summary
Zymfentra is a tumor necrosis factor (TNFα) blocker indicated for use in ulcerative colitis and Crohn's disease. It carries a boxed warning regarding the increased risk of serious infections and malignancies. It is recommended that live vaccines not be given concurrently. The safety and effectiveness of Zymfentra in pediatric patients less than 18 years of age have not been established (1).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of Zymfentra while maintaining optimal therapeutic outcomes.

References
1. Zymfentra [package insert]. Jersey City, NJ: Celltrion USA, Inc.; October 2023.

Policy History

Date	Action
March 2024	Addition to PA
June 2024	Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 13, 2024 and is effective on July 1, 2024.

Appendix 1 - List of Conventional Therapies

Conventional Therapy Options for CD
1. Mild to moderate disease – induction of remission: a. Oral budesonide, oral mesalamine b. Alternatives: metronidazole, ciprofloxacin
2. Mild to moderate disease – maintenance of remission: a. Azathioprine, mercaptopurine b. Alternatives: oral budesonide, methotrexate intramuscularly (IM)
3. Moderate to severe disease – induction of remission: a. Prednisone, methylprednisolone intravenously (IV) b. Alternatives: methotrexate IM
4. Moderate to severe disease – maintenance of remission: a. Azathioprine, mercaptopurine b. Alternative: methotrexate IM
5. Perianal and fistulizing disease – induction of remission c. Metronidazole ± ciprofloxacin
6. Perianal and fistulizing disease – maintenance of remission d. Azathioprine, mercaptopurine e. Alternative: methotrexate IM

Conventional Therapy Options for UC
1. Mild to moderate disease – induction of remission: a. Oral mesalamine (e.g., Asacol, Lialda, Pentasa), balsalazide, olsalazine b. Rectal mesalamine (e.g., Canasa, Rowasa) c. Rectal hydrocortisone (e.g., Colocort, Cortifoam) d. Alternatives: prednisone, azathioprine, mercaptopurine, sulfasalazine
2. Mild to moderate disease – maintenance of remission: a. Oral mesalamine, balsalazide, olsalazine, rectal mesalamine b. Alternatives: azathioprine, mercaptopurine, sulfasalazine
3. Severe disease – induction of remission: a. Prednisone, hydrocortisone IV, methylprednisolone IV b. Alternatives: cyclosporine IV, tacrolimus, sulfasalazine
4. Severe disease – maintenance of remission: a. Azathioprine, mercaptopurine b. Alternative: sulfasalazine
5. Pouchitis: a. Metronidazole, ciprofloxacin b. Alternative: rectal mesalamine

Appendix 2 – List of DMARDs

Conventional disease-modifying antirheumatic drugs (DMARDs)

Generic Name	Brand Name
azathioprine	Azasan, Imuran
cyclophosphamide	Cytoxan
cyclosporine	Neoral, Gengraf, Sandimmune
hydroxychloroquine	Plaquenil
leflunomide	Arava
methotrexate	Rheumatrex, Trexall
mycophenolate	Cellcept
sulfasalazine	Azulfidine, Sulfazine

Biological disease-modifying antirheumatic drugs (DMARDs)

Generic Name	Brand Name
abatacept	Orencia
adalimumab	Humira
anakinra	Kineret
brodalumab	Siliq
certolizumab	Cimzia
etanercept	Enbrel
golimumab	Simponi/Simponi Aria
guselkumab	Tremfya
infliximab	Remicade
infliximab	Zymfentra
ixekizumab	Taltz
risankizumab-rzaa	Skyrizi
rituximab	Rituxan
sarilumab	Kevzara
secukinumab	Cosentyx
spesolimab-sbzo	Spevigo
tildrakizumab-asmn	Ilumya
tocilizumab	Actemra
ustekinumab	Stelara
vedolizumab	Entyvio

Targeted synthetic disease-modifying antirheumatic drugs (DMARDs)

Generic Name	Brand Name
apremilast	Otezla
baricitinib	Olumiant

deucravacitinib	Sotyktu
tofacitinib	Xeljanz
upadactinib	Rinvoq

Appendix 3 - List of Preferred Products

Diagnosis	Standard Option/Basic Option Preferred Products	Blue Focus Preferred Products
Crohn's disease (CD)	*must try **TWO** preferred products: Humira** Rinvoq Skyrizi Stelara (SC)	Humira
Ulcerative colitis (UC)	*must try **TWO** preferred products: Humira** Rinvoq Stelara (SC)	Humira

**Including all preferred biosimilars (see reference product criteria)