

Writing Letters of Appeal for ZYMFENTRA[®]

Your medical opinion matters

When health insurers deny coverage or prior authorization, there are options. Patients, advocates, or healthcare providers can appeal these decisions.

Two types of appeals¹

✓ **Internal appeals** request an insurance company to conduct a full and fair review of its decision. *The insurance company must speed up its process for urgent cases.*

✓ **External review appeals** request a review by an independent third party. External review means the insurance company will not have the final say about paying the claim.

Learn how the process differs for each type of appeal at [healthcare.gov/appeal-insurance-company-decision](https://www.healthcare.gov/appeal-insurance-company-decision)



Tools to empower your appeals

The following pages offer advice on writing a Letter of Appeal for ZYMFENTRA and provide a letter template to help ensure your clinical input is taken into consideration.

NOTE: The use of this template does not guarantee approval or reimbursement for the prescribed ZYMFENTRA product. Furthermore, it is not intended to replace or influence the independent medical judgment of the healthcare provider.



Celltrion CONNECT[®] is here to help

Celltrion CONNECT and your dedicated FRM are available to assist with:

- Benefit verifications
- Access issues
- Prior authorizations
- Financial support

FRM, field reimbursement manager.

Reference: 1. How to appeal an insurance company decision. Healthcare.gov. Accessed January 15, 2025. <https://www.healthcare.gov/appeal-insurance-company-decision/>

Please see Important Safety Information on page 4 and full [Prescribing Information](#), including Boxed Warning.

Advice for Writing Letters of Appeal for ZYMFENTRA[®]

Information you will need to complete your Letter of Appeal

- ✓ Full name and date of birth of the patient
- ✓ Insurance policy/ID number of the patient
- ✓ Letters showing treatment denial, including explanation of benefits documents
- ✓ Case ID number
- ✓ Condensed medical history of the patient
 - Including diagnosis, ICD-10 codes, comorbidities, and allergies
- ✓ List of current and previous treatments
 - Including dates for starting, stopping, and cause(s) for discontinuation
- ✓ Overview of the patient's condition and symptoms
- ✓ Clinical support for your recommendations

Additional guidance for writing your Letter of Appeal

- **It is important to review the insurance plan's Explanation of Benefits**, as this will help you explain how your patient meets benefits criteria or why it makes sense to exclude your patient from certain criteria
- **Be sure to clearly state** why ZYMFENTRA is the most appropriate treatment option
- **Offer clinical rationale** to support ZYMFENTRA as your treatment choice
 - Include clinical data, such as patient chart notes and laboratory results
- **List any additional patient attributes and/or clinical factors** relevant to your clinical opinion
 - Consider attaching any clinical evidence you feel will support your recommendation for ZYMFENTRA (eg, Section 12 [Clinical Pharmacology] and Section 14 [Clinical Studies] in the full Prescribing Information for ZYMFENTRA)¹

For additional references, please reach out to the Celltrion CONNECT[®] Patient Support Program at 1-877-812-6662.

NOTE: Please exercise your medical judgment and discretion when providing a diagnosis and characterization of the patient's medical condition.

Keeping insurer timing and processes in mind

- **Review the procedure** for submitting your Letter of Appeal to ensure you meet insurer and state requirements
 - This includes mode of submission (eg, fax, phone, email, insurer website)
- **Internal appeals** need to be submitted within 6 months (180 days) of receiving a claim denial notice²
- **External review appeals** need to be submitted within 4 months (120 days) of receiving a claim denial notice³
- **Keep track** of your appeal/request status and follow up with the insurer as needed

ICD-10, International Classification of Diseases, Tenth Revision.

References: 1. ZYMFENTRA [prescribing information]. Jersey City, NJ. Celltrion Inc; 2025. Accessed September 24, 2025. https://zymfentra.b-cdn.net/zymfentra_prescribing_information_final.pdf 2. Internal appeals. Healthcare.gov. Accessed January 15, 2025. <https://www.healthcare.gov/appeal-insurance-company-decision/internal-appeals/> 3. External review. Healthcare.gov. Accessed January 15, 2025. <https://www.healthcare.gov/appeal-insurance-company-decision/external-review/>

Please see Important Safety Information on page 4 and full Prescribing Information, including Boxed Warning.

Helping you organize your response

You can also copy and paste the template page text into your practice's letterhead before making needed edits, and then print, fax, or mail it as needed.

[illegible]

Please see Important Safety Information on page 4 and full Prescribing Information, including Boxed Warning.

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS INFECTIONS and MALIGNANCY

SERIOUS INFECTIONS

Patients treated with TNF blockers, including 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.

Discontinue ZYMFENTRA if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis, including reactivation of latent tuberculosis.** Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Test patients for latent tuberculosis before ZYMFENTRA use and during therapy. Initiate treatment for latent infection prior to ZYMFENTRA use.
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis.** Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with ZYMFENTRA prior to initiating therapy in patients with chronic or recurrent infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with ZYMFENTRA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

MALIGNANCY

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

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including infliximab products. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. The majority of reported cases have occurred in patients with Crohn's disease or ulcerative colitis and most were in young adult males.

Contraindications

- ZYMFENTRA is contraindicated in patients with a history of a severe hypersensitivity reaction to infliximab-dyyb, other infliximab products, any of the inactive ingredients in ZYMFENTRA, or any murine proteins. Reactions have included anaphylaxis.

Warnings and Precautions

- **Serious infections:** Avoid in patients with active infection. If infection develops, conduct a prompt/complete diagnostic workup appropriate for immunocompromised patients and initiate antimicrobials. If systemic illness develops in patients who reside or travel to regions where mycoses are endemic, consider empiric antifungals.
- **Malignancies:** Malignancies, including lymphoma, were greater in TNF-blocker-treated patients. Consider the higher risk of hepatosplenic T-cell

lymphoma (HSTCL) with combination therapy versus increased risk of immunogenicity and hypersensitivity reactions with monotherapy.

- **Hepatitis B virus (HBV) reactivation:** Test for HBV infection before starting treatment. Monitor HBV carriers during and several months after therapy for active HBV infection. If reactivation occurs, stop ZYMFENTRA and begin anti-viral therapy.
- **Hepatotoxicity:** Severe hepatic reactions, some fatal or necessitating liver transplantation have occurred in patients receiving infliximab products. Monitor hepatic enzymes and liver function tests every 3-4 months during treatment; investigate liver enzyme elevations and interrupt treatment if drug-induced liver injury is suspected. Instruct patients to seek immediate medical attention if symptoms develop.
- **Congestive heart failure (CHF):** New onset or worsening symptoms may occur. Avoid in patients with CHF. Monitor for new/worsening symptoms when administering ZYMFENTRA.
- **Hematologic reactions:** Advise patients to seek immediate medical attention if signs and symptoms of cytopenia develop; consider stopping if significant hematologic abnormalities develop.
- **Hypersensitivity and other administration reactions:** Serious hypersensitivity reactions, including anaphylaxis have occurred with intravenous formulations of infliximab; discontinue ZYMFENTRA and start appropriate therapy.
- **Neurologic reactions:** Exacerbation or new onset CNS demyelinating disorders may occur; consider discontinuation of ZYMFENTRA.
- **Risk of infection with concurrent administration of other biological products:** Concurrent use with other immunosuppressive biologics may increase risk of infection.

- **Risk of additive immunosuppressive effects from prior biological products:** Consider the half-life and mode of action of prior biologics.

- **Autoimmunity:** Formation of autoantibodies and development of lupus-like syndrome may occur; discontinue ZYMFENTRA if symptoms develop.

- **Vaccinations and use of live vaccines/therapeutic infectious agents:** Prior to initiating ZYMFENTRA bring patients up to date with vaccinations. Live vaccines or therapeutic infectious agents should not be given with ZYMFENTRA. A 6-month waiting period following birth is recommended before the administration of live vaccines to infants exposed in utero to infliximab.

Common Adverse Reactions (≥3%)

- Ulcerative Colitis: COVID-19, anemia, arthralgia, injection site reaction, increased alanine aminotransferase, and abdominal pain.
- Crohn's Disease: COVID-19, headache, upper respiratory tract infection, injection site reaction, diarrhea, increased blood creatine phosphokinase, arthralgia, increased alanine aminotransferase, hypertension, urinary tract infection, neutropenia, dizziness, and leukopenia.

Drug Interactions

- Concurrent use with immunosuppressive biologics used to treat UC and CD is not recommended due to risk of infection.
- Formation of CYP450 enzymes may be suppressed by increased levels of cytokines during chronic inflammation. ZYMFENTRA could normalize the formation of CYP450 enzymes potentially resulting in decreased exposure of CYP450 substrates and requiring dose adjustments.

INDICATIONS AND USAGE

ZYMFENTRA® is indicated in adults for the maintenance treatment of moderately to severely active UC or moderately to severely active CD following an IV infliximab product.

Please see full [Prescribing Information](#), including **BOXED WARNING**.

**Sample Letter of Appeal – Product Change
(Healthcare Provider Letterhead)**

[Your name]
[Your address]
[Your city, state, zip code]
[Your phone number]
[Tax ID#]
[Date]

Patient Name: [Patient Name]
Patient Date of Birth: [Patient Date of Birth]
[Name of Insurance Plan]
Member ID: [Member ID #]
Group Number: [Group Number]
[Address of Insurance Plan]
Claim or Explanation of Benefit #: [Claim or Explanation of Benefit #]

Re: Action Required: Request for Reconsideration for ZYMFENTRA® (infliximab-dyyb) Subcutaneous Injection 120 mg for [Patient Name]

To whom it may concern:

My name is [Physician Name], and I am a [board-certified medical specialty] [NPI]. This letter serves as the [first/second] appeal for approval of ZYMFENTRA (infliximab-dyyb SC), which was originally denied to [Patient Name] on [date]. I am writing this letter to provide additional information to support my request to treat [Patient Name], who has been diagnosed with [condition], [ICD code(s)], with ZYMFENTRA, a subcutaneous infliximab prescription medication indicated in adults for the maintenance treatment of [moderately to severely active ulcerative colitis/moderately to severely active Crohn's disease] following treatment with an infliximab product given intravenously.¹

In brief, treating [Patient Name] with ZYMFENTRA is medically appropriate and necessary, and it should be covered and reimbursed. [Health Plan Name] determined ZYMFENTRA was not covered for [Patient Name] because [reason(s) for denial]. This letter provides my clinical rationale and relevant information about the patient's medical history and treatment.

Patient's Clinical History

[Must include: Patient's clinical/medical history, diagnosis, condition, and symptoms:]
[Patient Name] is [a/an] [age]-year-old [male/female] patient who has been diagnosed with [condition] [ICD-10-code(s)] as of [date of diagnosis]. [He/she] has been in my care since [date].

[Include any additional considerations here:]

Continued

My rationale for prescribing ZYMFENTRA is based on [include a brief disease course of the patient, including history of disease, laboratory results, symptoms, and previous treatments (including names, dosages, frequency, and length). If the patient has discontinued treatment, please include information on the reasons for such discontinuation, such as inability to tolerate a previous treatment, lack of response, and/or side effects. Include medical reasoning for choosing to bypass any alternative medications covered by the health plan.¹⁻⁴]

[UC] - PI

[The safety and efficacy of ZYMFENTRA was assessed in a randomized, double-blind, placebo-controlled clinical trial (UC Trial I) in adult subjects with moderately to severely active ulcerative colitis (UC). All participants received 3 intravenous induction doses of 5 mg/kg of infliximab-dyyb at Weeks 0, 2, and 6. At Week 10, clinical responders (N=438) were randomized (2:1) to ZYMFENTRA 120 mg SC or placebo every 2 weeks. The primary endpoint was the proportion of subjects achieving clinical remission (per modified Mayo score [(mMS)] as SFS of 0 or 1 point; RBS of 0 point; and ES of 0 or 1 point [(excluding friability)] at Week 54, while secondary endpoints included histologic-endoscopic mucosal improvement (an absolute ES of 0 or 1 point [(excluding friability)] from the mMS and an absolute Robarts Histopathology Index [(RHI)] score of ≤ 3 points with no lamina propria neutrophils, no neutrophils in epithelium, no erosion or ulceration), and corticosteroid-free remission (being in clinical remission by mMS in addition to not requiring any treatment with corticosteroid for at least 8 weeks at Week 54, among the subjects who used oral corticosteroids at baseline) at Week 54. The proportion of subjects meeting clinical remission at Week 54 was 43% in the ZYMFENTRA arm vs 21% in the placebo arm (treatment difference 21%, $P<0.0001$), while 36% in the ZYMFENTRA arm vs 17% in the placebo arm achieved histologic-endoscopic mucosal improvement at Week 54 (treatment difference 18%, $P<0.0001$). Thirty-seven percent of ZYMFENTRA-treated participants vs 18% of placebo participants achieved corticosteroid-free remission at Week 54 (treatment difference 17%, $P<0.05$).¹ The safety of ZYMFENTRA was also evaluated, and the most common adverse reactions reported in $>3\%$ of subjects and at a higher rate than placebo in UC Trial I were COVID-19 (10%), anemia (5%), arthralgia (4%), injection site reaction (3%), increased alanine aminotransferase (3%), and abdominal pain (3%). According to the ZYMFENTRA PI, following recommended SC maintenance doses of ZYMFENTRA (120 mg every 2 weeks) in adults from Week 10 after IV induction with infliximab-dyyb, steady state was achieved by Week 22 and the mean trough serum concentrations were 14.6 mcg/mL for patients with UC.]⁵

[CD] - PI

[The safety and efficacy of ZYMFENTRA was assessed in a randomized, double-blind, placebo-controlled clinical trial (CD Trial I) in adult subjects with moderately to severely active Crohn's disease (CD). All participants received 3 intravenous induction doses of 5 mg/kg of infliximab-dyyb at Weeks 0, 2, and 6. At Week 10, clinical responders (N=323) were randomized (2:1) to ZYMFENTRA 120 mg SC or placebo every 2 weeks. The co-primary endpoints were the proportion of subjects achieving clinical remission (absolute CDAI score of <150 points) and endoscopic response ($>50\%$ decrease in SES-CD from baseline value) at Week 54, while secondary endpoints included endoscopic remission (an absolute SES-CD score of ≤ 4 with no sub-score of >1) and corticosteroid-free remission (being in clinical remission in addition to not receiving any corticosteroid for at least 8 weeks prior to Week 54, among the subjects who used oral corticosteroids at baseline) at Week 54. The proportion of subjects meeting clinical remission at Week 54 was 63% in the ZYMFENTRA arm vs 30% in the placebo arm (treatment difference 35%, $P<0.0001$), while 50% in the ZYMFENTRA arm vs 18% in the placebo arm achieved endoscopic response at Week 54 (treatment difference 34%, $P<0.0001$). Thirty-five percent of ZYMFENTRA-treated participants vs 10% of placebo participants achieved endoscopic remission at Week 54 (treatment difference 25%, $P<0.0001$) and corticosteroid-free remission was met by 40% vs 21% at Week 54 in the ZYMFENTRA vs placebo arms, respectively (treatment difference 19%, $P<0.05$).¹

Continued

The safety of ZYMFENTRA was also evaluated, and the most common adverse reactions reported in $\geq 3\%$ of subjects and at a higher rate than placebo in CD Trial I were COVID-19 (10%), headache (8%), upper respiratory tract infection (7%), injection site reaction (5%), diarrhea (5%), increased blood creatine phosphokinase (4%), arthralgia (4%), increased alanine aminotransferase (4%), hypertension (3%), urinary tract infection (3%), neutropenia (3%), dizziness (3%), and leukopenia (3%). According to the ZYMFENTRA PI, following recommended SC maintenance doses of ZYMFENTRA (120 mg every 2 weeks) in adults from Week 10 after IV induction with infliximab-dyyb, steady state was achieved by Week 22 and the mean trough serum concentrations were 14.6 mcg/mL for patients with CD.]⁵

Treatment Plan

On October 23, 2023, the FDA approved ZYMFENTRA for use in adults for the maintenance treatment of **[moderately to severely active ulcerative colitis/moderately to severely active Crohn's disease]** following treatment with an infliximab product given intravenously.¹ **[Include the plan of treatment (dosage, length of treatment) and clinical practice guidelines that support the use of ZYMFENTRA.]** **[Consider mentioning experts in the field who also support the treatment].**

Summary

Based on the patient's condition and medical history, as well as my experience treating patients with **[diagnosis]**, I believe treatment with ZYMFENTRA is warranted, appropriate, and medically necessary in this case. The accompanying package insert provides the approved clinical information for ZYMFENTRA. I have attached relevant lab test analyses and medical records to support my decision.

I am requesting an immediate and expedited review of this appeal, and the enclosed documents and supporting evidence by my office and by a board-certified and specialty-matched physician who can render a decision based upon the standards of care outlined above. If you have any further questions about this matter, please contact me at **[Physician Phone Number]**, via e-mail at **[Physician Email]**, or by fax at **[Provider Fax Number]**. I look forward to receiving your timely response and approval of this claim.

Once approved for ZYMFENTRA, I will discontinue the treatment/prescription of **[alternate BRAND (generic) name]**. If you do not feel that the information provided has established medical necessity, please provide me with your detailed rationale based upon the standards of care, the specialty of the physician who reviewed this case, and whether they are board certified in an applicable medical specialty.

Sincerely,

[Physician Name]

[Physician Signature]

[Physician Address]

[Physician Phone Number]

Continued

Enclosures

[List enclosures, which may include medical records/clinical notes for ZYMFENTRA, ZYMFENTRA Prescribing Information, Letter of Medical Exception and other supporting documentation]

[Include Indication and Important Safety Information]

[Include full Prescribing Information, including Patient Information]

References

1. Rubin DT, Ananthakrishnan AN, Siegel CA, Barnes EL, Long MD. ACG Clinical Guideline Update: Ulcerative Colitis in Adults. *Am J Gastroenterol*. 2025;120(6):1187-1224. doi: 10.14309/ajg.0000000000003463
2. Lichtenstein GR, Loftus EV, Afzali A, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol*. 2025;120(6):1225-1264. doi: 10.14309/ajg.0000000000003465
3. Singh S, Loftus EV, Limketkai BN, et al; AGA Clinical Guidelines Committee. AGA Living Clinical Practice Guideline on Pharmacological Management of Moderate-to-Severe Ulcerative Colitis. *Gastroenterology*. 2024;167(7):1307-1343. doi: 10.1053/j.gastro.2024.10.001
4. Feuerstein JD, Ho EY, Shmidt E, et al; American Gastroenterological Association Institute Clinical Guidelines Committee. AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. *Gastroenterology*. 2021;160(7):2496-2508. doi: 10.1053/j.gastro.2021.04.022
5. ZYMFENTRA [prescribing information]. Jersey City, NJ. Celltrion Inc; 2024. Accessed September 24, 2025. https://zymfentra.b-cdn.net/zymfentra_prescribing_information_final.pdf
6. Colombel J-F, Sandborn WJ, Schreiber S, et al. Subcutaneous infliximab (CT-P13 SC) as maintenance therapy for Crohn's disease and ulcerative colitis: 2-year results from open-label extensions of two randomized controlled trials (LIBERTY). *J Crohns Colitis*. 2025;19(6):jjaf060. doi: 10.1093/ecco-jcc/jjaf060

[Include other relevant references and publications regarding prescribed medicine]

[Copy of patient denial letter]

[Clinical progress notes] [Patient's lab results]

[Documentation of Hospitalization/Emergency Room visits and/or unscheduled office visits]

[List of medications provided, including dosages, dates used, and if samples were given]



Please click here to download and customize the Letter of Appeal.