IOWA | Health and Human Services

PDL DRUG REVIEW

Proprietary Name: Zymfentra®
Common Name: infliximab-dyyb injection
PDL Category: Anti-Inflammatories, Non-NSAID

Comparable Products	Preferred Drug List Status
Humira (adalimumab)	Preferred with Conditions
Simponi (golimumab)	Preferred with Conditions
Stelara (Ustekinumab)	Non-Preferred with Conditions

Pharmacology/Usage: Infliximab-dyyb, the active ingredient of Zymfentra®, is a tumor necrosis factor (TNF) blocker. It is a chimeric IgG1κ monoclonal antibody. Infliximab-dyyb 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.

Indication: 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 treatment with an infliximab product administered intravenously.

There is no pregnancy category for this medication; however, the risk summary indicates that available data from reports of pregnancy in clinical trials with Zymfentra® are not sufficient to identify a drug associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with inflammatory bowel disease (IBD) in pregnancy. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Solution for injection, available as:

- 120mg/ml in a single-dose prefilled syringe.
- 120mg/ml in a single-dose prefilled syringe with needle guard.
- 120mg/ml in a single-dose prefilled pen.

Recommended Dosage: Important dosage and administration information:

- Zymfentra® is indicated as maintenance treatment only, starting at week 10 and thereafter.
    - All patients must complete an intravenous (IV) induction regimen with an infliximab product before starting Zymfentra®. For induction dosing information, review the corresponding prescribing information for the chosen infliximab product.
- Zymfentra® is for subcutaneous (SC) use only.
- Zymfentra® is intended for use under the guidance and supervision of a healthcare professional. Once the provider determines that it is appropriate, patients may self-inject Zymfentra® or caregivers may inject Zymfentra® after proper training in SC injection technique.
- Inject into the front of the thighs, the abdomen except for the 2 inches around the navel, or the outer area of the upper arms (caregiver only). Rotate the injection site each time an injection is given. Allow at least 1.2 inches between the new injection site and the previous injection site.

- If an injection is missed, inject the next SC dose as soon as possible and then every 2 weeks thereafter.

The recommended dosage for maintenance treatment in UC or CD starting at week 10 and thereafter is 120mg SC once every two weeks. To switch patients who are responding to maintenance therapy with an infliximab product administered via IV, administer the first SC dose of Zymfentra® in place of the next scheduled IV infusion and every 2 weeks thereafter.

Drug Interactions: The concurrent use of Zymfentra® with other immunosuppressive biological products (e.g., anakinra and abatacept) used to treat UC and CD may increase the risk of infection and is not recommended. Consider the half-life and mode of action of prior biological products to avoid unintended additive immunosuppressive effects when starting Zymfentra®.

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines during chronic inflammation. Thus, Zymfentra®, an antagonist of TNFα, could normalize the formation of CYP450 enzymes potentially resulting in a decrease in exposure of CYP450 substrates. Upon initiation or discontinuation of TNF blockers, including Zymfentra®, in patients being treated with CYP450 substrates requiring therapeutic drug monitoring, monitor therapeutic parameters (e.g., INR for warfarin) or drug concentrations (e.g., cyclosporine or theophylline). Dosage adjustment may be needed to maintain drug concentrations or parameters within the therapeutic range. See prescribing information for specific drugs.

It is recommended that live vaccines not be given concurrently with Zymfentra®. It is also recommended that live vaccines not be given to infants after in utero exposure to infliximab products for 6 months following birth.

It is recommended that therapeutic infectious agents not be given concurrently with Zymfentra®.

Box Warning: Zymfentra® has a box warning regarding serious infections and malignancy.

Regarding 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 (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before Zymfentra® use and during therapy. Start treatment for latent infection prior to Zymfentra® use.
    - Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. 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 Zymfentra® treatment prior to starting 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 TB in patients who tested negative for latent TB infection prior to starting therapy.

Regarding malignancy:

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

- Post marketing 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. Most of the reported cases have occurred in patients with Crohn's disease or ulcerative colitis and most were in young adult males.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Zymfentra®) minus reported % incidence for placebo in the UC trial. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included COVID-19 (4%), anemia (1%), arthralgia (3%), injection site reaction (1%), increased alanine aminotransferase (2%), and abdominal pain (2%).

Listed % incidence for adverse drug reactions= reported % incidence for drug (Zymfentra®) minus reported % incidence for placebo in the CD trial. Please note that an incidence of 0% means the incidence was the same as or less than placebo. The most frequently reported adverse events included COVID-19 (5%), headache (4%), upper respiratory tract infection (4%), injection site reaction (4%), diarrhea (4%), increased blood creatine phosphokinase (2%), arthralgia (1%), increased alanine aminotransferase (3%), hypertension (1%), urinary tract infection (1%), neutropenia (3%), dizziness (3%), and leukopenia (3%).

As discussed in the box warning, patients treated with Zymfentra® are at increased risk for developing serious infections that may lead to hospitalization or death. Treatment with Zymfentra® should not be started in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with comorbid-conditions, and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection. Refer to the prescribing information for additional information.

As mentioned in the box warning, malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF blockers, including infliximab products. Periodic skin examination is recommended for all patients during treatment with Zymfentra®, especially those with risk factors for skin cancer. Routine cervical cancer screening is recommended during Zymfentra® treatment. The potential role of TNF blockers in the development of malignancies is not known. Avoid Zymfentra® in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving Zymfentra®. Refer to the prescribing information for additional information.

Use of TNF blockers has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. Test patients for HBV before starting TNF blocker therapy, including Zymfentra®. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended. In patients who develop HBV reactivation, discontinue Zymfentra® and start antiviral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Thus, prescribers should use caution when considering resumption of Zymfentra® in this situation and monitor patients closely.

Hepatobiliary disorders have been reported in post marketing data in patients receiving infliximab products. Severe hepatic reactions occurred between two weeks to more than one year after starting infliximab products administered IV. In clinical trials, 3 subjects treated with Zymfentra® had drug induced liver injury based on hepatic transaminase elevations. Monitor hepatic enzymes and liver function tests every 3 to 4 months during treatment with Zymfentra®. Interrupt treatment if drug-induced liver injury is suspected, until this diagnosis is excluded.

Cases of worsening congestive heart failure (CHF) and new onset CHF, with and without identifiable precipitating factors, have been reported with TNF blockers, including infliximab products. Some of these

patients have been under 50 years of age, and some cases had a fatal outcome. Zymfentra® has not been studied in patients with a history of CHF. Avoid Zymfentra® in patients with CHF. If a decision is made to administer Zymfentra® to patients with CHF, closely monitor patients during therapy for new or worsening symptoms of heart failure and discontinue Zymfentra® if symptoms appear.

Reports of pancytopenia, including aplastic anemia, have been reported with TNF blocking agents. Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving infliximab products. The causal relationship to infliximab product therapy remains unclear. Although no high-risk group(s) has been identified, avoid Zymfentra® in patients who have ongoing or a history of significant hematologic abnormalities. Consider Zymfentra® discontinuation in patients who develop significant hematologic abnormalities.

In clinical trials with Zymfentra®, symptoms compatible with hypersensitivity reactions have been reported. There are no data on the risks of using Zymfentra® in patients who have experienced a severe hypersensitivity reaction towards another TNF blocker; in these patients, caution is needed.

Agents that inhibit TNF have been associated with CNS manifestation of systemic vasculitis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of CNS demyelinating disorders. Avoid the use of Zymfentra® in patients with these neurologic disorders and consider discontinuation of Zymfentra® if these disorders develop.

Treatment with TNF blockers, including Zymfentra®, may result in the formation of autoantibodies and in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Zymfentra®, discontinue treatment.

Prior to starting Zymfentra®, update vaccinations per current vaccination guidelines.

Contraindications: In patients with a history of a severe hypersensitivity reaction to infliximab-dyyb, other infliximab products, any of the inactive ingredients, or any murine proteins.

Manufacturer: Celltrion, Inc.

Analysis: The safety and efficacy of Zymfentra® were assessed in a randomized, double-blind, placebo-controlled clinical trial (*UC Trial I*) that included adult subjects with moderately to severely active UC (defined as a modified Mayo score [mMS] between 5 to 9 with endoscopic subscore [ES] of 2 or 3). The mMS is a 3-component Mayo score (0-9), which consists of the following sub scores (0 to 3 for each sub score): stool frequency (SFS), rectal bleeding (RBS), and findings on centrally read endoscopy score (ES). An ES of 2 was defined by marked erythema, lack of vascular pattern, any friability, and/or erosions, and a score of 3 was defined by spontaneous bleeding and ulceration.

Subjects had demonstrated an inadequate response or intolerance to treatment with corticosteroids alone or in combination with 6-mercaptopurine or azathioprine. Subjects were permitted to use stable doses of oral aminosalicylates, oral corticosteroids (prednisone ≤20mg/day or equivalent, budesonide ≤9mg/day), UC-related antibiotics, and/or immunomodulatory agents (azathioprine, 6-mercaptopurine, or methotrexate). Corticosteroid tapering was permitted after week 10.

All subjects received 3 IV induction doses of 5mg/kg of infliximab-dyyb at weeks 0, 2, and 6. In order to be randomized to treatment, subjects had to be in clinical response at week 10. Clinical response was defined as a decrease from baseline in the mMS of at least 2 points and at least 30% with an accompanying decrease in the RBS of at least 1 point or absolute RBS of 0 or 1 point. Patients (N=438) were randomized at week 10 in a double-blind manner to Zymfentra® 120mg SC or placebo every two weeks.

Subjects in the double-blind phase had a mean age of 39 years (range 18 to 75), while 44% were female and 98% were white. At the time of randomization into the double-blind phase (week 10), 92% were receiving aminosalicylates, 41% were receiving oral corticosteroids, and 22% were receiving immunomodulators, including azathioprine, 6-mercaptopurine, or methotrexate. In addition, about 10% of randomized subjects had prior exposure to biological products or JAK inhibitors.

The primary endpoint was the proportion of subjects in clinical remission at week 54. Secondary endpoints included the proportion of subjects achieving histologic-endoscopic mucosal improvement and corticosteroid-free remission at week 54. Results are presented in the table below, which was adapted from the prescribing information.

	Zymfentra®	Placebo	Treatment difference
Clinical Remission at week 54 (primary endpoint)			
Total population	N=294 (43%)	N=144 (21%)	21% (p<0.0001) NNT=5
No prior biological product/JAK inhibitor exposure	N=265 (45%)	N=131 (21%)	
Prior biological product/JAK inhibitor exposure	N=29 (31%)	N=13 (15%)	
Histologic-Endoscopic Mucosal Improvement at week 54			
Total population	N=294 (36%)	N=144 (17%)	18% (p<0.0001)
No prior biological product/JAK inhibitor exposure	N=265 (36%)	N=131 (18%)	
Prior biological product/JAK inhibitor exposure	N=29 (31%)	N=13 (8%)	
Corticosteroid-Free Remission at week 54			
Total population	N=120 (37%)	N=61 (18%)	17% (p<0.05)
No prior biological product/JAK inhibitor exposure	N=107 (36%)	N=56 (18%)	
Prior biological product/JAK inhibitor exposure	N=13 (38%)	N=5 (20%)	

The relationship between histologic-endoscopic mucosal improvement at week 54 and disease progression and longer-term outcomes after week 54 was not evaluated in UC Trial 1.

The safety and efficacy of Zymfentra® were assessed in a randomized, double-blind, placebo-controlled clinical trial (*CD Trial I*) that included adult subjects with moderately to severely active CD, defined as Crohn's Disease Activity Index (CDAI) score of 220 to 450 points, and a centrally-reviewed Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) of ≥6 points for ileal-colonic CD (or ≥4 points for isolated ileal disease).

Subjects had demonstrated an inadequate response or intolerance to treatment with corticosteroids and/or immunosuppressants. Subjects were permitted to use stable doses of oral aminosalicylates, oral corticosteroids (prednisone ≤20mg/day or equivalent, budesonide ≤9mg/day), CD-related antibiotics, and/or immunomodulatory agents (azathioprine, 6-mercaptopurine, or methotrexate). Corticosteroid dose was tapered after week 10. All subjects received 3 IV induction doses of 5mg/kg infliximab-dyyb at weeks 0, 2, and 6. In order to be randomized to treatment in this trial, subjects had to be in clinical response at week 10. Clinical response was defined as a decrease from baseline in CDAI of at least 100 points (i.e., CDAI-100 responders). At week 10, subjects (N=323) were randomized in a double-blind fashion to Zymfentra® 120mg SC or placebo every 2 weeks.

Subjects in the double-blind phase had a mean age of 35 years (range 18 to 75), while 40% were female and 91% were white. At the time of randomization into the double-blind phase (week 10), 61% were

receiving aminosalicylates, 40% were receiving oral corticosteroids, and 32% were receiving immunomodulators, including azathioprine, 6-mercaptopurine, or methotrexate. In addition, 11% of randomized subjects had prior exposure to biological products.

The co-primary endpoints were clinical remission (based on CDAI) and endoscopic response at week 54. Secondary endpoints included endoscopic remission and corticosteroid-free remission at week 54. Results are presented in the table below, which was adapted from the prescribing information.

	Zymfentra®	Placebo	Treatment difference
Clinical Remission (based on CDAI) at week 54			
Total population	N=216 (63%)	N=107 (30%)	35% (p<0.0001) NNT=3
No prior biological product exposure	N=191 (62%)	N=98 (31%)	
Prior biological product exposure	N=25 (72%)	N=9 (22%)	
Endoscopic Response at week 54			
Total population	N=216 (50%)	N=107 (18%)	34% (p<0.0001)
No prior biological product exposure	N=191 (51%)	N=98 (17%)	
Prior biological product exposure	N=25 (48%)	N=9 (22%)	
Endoscopic Remission at week 54			
Total population	N=216 (35%)	N=107 (10%)	25% (p<0.0001)
No prior biological product exposure	N=191 (35%)	N=98 (10%)	
Prior biological product exposure	N=25 (36%)	N=9 (11%)	
Corticosteroid-Free Remission at week 54			
Total population	N=92 (40%)	N=43 (21%)	19% (p<0.05)
No prior biological product exposure	N=81 (35%)	N=40 (23%)	
Prior biological product exposure	N=11 (82%)	N=3 (0%)	

Place in Therapy: Zymfentra® is a TNF blocker indicated in adults for maintenance treatment of moderately to severely active ulcerative colitis following treatment with an infliximab product administered intravenously, as well as in adults for maintenance treatment of moderately to severely active Crohn's disease following treatment with an infliximab product administered intravenously. Zymfentra® is indicated as maintenance treatment only, starting at week 10 and thereafter. All patients must complete an IV induction regimen with an infliximab product before starting Zymfentra®, which is for subcutaneous use only. This product does have a box warning regarding serious infections and malignancy. The safety and efficacy of Zymfentra® was demonstrated in two phase 3 studies, including the UC Trial I and the CD Trial I. Statistically significant differences were observed with Zymfentra® as compared with placebo for the primary endpoints in both studies.

A 2024 comparative analysis by Peyrin-Biroulet et al[2] included 7 randomized controlled studies to compare induction and maintenance infliximab therapy with vedolizumab therapy for patients with CD and UC.[2] In patients with CD, infliximab SC demonstrated numerically better efficacy than vedolizumab during the maintenance phase. In UC patients, efficacy was similar between infliximab SC and vedolizumab during the maintenance phase.

Summary

There is no evidence at this time to support that Zymfentra® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Zymfentra® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Zymfentra® [package insert]. Jersey City, NJ: Celltrion USA, Inc; 2024.
[2] Peyrin-Biroulet L, Arkkila P, Armuzzi A, et al. Comparative efficacy and safety of subcutaneous infliximab and vedolizumab in patients with Crohn's disease and ulcerative colitis included in randomized controlled trials. *BMC Gastroenterol*. 2024; 24(1): 121.