

Infliximab-dyyb (ZYMFENTRA) for SC Injection

in Crohn's Disease and Ulcerative Colitis

National Drug Mini-monograph

May 2024

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: 5-ASA, 5-aminosalicylic acid; AAE, anticipated absolute effect per 1000 cases; AS, ankylosing spondylitis; CD, Crohn's disease; csIMM, conventional synthetic immunomodulator; IV, intravenous; CDAI, Crohn's Disease Activity Index; CDAI-100, decrease of ≥ 100 points on CDAI; CS, Corticosteroids; HEM, histologic-endoscopic mucosal; IST, immunosuppressant therapy; JAKI, Janus kinase inhibitor; L, line; MMS, modified Mayo score (0–9); MMS-2/30, decrease from baseline of at least 2 points and at least 30% on the MMS; NC, national contract; pCD, pediatric Crohn's disease; PEM, primary efficacy measure; PsA, psoriatic arthritis; PsO, plaque psoriasis; pUC, pediatric ulcerative colitis; Q, GRADE quality of evidence; RA, rheumatoid arthritis; RBS, rectal bleeding score; RBS-1/0–1, RBS decrease from baseline of at least 1 point or absolute RBS of 0 or 1 point; SC, subcutaneous; SDP, single-dose prefilled; SES-CD, Simplified Endoscopic Activity Score; SFS, stool frequency score; TNFI, tumor necrosis factor inhibitor; UC, ulcerative colitis

FDA APPROVAL INFORMATION	Description / MOA	Infliximab-dyyb (CT-P13) is a TNFI that is an FDA-approved biosimilar to infliximab (REMICADE). Infliximab-dyyb for SC injection is the first infliximab product approved for SC administration.
	Indications Under Review¹	Maintenance treatment of adults with <ul style="list-style-type: none"> moderately to severely active Crohn's disease following treatment with an infliximab product administered intravenously. moderately to severely active ulcerative colitis following treatment with an infliximab product administered intravenously. <p><i>PBM Note: Unlike IV infliximab or biosimilars, SC infliximab-dyyb lacks an indication for fistulizing CD.</i></p>
	Dosage Regimen	<u>Week 10 and on:</u> 120 mg subcutaneously once every 2 weeks. To switch patients who are responding to maintenance therapy with an infliximab product administered intravenously, administer the first SC dose of infliximab-dyyb in place of the next scheduled IV infusion and every 2 weeks thereafter.
	Dosage Forms Under Review	Injection: 120 mg/mL in SDP syringe, SDP syringe with needle shield, or SDP pen.

EFFICACY CONSIDERATIONS	Trial	LIBERTY CD (NCT03945019)^{2,3,4,5,6}																								
	Design	DB PC RCT (2:1) Co-PEMs: Clinical remission (CDAI-based) and endoscopic response at Week 54																								
	Population	Moderate to severe, active CD (CDAI 220–450 and SES-CD of ≥ 6 points for ileal-colonic CD or ≥ 4 points for isolated ileal disease; inadequate response or intolerance to CS and/or IST. All patients received IV infliximab-dyyb 5 mg/kg at Weeks 0, 2 and 6 and had to be CDAI-100 responders at Week 10. <i>Permitted treatments:</i> Stable doses of oral 5-ASAs, oral CS (prednisone ≤ 20 mg/d or equivalent; budesonide ≤ 9 mg/d; CS doses tapered after Week 10), CD-related antibiotics, csIMMs (azathioprine, 6-mercaptopurine, methotrexate). <i>Baseline Characteristics:</i> Mean age 35 (18–75) y; 60% male; 91% White; 61% on 5-ASAs, 40% oral CS, 32% on csIMMs, 11% prior biologic.																								
	Intervention	Infliximab-dyyb 120 mg SC Q2Wk																								
	Comparator	Placebo SC Q2Wk																								
	Results	Efficacy Measures at Week 54																								
		<table border="1"> <thead> <tr> <th>Measure, n/N (%)</th> <th>SC Infliximab-dyyb</th> <th>Placebo</th> <th>RR (95% CI)</th> <th>AAE (95% CI)</th> </tr> </thead> <tbody> <tr> <td>Clinical remission</td> <td>144/231 (62)</td> <td>36/112 (32)</td> <td>1.9 (1.46, 2.58)</td> <td>302 (195, 409)</td> </tr> <tr> <td>Endoscopic response</td> <td>118/216 (50)</td> <td>19/107 (18)</td> <td>3.1 (2.01, 4.71)</td> <td>369 (270, 467)</td> </tr> <tr> <td>Endoscopic remission</td> <td>76/216 (35)</td> <td>11/107 (10)</td> <td>3.4 (1.90, 6.16)</td> <td>249 (163, 335)</td> </tr> <tr> <td>CS-free remission</td> <td>37/92 (40)</td> <td>9/43 (21)</td> <td>1.9 (1.02, 3.62)</td> <td>193 (35, 350)</td> </tr> </tbody> </table>	Measure, n/N (%)	SC Infliximab-dyyb	Placebo	RR (95% CI)	AAE (95% CI)	Clinical remission	144/231 (62)	36/112 (32)	1.9 (1.46, 2.58)	302 (195, 409)	Endoscopic response	118/216 (50)	19/107 (18)	3.1 (2.01, 4.71)	369 (270, 467)	Endoscopic remission	76/216 (35)	11/107 (10)	3.4 (1.90, 6.16)	249 (163, 335)	CS-free remission	37/92 (40)	9/43 (21)	1.9 (1.02, 3.62)
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Subgroup Analyses. Clinical remission rates were 118/191 (62%) vs 30/98 (31%) on SC infliximab-dyyb vs placebo for a treatment effect (absolute difference) of 31 percentage points (95% CI 19.7, 42.6) in biologic-naïve patients. The corresponding results in biologic-exposed patients were 18/24 (72%) vs 2/9 (22%), respectively, for a treatment effect of 50 percentage points (17.4, 82.1).

Limitations

Lack of evidence in fistulizing CD.

Trial

LIBERTY UC⁷

Design

DB PC RCT

PEM: Clinical remission at Week 54. Clinical remission was defined as MMS SFS of 0 or 1 point, RBS of 0 points, and endoscopic subscore of 0 or 1 points excluding friability.

Population

Moderate to severe, active UC (MMS 5–9 with endoscopic subscore of 2 or 3); inadequate response or intolerance to CS alone or in combination with 6-MP or AZP.

All patients received infliximab-dyyb 5 mg/kg IV at Weeks 0, 2 and 6 and had to be in clinical response at Week 10. Clinical response was defined as MMS-2/30 with RBS-1/0–1.

Permitted treatments: Stable doses of oral 5-ASAs, oral CS (prednisone ≤ 20 mg/d or equivalent, budesonide ≤ 9 mg/d; CS tapering permitted after Week 10), UC-related antibiotics, csIMMs (AZP, 6MP, or MTX).

Baseline Characteristics. Mean age 39 (18–75) y; 56% male; 98% White; 92% on 5-ASAs, 41% on oral CS, 22% on csIMM, 10% had prior exposure to biologics or JAKIs.

Intervention

Infliximab-dyyb 120 mg SC Q2Wk

Comparator

Placebo SC Q2Wk

Results

Outcome Measures at Week 54

Measure, n/N (%)	SC Infliximab-dyyb	Placebo	RR (95% CI)	AAE (95% CI)
Clinical remission	126/294 (43)	30/144 (21)	2.1 (1.46, 2.90)	220 (133, 307)
HEM improvement	106/294 (36)	24/144 (17)	2.2 (1.46, 3.21)	194 (112, 276)
CS-free remission	44/120 (37)	11/61 (18)	2.0 (1.13, 3.65)	186 (57, 316)

Subgroup Analyses. In biologic- or JAKI-naïve patients, clinical remission was achieved in 119/265 (45%) vs 28/131 (21%) of the SC infliximab-dyyb vs placebo groups, respectively, for a treatment effect of 23.5 percentage points (14.3, 32.8). In biologic- or JAKI-exposed patients, the corresponding results were 9/29 (31%) vs 2/13 (15%) with a treatment effect of 15.6 (10.2, 41.5), respectively.

Phase 1 RCT

A phase 1 MC OL RCT in 131 adults with active CD (n = 53) or UC (n = 78) showed that, following IV induction doses at Weeks 0 and 2, IV infliximab-dyyb every 8 Weeks from Weeks 6 to 22 then SC doses every 2 Weeks from Week 30 to Week 54 was comparable to SC doses every 2 Weeks from Weeks 6 to 54 in clinical remission rates at Weeks 30 and 54.⁸

REMSWITCH Study

A French MC observational study showed that switching IBD patients in clinical remission from IV infliximab 5 mg/kg every 8 weeks (5q8w), 10 mg/kg every 8 weeks (10q8w), 10 mg/kg every 6 weeks (10q6w), or 10 mg/kg every 4 weeks (10q4w) to SC infliximab 120 mg every 2 weeks was associated with relapse risks of 10.2% (5q8w), 7.3% (10q8w), 16.7% (10q6w) and 66.7% (10q4w). Escalation of the SC dose to 240 mg every 2 weeks achieved clinical remission in 93.3% (14/15) of patients. Serum infliximab levels increased after the switch to SC doses except in the 10q4w group.

Elective Switching

A 12-month retrospective MC cohort study in patients with CD (n = 115), UC (n = 60), or IBD-unspecified (n = 6) showed that switching from IV infliximab (5 mg/kg every 8 weeks [n = 131] or every 4–6 weeks [n = 50]) to SC infliximab-dyyb (120 mg every 2 weeks [n = 131] or once weekly [n = 50]) was associated with treatment persistence in 167 patients (92.3%).⁹ There was no difference in persistence rates between every-2-week and once-weekly SC dosages. Of 25 patients with perianal CD, 2 (8%) experienced worsening of disease activity requiring further evaluation under anesthesia. No significant differences were observed in clinical or biochemical outcome measures. Median infliximab levels increased from 8.9 µg/dL on IV to 16.0 µg/dL on SC dosages at 3 months, then stabilized. Of 14 patients who developed antibodies to infliximab, 2 were “significant” and led to discontinuation of SC infliximab. There were no serious adverse events or colectomies.

This monograph does not review the following: An early pharmacokinetic study of SC infliximab-dyyb,¹⁰ the post hoc analysis comparing SC infliximab-dyyb monotherapy with combination therapy with immunosuppressants in IBD,¹¹ or SC infliximab-dyyb uses other than IBD.

SAFETY CONSIDERATIONS	Boxed Warnings	Serious infections and malignancy
	Contraindications	History of severe hypersensitivity to infliximab-dyyb, other infliximab products, any of the inactive ingredients in ZYMFENTRA, or to any murine proteins. <i>PBM Note: Unlike INFLECTRA at doses > 5 mg/kg, ZYMFENTRA is not contraindicated in moderate or severe heart failure. However, there is a Warning to avoid ZYMFENTRA in patients with congestive heart failure (CHF; not studied) and, if ZYMFENTRA is used in a patient with CHF, to monitor the patient closely and discontinue therapy if symptoms of CHF develop.</i>
	Other Warnings	Similar to INFLECTRA, except ZYMFENTRA lacks a warning for cardiovascular and cerebrovascular reactions.

Source: 1

OTHER CONSIDERATIONS	Pharmacokinetics	SC infliximab is associated with generally more stable and higher trough levels but lower peak levels than IV administration. ¹² The effects of these pharmacokinetic differences on treatment persistence and immunogenicity are uncertain.
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PLACE IN THERAPY	DRUG	BRAND	VANF	CFU	FDA-approved CD and UC Indications*	Approved CD and UC Treatment Phase
		Infliximab-dyyb SC 120 mg/mL	ZYMFENTRA	No	No	CD after treatment with an IV infliximab product UC after treatment with an IV infliximab product
	Infliximab IV†	REMICADE	No	No	2 nd L in CD‡ after inadequate response to conventional therapy	Induction and maintenance
	Infliximab-abda IV†	RENFLXIS	Yes (NC)	No, PA-F [¶]	1 st L in fistulizing CD [§]	
	Infliximab-axxq IV†	AVSOLA	No	No	2 nd L in UC [¶] after inadequate response to conventional therapy	
	Infliximab-dyyb IV†	INFLECTRA	No	No		
	Infliximab-qbtx IV†	IXIFI	No	No		

* Refers to moderately to severely active CD or UC

† 100 mg/VL injection for IV infusion

‡ Includes reducing signs and symptoms and inducing and maintaining clinical remission

§ Includes reducing number of fistulas and maintaining fistula closure

¶ Includes reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use

|| Prior authorization at the facility level, restricted to providers appropriate for prescribing TNFIs.

VHA PLACE IN THERAPY	Potential Use in VHA	1. SC infliximab-dyyb may be used for maintenance therapy in patients who (a) experience a clinical response / improvement in moderate to severe, active CD or moderate to severe, active UC at Week 10 or thereafter following IV induction doses of infliximab / biosimilar at Weeks 0, 2, and 6; (b) are clinically stable and are receiving IV infliximab / biosimilar to maintain clinical remission; or (c) are unable to adhere with IV maintenance infusion schedules.
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