1 INDICATIONS AND USAGE

1.1 Crohn's Disease

AVSOLA is indicated for:

- reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response to conventional therapy.

- reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing CD.

1.2 Pediatric Crohn's Disease

AVSOLA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active CD who have had an inadequate response to conventional therapy.

1.3 Ulcerative Colitis

AVSOLA is indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy.

1.4 Pediatric Ulcerative Colitis

AVSOLA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active UC who have had an inadequate response to conventional therapy.

1.5 Rheumatoid Arthritis

AVSOLA, in combination with methotrexate, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis (RA).

1.6 Ankylosing Spondylitis

AVSOLA is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS).

1.7 Psoriatic Arthritis

AVSOLA is indicated for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in adult patients with psoriatic arthritis (PsA).

1.8 Plaque Psoriasis

AVSOLA is indicated for the treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis (Ps) who are candidates for systemic therapy and when other systemic therapies are medically less appropriate. AVSOLA should only be administered to patients who will be closely

produced by synoviocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab products can be lysed *in vitro* or *in vivo*. Infliximab products inhibit the functional activity of TNFα in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T-lymphocytes and epithelial cells. The relationship of these biological response markers to the mechanism(s) by which infliximab products exert their clinical effects is unknown. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab products prevent disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and when administered after disease onset, allow eroded joints to heal.

12.2 Pharmacodynamics

Elevated concentrations of TNFα have been found in involved tissues and fluids of patients with RA, CD, UC, AS, PsA and Ps. In RA, treatment with infliximab products reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion [E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)], chemoattraction [IL-8 and monocyte chemotactic protein (MCP-1)] and tissue degradation [matrix metalloproteinase (MMP) 1 and 3]. In CD, treatment with infliximab products reduced infiltration of inflammatory cells and TNFα production in inflamed areas of the intestine, and reduced the proportion of mononuclear cells from the lamina propria able to express TNFα and interferon. After treatment with infliximab products, patients with RA or CD exhibited decreased levels of serum IL-6 and C-reactive protein (CRP) compared to baseline. Peripheral blood lymphocytes from patients treated with infliximab products showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared to cells from untreated patients. In PsA, treatment with infliximab products resulted in a reduction in the number of T-cells and blood vessels in the synovium and psoriatic skin lesions as well as a reduction of macrophages in the synovium. In Ps, infliximab products treatment may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which infliximab products exert their clinical effects is unknown.

12.3 Pharmacokinetics

In adults, single intravenous (IV) infusions of 3 mg/kg to 20 mg/kg (two times the maximum recommended dose for any indication) of infliximab showed a linear relationship between the dose administered and the maximum serum concentration. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment. Pharmacokinetic results for single doses of 3 mg/kg to 10 mg/kg in RA, 5 mg/kg in CD, and 3 mg/kg to 5 mg/kg in Ps indicate that the median terminal half-life of infliximab is 7.7 to 9.5 days.

Following an initial dose of infliximab, repeated infusions at 2 and 6 weeks resulted in predictable concentration-time profiles following each treatment. No systemic accumulation of infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4- or 8-week intervals. Development of antibodies to infliximab increased infliximab clearance. At 8 weeks after a maintenance dose of 3 to 10 mg/kg of infliximab, median infliximab serum concentrations ranged from approximately 0.5 to 6 mcg/mL; however, infliximab concentrations were not detectable (<0.1 mcg/mL) in patients who became positive for antibodies to infliximab. No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight, or gender. It is not known if there are differences in clearance or volume of distribution in patients with marked impairment of hepatic or renal function.

Infliximab pharmacokinetic characteristics (including peak and trough concentrations and terminal half-life) were similar in pediatric (aged 6 to 17 years) and adult patients with CD or UC following the administration of 5 mg/kg infliximab.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 6-month study in CD-1 mice was conducted to assess the tumorigenic potential of cV1q anti-mouse TNFα, an analogous antibody. No evidence of tumorigenicity was observed in mice that received intravenous doses of 10 mg/kg or 40 mg/kg cV1q given weekly. The relevance of this study for human risk is unknown. No impairment of fertility or reproductive performance indices were observed in male or female mice that received cV1q, an analogous mouse antibody, at intravenous doses up to 40 mg/kg given weekly.

14 CLINICAL STUDIES

14.1 Adult Crohn's Disease

Active Crohn's Disease in Adults

The safety and efficacy of single and multiple doses of infliximab were assessed in 2 randomized, double-blind, placebo-controlled clinical studies in 653 adult patients with moderate to severely active CD [Crohn's Disease Activity Index (CDAI) ≥220 and ≤400] with an inadequate response to prior conventional therapies. Concomitant stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents were permitted and 92% of patients continued to receive at least one of these medications.

In the single-dose trial of 108 adult patients, 16% (4/25) of placebo patients achieved a clinical response (decrease in CDAI ≥70 points) at Week 4 vs. 81% (22/27) of patients receiving 5 mg/kg infliximab ($p<0.001$, two-sided, Fisher's Exact test). Additionally, 4% (1/25) of placebo patients and 48% (13/27) of patients receiving 5 mg/kg infliximab achieved clinical remission (CDAI<150) at Week 4.

In a multidose trial (ACCENT I [Study Crohn's I]), 545 adult patients received 5 mg/kg at Week 0 and were then randomized to one of three treatment groups; the placebo maintenance group received placebo at Weeks 2 and 6, and then every 8 weeks; the 5 mg/kg maintenance group received 5 mg/kg at Weeks 2 and 6, and then every 8 weeks; and the 10 mg/kg maintenance group received 5 mg/kg at Weeks 2 and 6, and then 10 mg/kg every 8 weeks. Patients in response at Week 2 were randomized and analyzed separately from those not in response at Week 2. Corticosteroid taper was permitted after Week 6.

At Week 2, 57% (311/545) of patients were in clinical response. At Week 30, a significantly greater proportion of these patients in the 5 mg/kg and 10 mg/kg maintenance groups achieved clinical remission compared to patients in the placebo maintenance group (Table 3).

Additionally, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg infliximab maintenance groups were in clinical remission and were able to discontinue corticosteroid use compared to patients in the placebo maintenance group at Week 54 (Table 3).

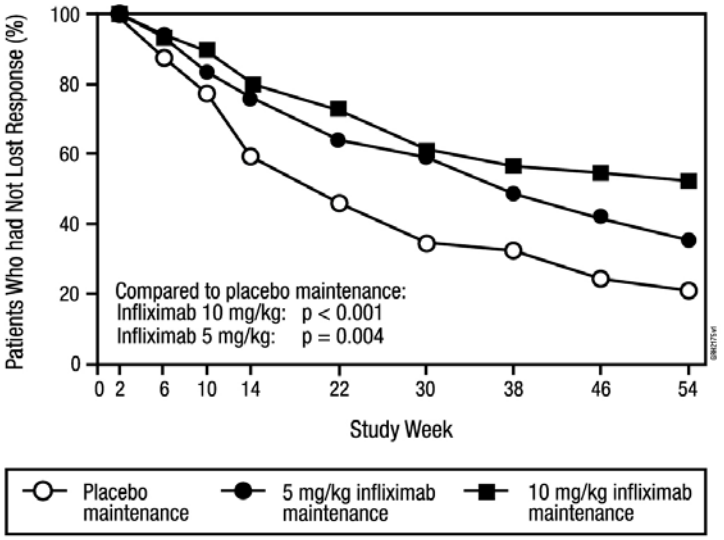
Table 3: Clinical Remission and Steroid Withdrawal in Adult Patients with CD (Study Crohn's I)

	Single 5 mg/kg Dose[a]	Three-Dose Induction[b]	
	Placebo Maintenance	Infliximab Maintenance q8 wks	
		5 mg/kg	10 mg/kg
Week 30	25/102	41/104	48/105
Clinical remission	25%	39%	46%
P-value[c]		0.022	0.001
Week 54	6/54	14/56	18/53
Patients in remission able to discontinue corticosteroid use[d]	11%	25%	34%
P-value[c]		0.059	0.005

[a] Infliximab at Week 0
[b] Infliximab 5 mg/kg administered at Weeks 0, 2 and 6
[c] *P*-values represent pairwise comparisons to placebo
[d] Of those receiving corticosteroids at baseline

Patients in the infliximab maintenance groups (5 mg/kg and 10 mg/kg) had a longer time to loss of response than patients in the placebo maintenance group (Figure 1). At Weeks 30 and 54, significant improvement from baseline was seen among the 5 mg/kg and 10 mg/kg infliximab-treated groups compared to the placebo group in the disease-specific inflammatory bowel disease questionnaire (IBDQ), particularly the bowel and systemic components, and in the physical component summary score of the general health-related quality of life questionnaire SF-36.

Figure 1: Kaplan-Meier Estimate of the Proportion of Adults with CD Who Had Not Lost Response through Week 54 (Study Crohn's I)



In a subset of 78 patients who had mucosal ulceration at baseline and who participated in an endoscopic substudy, 13 of 43 patients in the infliximab maintenance group had endoscopic evidence of mucosal healing compared to 1 of 28 patients in the placebo group at Week 10. Of the infliximab-treated patients showing mucosal healing at Week 10, 9 of 12 patients also showed mucosal healing at Week 54.

Patients who achieved a response and subsequently lost response were eligible to receive infliximab on an episodic basis at a dose that was 5 mg/kg higher than the dose to which they were randomized. The majority of such patients responded to the higher dose. Among patients who were not in response at Week 2, 59% (92/157) of infliximab maintenance patients responded by Week 14 compared to 51% (39/77) of placebo maintenance patients. Among patients who did not respond by Week 14, additional therapy did not result in significantly more responses *[see Dosage and Administration (2)]*.

Fistulizing Crohn's Disease in Adults

The safety and efficacy of infliximab were assessed in 2 randomized, double-blind, placebo-controlled studies in adult patients with fistulizing CD with fistula(s) that were of at least 3 months duration. Concurrent use of stable doses of corticosteroids, 5-aminosalicylates, antibiotics, MTX, 6-mercaptopurine (6-MP) and/or azathioprine (AZA) was permitted.

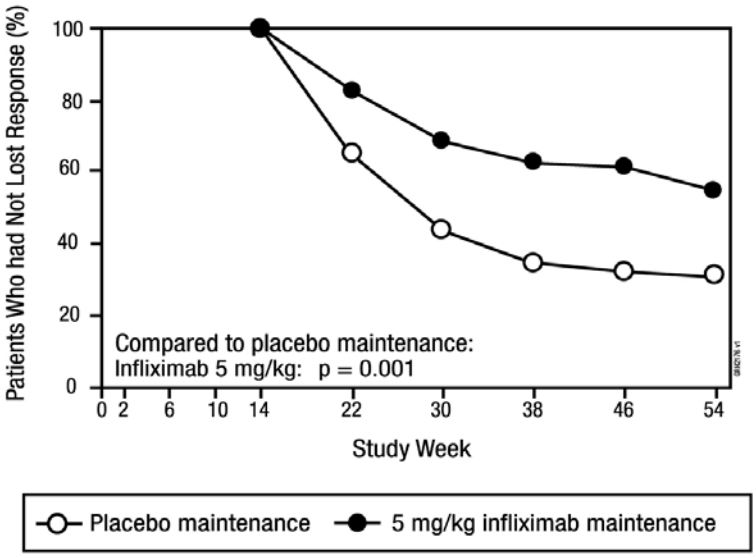
In the first trial, 94 adult patients received 3 doses of either placebo or infliximab at Weeks 0, 2 and 6. Fistula response (≥50% reduction in number of enterocutaneous fistulas draining upon gentle compression on at least 2 consecutive visits without an increase in medication or surgery for CD) was seen in 68% (21/31) of patients in the 5 mg/kg infliximab group (P=0.002) and 56% (18/32) of patients in the 10 mg/kg infliximab group (P=0.021) vs. 26% (8/31) of patients in the placebo arm. The median time to onset of response and median duration of response in infliximab-treated patients was 2 and 12 weeks, respectively. Closure of all fistulas was achieved in 52% of infliximab-treated patients compared with 13% of placebo-treated patients (P<0.001).

In the second trial (ACCENT II [Study Crohn's II]), adult patients who were enrolled had to have at least 1 draining enterocutaneous (perianal, abdominal) fistula. All patients received 5 mg/kg infliximab at Weeks 0, 2 and 6. Patients were randomized to placebo or 5 mg/kg infliximab maintenance at Week 14. Patients received maintenance doses at Week 14 and then every 8 weeks through Week 46. Patients who were in fistula response (fistula response was defined the same as in the first trial) at both Weeks 10 and 14 were randomized separately from those not in response. The primary endpoint was time from randomization to loss of response among those patients who were in fistula response.

Among the randomized patients (273 of the 296 initially enrolled), 87% had perianal fistulas and 14% had abdominal fistulas. Eight percent also had rectovaginal fistulas. Greater than 90% of the patients had received previous immunosuppressive and antibiotic therapy.

At Week 14, 65% (177/273) of patients were in fistula response. Patients randomized to infliximab maintenance had a longer time to loss of fistula response compared to the placebo maintenance group (Figure 2). At Week 54, 38% (33/87) of infliximab-treated patients had no draining fistulas compared with 22% (20/90) of placebo-treated patients (P=0.02). Compared to placebo maintenance, patients on infliximab maintenance had a trend toward fewer hospitalizations.

Figure 2: Life Table Estimates of the Proportion of Adult CD Patients Who Had Not Lost Fistula Response through Week 54 (Study Crohn's II)



Patients who achieved a fistula response and subsequently lost response were eligible to receive infliximab maintenance therapy at a dose that was 5 mg/kg higher than the dose to which they were randomized. Of the placebo maintenance patients, 66% (25/38) responded to 5 mg/kg infliximab, and 57% (12/21) of infliximab maintenance patients responded to 10 mg/kg.

Patients who had not achieved a response by Week 14 were unlikely to respond to additional doses of infliximab.

Similar proportions of patients in either group developed new fistulas (17% overall) and similar numbers developed abscesses (15% overall).

14.2 Pediatric Crohn's Disease

The safety and efficacy of infliximab were assessed in a randomized, open-label study (Study Peds Crohn's) in 112 pediatric patients aged 6 to 17 years old with moderately to severely active CD and an inadequate response to conventional therapies. The median age was 13 years and the median Pediatric Crohn's Disease Activity Index (PCDAI) was 40 (on a scale of 0 to 100). All patients were required to be on a stable dose of 6-MP, AZA, or MTX; 35% were also receiving corticosteroids at baseline.

All patients received induction dosing of 5 mg/kg infliximab at Weeks 0, 2, and 6. At Week 10, 103 patients were randomized to a maintenance regimen of 5 mg/kg of infliximab given either every 8 weeks or every 12 weeks.

At Week 10, 88% of patients were in clinical response (defined as a decrease from baseline in the PCDAI score of ≥15 points and total PCDAI score of ≤30 points), and 59% were in clinical remission (defined as PCDAI score of ≤10 points). The proportion of pediatric patients achieving clinical response at Week 10 compared favorably with the proportion of adults achieving a clinical response in Study Crohn's I. The study definition of clinical response in Study Peds Crohn's was based on the PCDAI score, whereas the CDAI score was used in the adult Study Crohn's I.

At both Week 30 and Week 54, the proportion of patients in clinical response was greater in the every 8-week treatment group than in the every 12-week treatment group (73% vs. 47% at Week 30, and 64% vs. 33% at Week 54). At both Week 30 and Week 54, the proportion of patients in clinical remission was also greater in the every 8-week treatment group than in the every 12-week treatment group (60% vs. 35% at Week 30, and 56% vs. 24% at Week 54), (Table 4).

For patients in Study Peds Crohn's receiving corticosteroids at baseline, the proportion of patients able to discontinue corticosteroids while in remission at Week 30 was 46% for the every 8-week maintenance group and 33% for the every 12-week maintenance group. At Week 54, the proportion of patients able to discontinue corticosteroids while in remission was 46% for the every 8-week maintenance group and 17% for the every 12-week maintenance group.

Table 4: Response and Remission in Study Peds Crohn's

	5 mg/kg Infliximab	
	Every 8-Week Treatment Group	**Every 12-Week Treatment Group**
Patients randomized	52	51
Clinical Response[a]		
Week 30	73%[d]	47%
Week 54	64%[d]	33%
Clinical Remission[b]		
Week 30	60%[c]	35%
Week 54	56%[d]	24%

[a] Defined as a decrease from baseline in the PCDAI score of ≥15 points and total score of ≤30 points.
[b] Defined as a PCDAI score of ≤10 points.
[c] *P*-value <0.05
[d] *P*-value <0.01

14.3 Adult Ulcerative Colitis

The safety and efficacy of infliximab were assessed in 2 randomized, double-blind, placebo-controlled clinical studies in 728 adult patients with moderately to severely active UC (Mayo score 6 to 12 [of possible range 0 to 12], Endoscopy subscore ≥2) with an inadequate response to conventional oral therapies (Studies UC I and UC II). Concomitant treatment with stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents was permitted. Corticosteroid taper was permitted after Week 8. Patients were randomized at week 0 to receive either placebo, 5 mg/kg infliximab or 10 mg/kg infliximab at Weeks 0, 2, 6, and every 8 weeks thereafter through Week 46 in Study UC I, and at Weeks 0, 2, 6, and every 8 weeks thereafter through Week 22 in Study UC II. In Study UC II, patients were allowed to continue blinded therapy to Week 46 at the investigator's discretion.

Adult patients in Study UC I had failed to respond or were intolerant to oral corticosteroids, 6-MP, or AZA. Adult patients in Study UC II had failed to respond or were intolerant to the above treatments and/or aminosalicylates. Similar proportions of patients in Studies UC I and UC II were receiving corticosteroids (61% and 51%, respectively), 6-MP/AZA (49% and 43%) and aminosalicylates (70% and 75%) at baseline. More patients in Study UC II than UC I were taking solely aminosalicylates for UC (26% vs. 11%, respectively). Clinical response was defined as a decrease from baseline in the Mayo score by ≥30% and ≥3

points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.

Clinical Response, Clinical Remission, and Mucosal Healing

In both Study UC I and Study UC II, greater percentages of patients in both infliximab groups achieved clinical response, clinical remission and mucosal healing than in the placebo group. Each of these effects was maintained through the end of each trial (Week 54 in Study UC I, and Week 30 in Study UC II). In addition, a greater proportion of patients in infliximab groups demonstrated sustained response and sustained remission than in the placebo groups (Table 5).

Of patients on corticosteroids at baseline, greater proportions of adult patients in the infliximab treatment groups were in clinical remission and able to discontinue corticosteroids at Week 30 compared with the patients in the placebo treatment groups (22% in infliximab treatment groups vs. 10% in placebo group in Study UC I; 23% in infliximab treatment groups vs. 3% in placebo group in Study UC II). In Study UC I, this effect was maintained through Week 54 (21% in infliximab treatment groups vs. 9% in placebo group). The infliximab-associated response was generally similar in the 5 mg/kg and 10 mg/kg dose groups.

Table 5: Response, Remission and Mucosal Healing in Adult UC Studies (Studies UC I and UC II)

	Study UC I			**Study UC II**		
	Placebo	**5 mg/kg Infliximab**	**10 mg/kg Infliximab**	**Placebo**	**5 mg/kg Infliximab**	**10 mg/kg Infliximab**
Patients randomized	121	121	122	123	121	120
Clinical Response[a, d]						
Week 8	37%	69%*	62%*	29%	65%*	69%*
Week 30	30%	52%*	51%**	26%	47%*	60%*
Week 54	20%	45%*	44%*	NA	NA	NA
Sustained Response[d]						
(Clinical response at both Weeks 8 and 30)	23%	49%*	46%*	15%	41%*	53%*
(Clinical response at Weeks 8, 30, and 54)	14%	39%*	37%*	NA	NA	NA
Clinical Remission[b, d]						
Week 8	15%	39%*	32%**	6%	34%*	28%*
Week 30	16%	34%**	37%*	11%	26%**	36%*
Week 54	17%	35%**	34%**	NA	NA	NA
Sustained Remission[d]						
(Clinical remission at both Weeks 8 and 30)	8%	23%**	26%*	2%	15%*	23%*
(Clinical remission at Weeks 8, 30 and 54)	7%	20%**	20%**	NA	NA	NA

	Study UC I			Study UC II		
	Placebo	**5 mg/kg Infliximab**	**10 mg/kg Infliximab**	**Placebo**	**5 mg/kg Infliximab**	**10 mg/kg Infliximab**
Patients randomized	121	121	122	123	121	120
Mucosal Healing[c, d]						
Week 8	34%	62%*	59%*	31%	60%*	62%*
Week 30	25%	50%*	49%*	30%	46%**	57%*
Week 54	18%	45%*	47%*	NA	NA	NA

* $P<0.001$, ** $P<0.01$

[a] Defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1 (The Mayo score consists of the sum of four subscores: stool frequency, rectal bleeding, physician's global assessment and endoscopy findings).

[b] Defined as a Mayo score ≤2 points, no individual subscore >1.

[c] Defined as a 0 or 1 on the endoscopy subscore of the Mayo score.

[d] Patients who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in clinical response, clinical remission or mucosal healing from the time of the event onward.

The improvement with infliximab was consistent across all Mayo subscores through Week 54 (Study UC I shown in Table 6; Study UC II through Week 30 was similar).

Table 6: Proportion of Adult UC Patients in Study UC I with Mayo Subscores Indicating Inactive or Mild Disease through Week 54

	Study UC I		
		Infliximab	
	Placebo	**5 mg/kg**	**10 mg/kg**
	(n=121)	**(n=121)**	**(n=122)**
Stool frequency			
Baseline	17%	17%	10%
Week 8	35%	60%	58%
Week 30	35%	51%	53%
Week 54	31%	52%	51%
Rectal bleeding			
Baseline	54%	40%	48%
Week 8	74%	86%	80%
Week 30	65%	74%	71%
Week 54	62%	69%	67%
Physician's Global Assessment			
Baseline	4%	6%	3%
Week 8	44%	74%	64%
Week 30	36%	57%	55%

	Study UC I		
		Infliximab	
	Placebo	5 mg/kg	10 mg/kg
	(n=121)	(n=121)	(n=122)
Week 54	26%	53%	53%
Endoscopy findings			
Baseline	0%	0%	0%
Week 8	34%	62%	59%
Week 30	26%	51%	52%
Week 54	21%	50%	51%

14.4 Pediatric Ulcerative Colitis

The safety and effectiveness of infliximab products for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients aged 6 years and older with moderately to severely active UC who have had an inadequate response to conventional therapy are supported by evidence from adequate and well-controlled studies of infliximab in adults. Additional safety and pharmacokinetic data were collected in an open-label pediatric UC trial in 60 pediatric patients aged 6 through 17 years (median age 14.5 years) with moderately to severely active UC (Mayo score of 6 to 12; Endoscopic subscore ≥2) and an inadequate response to conventional therapies. At baseline, the median Mayo score was 8, 53% of patients were receiving immunomodulator therapy (6-MP/AZA/MTX), and 62% of patients were receiving corticosteroids (median dose 0.5 mg/kg/day in prednisone equivalents). Discontinuation of immunomodulators and corticosteroid taper were permitted after Week 0.

All patients received induction dosing of 5 mg/kg infliximab at Weeks 0, 2, and 6. Patients who did not respond to infliximab at Week 8 received no further infliximab and returned for safety follow-up. At Week 8, 45 patients were randomized to a maintenance regimen of 5 mg/kg infliximab given either every 8 weeks through Week 46 or every 12 weeks through Week 42. Patients were allowed to change to a higher dose and/or more frequent administration schedule if they experienced loss of response.

Clinical response at Week 8 was defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, including a decrease in the rectal bleeding subscore by ≥1 points or achievement of a rectal bleeding subscore of 0 or 1.

Clinical remission at Week 8 was measured by the Mayo score, defined as a Mayo score of ≤2 points with no individual subscore >1. Clinical remission was also assessed at Week 8 and Week 54 using the Pediatric Ulcerative Colitis Activity Index (PUCAI)[1] score and was defined by a PUCAI score of <10 points.

Endoscopies were performed at baseline and at Week 8. A Mayo endoscopy subscore of 0 indicated normal or inactive disease and a subscore of 1 indicated mild disease (erythema, decreased vascular pattern, or mild friability).

Of the 60 patients treated, 44 were in clinical response at Week 8. Of 32 patients taking concomitant immunomodulators at baseline, 23 achieved clinical response at Week 8, compared to 21 of 28 of those not taking concomitant immunomodulators at baseline. At Week 8, 24 of 60 patients were in clinical remission as measured by the Mayo score and 17 of 51 patients were in remission as measured by the PUCAI score.

At Week 54, 8 of 21 patients in the every 8-week maintenance group and 4 of 22 patients in the every 12-week maintenance group achieved remission as measured by the PUCAI score.

During maintenance phase, 23 of 45 randomized patients (9 in the every 8-week group and 14 in the every 12-week group) required an increase in their dose and/or increase in frequency of infliximab administration due to loss of response. Nine of the 23 patients who required a change in dose had achieved remission at Week 54. Seven of those patients received the 10 mg/kg every 8-week dosing.

14.5 Rheumatoid Arthritis

The safety and efficacy of infliximab in adult patients with RA were assessed in 2 multicenter, randomized, double-blind, pivotal trials: ATTRACT (Study RA I) and ASPIRE (Study RA II). Concurrent use of stable doses of folic acid, oral corticosteroids (≤10 mg/day) and/or non-steroidal anti-inflammatory drugs (NSAIDs) was permitted.

Study RA I was a placebo-controlled study of 428 patients with active RA despite treatment with MTX. Patients enrolled had a median age of 54 years, median disease duration of 8.4 years, median swollen and tender joint count of 20 and 31 respectively, and were on a median dose of 15 mg/wk of MTX. Patients received either placebo + MTX or one of 4 doses/schedules of infliximab + MTX: 3 mg/kg or 10 mg/kg of infliximab by IV infusion at Weeks 0, 2 and 6 followed by additional infusions every 4 or 8 weeks in combination with MTX.

Study RA II was a placebo-controlled study of 3 active treatment arms in 1004 MTX naive patients of 3 or fewer years duration active RA. Patients enrolled had a median age of 51 years with a median disease duration of 0.6 years, median swollen and tender joint count of 19 and 31, respectively, and >80% of patients had baseline joint erosions. At randomization, all patients received MTX (optimized to 20 mg/wk by Week 8) and either placebo, 3 mg/kg or 6 mg/kg infliximab at Weeks 0, 2, and 6 and every 8 weeks thereafter.

Data on use of infliximab products without concurrent MTX are limited *[see Adverse Reactions (6.1)]*.

Clinical Response

In Study RA I, all doses/schedules of infliximab + MTX resulted in improvement in signs and symptoms as measured by the American College of Rheumatology response criteria (ACR 20) with a higher percentage of patients achieving an ACR 20, 50 and 70 compared to placebo + MTX (Table 7). This improvement was observed at Week 2 and maintained through Week 102. Greater effects on each component of the ACR 20 were observed in all patients treated with infliximab + MTX compared to placebo + MTX (Table 8). More patients treated with infliximab reached a major clinical response than placebo-treated patients (Table 7). In Study RA II, after 54 weeks of treatment, both doses of infliximab + MTX resulted in statistically significantly greater response in signs and symptoms compared to MTX alone as measured by the proportion of patients achieving ACR 20, 50 and 70 responses (Table 7). More patients treated with infliximab reached a major clinical response than placebo-treated patients (Table 7).

Table 7: ACR Response (percent of patients) in Adult RA Patients (Studies RA I and RA II)

	Study RA I					Study RA II		
		Infliximab + MTX					Infliximab + MTX	
		3 mg/kg		10 mg/kg			3 mg/kg	6 mg/kg
Response	**Placebo + MTX**	**q8 wks**	**q4 wks**	**q8 wks**	**q4 wks**	**Placebo + MTX**	**q8 wks**	**q8 wks**
	(n=88)	**(n=86)**	**(n=86)**	**(n=87)**	**(n=81)**	**(n=274)**	**(n=351)**	**(n=355)**
ACR 20								
Week 30	20%	50%[a]	50%[a]	52%[a]	58%[a]	N/A	N/A	N/A
Week 54	17%	42%[a]	48%[a]	59%[a]	59%[a]	54%	62%[c]	66%[a]
ACR 50								
Week 30	5%	27%[a]	29%[a]	31%[a]	26%[a]	N/A	N/A	N/A
Week 54	9%	21%[c]	34%[a]	40%[a]	38%[a]	32%	46%[a]	50%[a]
ACR 70								
Week 30	0%	8%[b]	11%[b]	18%[a]	11%[a]	N/A	N/A	N/A
Week 54	2%	11%[c]	18%[a]	26%[a]	19%[a]	21%	33%[b]	37%[a]
Major clinical response[d]	0%	7%[c]	8%[b]	15%[a]	6%[c]	8%	12%	17%[a]

[a] $P \leq 0.001$
[b] $P < 0.01$
[c] $P < 0.05$
[d] A major clinical response was defined as a 70% ACR response for 6 consecutive months (consecutive visits spanning at least 26 weeks) through Week 102 for Study RA I and Week 54 for Study RA II.

Table 8: Components of ACR 20 at baseline and 54 weeks (Study RA I)

	Placebo + MTX		Infliximab + MTX[a]	
Parameter (medians)	**(n=88)**		**(n=340)**	
	Baseline	**Week 54**	**Baseline**	**Week 54**
No. of Tender Joints	24	16	32	8
No. of Swollen Joints	19	13	20	7
Pain[b]	6.7	6.1	6.8	3.3
Physician's Global Assessment[b]	6.5	5.2	6.2	2.1
Patient's Global Assessment[b]	6.2	6.2	6.3	3.2
Disability Index (HAQ-DI)[c]	1.8	1.5	1.8	1.3
CRP (mg/dL)	3.0	2.3	2.4	0.6

[a] All doses/schedules of infliximab + MTX
[b] Visual Analog Scale (0=best, 10=worst)

[c] Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0=best, 3=worst)

Radiographic Response

Structural damage in both hands and feet was assessed radiographically at Week 54 by the change from baseline in the van der Heijde-modified Sharp (vdH-S) score, a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet.

In Study RA I, approximately 80% of patients had paired X-ray data at 54 weeks and approximately 70% at 102 weeks. The inhibition of progression of structural damage was observed at 54 weeks (Table 9) and maintained through 102 weeks.

In Study RA II, >90% of patients had at least 2 evaluable X-rays. Inhibition of progression of structural damage was observed at Weeks 30 and 54 (Table 9) in the infliximab + MTX groups compared to MTX alone. Patients treated with infliximab + MTX demonstrated less progression of structural damage compared to MTX alone, whether baseline acute phase reactants (ESR and CRP) were normal or elevated: patients with elevated baseline acute phase reactants treated with MTX alone demonstrated a mean progression in vdH-S score of 4.2 units compared to patients treated with infliximab + MTX who demonstrated 0.5 units of progression; patients with normal baseline acute phase reactants treated with MTX alone demonstrated a mean progression in vdH-S score of 1.8 units compared to infliximab + MTX who demonstrated 0.2 units of progression. Of patients receiving infliximab + MTX, 59% had no progression (vdH-S score ≤0 unit) of structural damage compared to 45% of patients receiving MTX alone. In a subset of patients who began the study without erosions, infliximab + MTX maintained an erosion-free state at 1 year in a greater proportion of patients than MTX alone, 79% (77/98) vs. 58% (23/40), respectively (P<0.01). Fewer patients in the infliximab + MTX groups (47%) developed erosions in uninvolved joints compared to MTX alone (59%).

Table 9: Radiographic Change from Baseline to Week 54 in Adult RA Patients (Studies RA I and RA II)

	Study RA I			**Study RA II**		
		Infliximab + MTX			**Infliximab + MTX**	
		3 mg/kg	**10 mg/kg**		**3 mg/kg**	**6 mg/kg**
	Placebo + MTX	**q8 wks**	**q8 wks**	**Placebo + MTX**	**q8 wks**	**q8 wks**
	(n=64)	**(n=71)**	**(n=77)**	**(n=282)**	**(n=359)**	**(n=363)**
Total Score						
Baseline						
Mean	79	78	65	11.3	11.6	11.2
Median	55	57	56	5.1	5.2	5.3
Change from baseline						
Mean	6.9	1.3[a]	0.2[a]	3.7	0.4[a]	0.5[a]
Median	4.0	0.5	0.5	0.4	0.0	0.0

	Study RA I			Study RA II		
		Infliximab + MTX			Infliximab + MTX	
		3 mg/kg	10 mg/kg		3 mg/kg	6 mg/kg
	Placebo + MTX	q8 wks	q8 wks	Placebo + MTX	q8 wks	q8 wks
	(n=64)	(n=71)	(n=77)	(n=282)	(n=359)	(n=363)
Erosion Score						
Baseline						
Mean	44	44	33	8.3	8.8	8.3
Median	25	29	22	3.0	3.8	3.8
Change from baseline						
Mean	4.1	0.2[a]	0.2[a]	3.0	0.3[a]	0.1[a]
Median	2.0	0.0	0.5	0.3	0.0	0.0
JSN Score						
Baseline						
Mean	36	34	31	3.0	2.9	2.9
Median	26	29	24	1.0	1.0	1.0
Change from baseline						
Mean	2.9	1.1[a]	0.0[a]	0.6	0.1[a]	0.2
Median	1.5	0.0	0.0	0.0	0.0	0.0

[a] $P<0.001$ for each outcome against placebo.

Physical Function Response

Physical function and disability were assessed using the Health Assessment Questionnaire (HAQ-DI) and the general health-related quality of life questionnaire SF-36.

In Study RA I, all doses/schedules of infliximab + MTX showed significantly greater improvement from baseline in HAQ-DI and SF-36 physical component summary score averaged over time through Week 54 compared to placebo + MTX, and no worsening in the SF-36 mental component summary score. The median (interquartile range) improvement from baseline to Week 54 in HAQ-DI was 0.1 (-0.1, 0.5) for the placebo + MTX group and 0.4 (0.1, 0.9) for infliximab + MTX ($p<0.001$). Both HAQ-DI and SF-36 effects were maintained through Week 102. Approximately 80% of patients in all doses/schedules of infliximab + MTX remained in the trial through 102 weeks.

In Study RA II, both infliximab treatment groups showed greater improvement in HAQ-DI from baseline averaged over time through Week 54 compared to MTX alone; 0.7 for infliximab + MTX vs. 0.6 for MTX alone ($P\leq0.001$). No worsening in the SF-36 mental component summary score was observed.

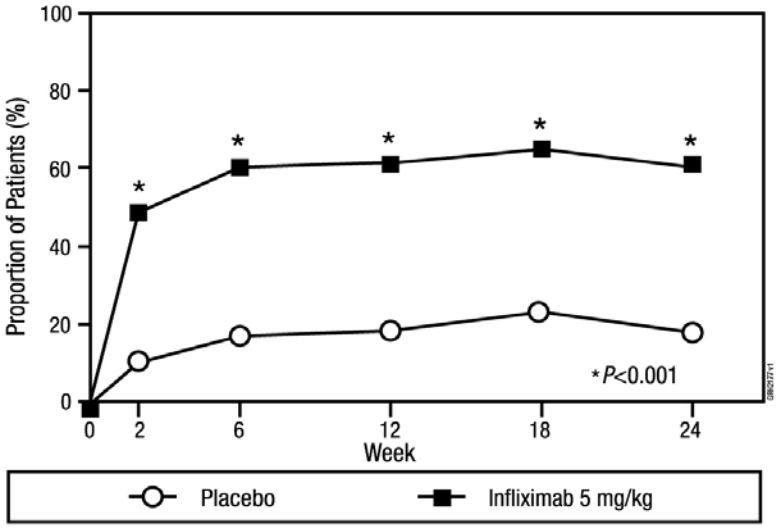
14.6 Ankylosing Spondylitis

The safety and efficacy of infliximab were assessed in a randomized, multicenter, double-blind, placebo-controlled study in 279 adult patients with active AS. Patients were between 18 and 74 years of age,

and had AS as defined by the modified New York criteria for Ankylosing Spondylitis. Patients were to have had active disease as evidenced by both a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score >4 (possible range 0-10) and spinal pain >4 (on a Visual Analog Scale [VAS] of 0-10). Patients with complete ankylosis of the spine were excluded from study participation, and the use of Disease-Modifying Anti-Rheumatic Drugs (DMARDs) and systemic corticosteroids were prohibited. Doses of 5 mg/kg of infliximab or placebo were administered intravenously at Weeks 0, 2, 6, 12 and 18.

At 24 weeks, improvement in the signs and symptoms of AS, as measured by the proportion of patients achieving a 20% improvement in ASAS response criteria (ASAS 20), was seen in 60% of patients in the infliximab-treated group vs. 18% of patients in the placebo group ($p<0.001$). Improvement was observed at Week 2 and maintained through Week 24 (Figure 3 and Table 10).

Figure 3: Proportion of Adult AS Patients Who Achieved a ASAS 20 Response



At 24 weeks, the proportions of patients achieving a 50% and a 70% improvement in the signs and symptoms of AS, as measured by ASAS response criteria (ASAS 50 and ASAS 70, respectively), were 44% and 28%, respectively, for patients receiving infliximab, compared to 9% and 4%, respectively, for patients receiving placebo ($P<0.001$, infliximab vs. placebo). A low level of disease activity (defined as a value <20 [on a scale of 0-100 mm] in each of the 4 ASAS response parameters) was achieved in 22% of infliximab-treated patients vs. 1% in placebo-treated patients ($P<0.001$).

Table 10: Components of AS Disease Activity

	Placebo (n=78)		Infliximab 5 mg/kg (n=201)		
	Baseline	**24 Weeks**	**Baseline**	**24 Weeks**	***P*-value**
ASAS 20 response					
Criteria (Mean)					
Patient Global Assessment[a]	6.6	6.0	6.8	3.8	<0.001
Spinal pain[a]	7.3	6.5	7.6	4.0	<0.001
BASFI[b]	5.8	5.6	5.7	3.6	<0.001
Inflammation[c]	6.9	5.8	6.9	3.4	<0.001
Acute Phase Reactants					
Median CRP[d] (mg/dL)	1.7	1.5	1.5	0.4	<0.001
Spinal Mobility (cm, Mean)					
Modified Schober's test[e]	4.0	5.0	4.3	4.4	0.75
Chest expansion[e]	3.6	3.7	3.3	3.9	0.04
Tragus to wall[e]	17.3	17.4	16.9	15.7	0.02
Lateral spinal flexion[e]	10.6	11.0	11.4	12.9	0.03

[a] Measured on a VAS with 0= "none" and 10= "severe"
[b] Bath Ankylosing Spondylitis Functional Index (BASFI), average of 10 questions
[c] Inflammation, average of last 2 questions on the 6-question BASDAI
[d] CRP normal range 0-1.0 mg/dL
[e] Spinal mobility normal values: modified Schober's test: >4 cm; chest expansion: >6 cm; tragus to wall: <15 cm; lateral spinal flexion: >10 cm

The median improvement from baseline in the general health-related quality-of-life questionnaire SF-36 physical component summary score at Week 24 was 10.2 for the infliximab group vs. 0.8 for the placebo group ($P<0.001$). There was no change in the SF-36 mental component summary score in either the infliximab group or the placebo group.

Results of this study were similar to those seen in a multicenter double-blind, placebo-controlled study of 70 patients with AS.

14.7 Psoriatic Arthritis

Safety and efficacy of infliximab were assessed in a multicenter, double-blind, placebo-controlled study in 200 adult patients with active PsA despite DMARD or NSAID therapy (≥5 swollen joints and ≥5 tender joints) with 1 or more of the following subtypes: arthritis involving DIP joints (n=49), arthritis mutilans (n=3), asymmetric peripheral arthritis (n=40), polyarticular arthritis (n=100), and spondylitis with peripheral arthritis (n=8). Patients also had Ps with a qualifying target lesion ≥2 cm in diameter. Forty-six percent of patients continued on stable doses of methotrexate (≤25 mg/week). During the 24-week double-blind phase, patients received either 5 mg/kg infliximab or placebo at Weeks 0, 2, 6, 14, and 22 (100 patients in each group). At Week 16, placebo patients with <10% improvement from baseline in both swollen and tender joint counts were switched to infliximab induction (early escape). At Week 24, all placebo-treated patients crossed over to infliximab induction. Dosing continued for all patients through Week 46.

Clinical Response

Treatment with infliximab resulted in improvement in signs and symptoms, as assessed by the ACR criteria, with 58% of infliximab-treated patients achieving ACR 20 at Week 14, compared with 11% of placebo-treated patients ($P<0.001$). The response was similar regardless of concomitant use of methotrexate. Improvement was observed as early as Week 2. At 6 months, the ACR 20/50/70 responses were achieved by 54%, 41%, and 27%, respectively, of patients receiving infliximab compared to 16%, 4%, and 2%, respectively, of patients receiving placebo. Similar responses were seen in patients with each of the subtypes of PsA, although few patients were enrolled with the arthritis mutilans and spondylitis with peripheral arthritis subtypes.

Compared to placebo, treatment with infliximab resulted in improvements in the components of the ACR response criteria, as well as in dactylitis and enthesopathy (Table 11). The clinical response was maintained through Week 54. Similar ACR responses were observed in an earlier randomized, placebo-controlled study of 104 PsA patients, and the responses were maintained through 98 weeks in an open-label extension phase.

Table 11: Components of ACR 20 and Percentage of Adult PsA Patients with 1 or More Joints with Dactylitis and Percentage of Adult PsA Patients with Enthesopathy at Baseline and Week 24

	Placebo		**Infliximab 5 mg/kg[a]**	
Patients Randomized	**(n=100)**		**(n=100)**	
	Baseline	**Week 24**	**Baseline**	**Week 24**
Parameter (medians)				
No. of Tender Joints[b]	24	20	20	6
No. of Swollen Joints[c]	12	9	12	3
Pain[d]	6.4	5.6	5.9	2.6
Physician's Global Assessment[d]	6.0	4.5	5.6	1.5
Patient's Global Assessment[d]	6.1	5.0	5.9	2.5
Disability Index (HAQ-DI)[e]	1.1	1.1	1.1	0.5
CRP (mg/dL)[f]	1.2	0.9	1.0	0.4
% Patients with 1 or more digits with dactylitis	41	33	40	15
% Patients with enthesopathy	35	36	42	22

[a] $P<0.001$ for percent change from baseline in all components of ACR 20 at Week 24, $P<0.05$ for % of patients with dactylitis, and $P=0.004$ for % of patients with enthesopathy at Week 24
[b] Scale 0-68
[c] Scale 0-66
[d] Visual Analog Scale (0=best, 10=worst)
[e] Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0=best, 3=worst)
[f] Normal range 0-0.6 mg/dL

Improvement in Psoriasis Area and Severity Index (PASI) in PsA patients with baseline body surface area (BSA) ≥3% (n=87 placebo, n=83 infliximab) was achieved at Week 14, regardless of concomitant

methotrexate use, with 64% of infliximab-treated patients achieving at least 75% improvement from baseline vs. 2% of placebo-treated patients; improvement was observed in some patients as early as Week 2. At 6 months, the PASI 75 and PASI 90 responses were achieved by 60% and 39%, respectively, of patients receiving infliximab compared to 1% and 0%, respectively, of patients receiving placebo. The PASI response was generally maintained through Week 54. *[see Clinical Studies (14.8)]*.

Radiographic Response

Structural damage in both hands and feet was assessed radiographically by the change from baseline in the van der Heijde-Sharp (vdH-S) score, modified by the addition of hand DIP joints. The total modified vdH-S score is a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing (JSN) in the hands and feet. At Week 24, infliximab-treated patients had less radiographic progression than placebo-treated patients (mean change of −0.70 vs. 0.82, $P<0.001$). Infliximab-treated patients also had less progression in their erosion scores (−0.56 vs 0.51) and JSN scores (−0.14 vs 0.31). The patients in the infliximab group demonstrated continued inhibition of structural damage at Week 54. Most patients showed little or no change in the vdH-S score during this 12-month study (median change of 0 in both patients who initially received infliximab or placebo). More patients in the placebo group (12%) had readily apparent radiographic progression compared with the infliximab group (3%).

Physical Function

Physical function status was assessed using the HAQ Disability Index (HAQ-DI) and the SF-36 Health Survey. Infliximab-treated patients demonstrated significant improvement in physical function as assessed by HAQ-DI (median percent improvement in HAQ-DI score from baseline to Week 14 and 24 of 43% for infliximab-treated patients vs 0% for placebo-treated patients).

During the placebo-controlled portion of the trial (24 weeks), 54% of infliximab-treated patients achieved a clinically meaningful improvement in HAQ-DI (≥0.3 unit decrease) compared to 22% of placebo-treated patients. Infliximab-treated patients also demonstrated greater improvement in the SF-36 physical and mental component summary scores than placebo-treated patients. The responses were maintained for up to 2 years in an open-label extension study.

14.8 Plaque Psoriasis

The safety and efficacy of infliximab were assessed in 3 randomized, double-blind, placebo-controlled studies in patients 18 years of age and older with chronic, stable Ps involving ≥10% BSA, a minimum PASI score of 12, and who were candidates for systemic therapy or phototherapy. Patients with guttate, pustular, or erythrodermic psoriasis were excluded from these studies. No concomitant anti-psoriatic therapies were allowed during the study, with the exception of low-potency topical corticosteroids on the face and groin after Week 10 of study initiation.

Study I (EXPRESS) evaluated 378 patients who received placebo or infliximab at a dose of 5 mg/kg at Weeks 0, 2, and 6 (induction therapy), followed by maintenance therapy every 8 weeks. At Week 24, the placebo group crossed over to infliximab induction therapy (5 mg/kg), followed by maintenance therapy every 8 weeks. Patients originally randomized to infliximab continued to receive infliximab 5 mg/kg every 8 weeks through Week 46. Across all treatment groups, the median baseline PASI score was 21 and the baseline Static Physician Global Assessment (sPGA) score ranged from moderate (52% of patients) to marked (36%) to severe (2%). In addition, 75% of patients had a BSA >20%. Seventy-one percent of patients previously received systemic therapy, and 82% received phototherapy.

Study II (EXPRESS II) evaluated 835 patients who received placebo or infliximab at doses of 3 mg/kg or 5 mg/kg at Weeks 0, 2, and 6 (induction therapy). At Week 14, within each infliximab dose group, patients were randomized to either scheduled (every 8 weeks) or as needed (PRN) maintenance treatment through Week 46. At Week 16, the placebo group crossed over to infliximab induction therapy (5 mg/kg), followed by maintenance therapy every 8 weeks. Across all treatment groups, the median baseline PASI score was 18, and 63% of patients had a BSA >20%. Fifty-five percent of patients previously received systemic therapy, and 64% received a phototherapy.

Study III (SPIRIT) evaluated 249 patients who had previously received either psoralen plus ultraviolet A treatment (PUVA) or other systemic therapy for their psoriasis. These patients were randomized to receive either placebo or infliximab at doses of 3 mg/kg or 5 mg/kg at Weeks 0, 2, and 6. At Week 26, patients with a sPGA score of moderate or worse (greater than or equal to 3 on a scale of 0 to 5) received an additional dose of the randomized treatment. Across all treatment groups, the median baseline PASI score was 19, and the baseline sPGA score ranged from moderate (62% of patients) to marked (22%) to severe (3%). In addition, 75% of patients had a BSA >20%. Of the enrolled patients, 114 (46%) received the Week 26 additional dose.

In Studies I, II and III, the primary endpoint was the proportion of patients who achieved a reduction in score of at least 75% from baseline at Week 10 by the PASI (PASI 75). In Study I and Study III, another evaluated outcome included the proportion of patients who achieved a score of "cleared" or "minimal" by the sPGA. The sPGA is a 6-category scale ranging from "5 = severe" to "0 = cleared" indicating the physician's overall assessment of the psoriasis severity focusing on induration, erythema, and scaling. Treatment success, defined as "cleared" or "minimal," consisted of none or minimal elevation in plaque, up to faint red coloration in erythema, and none or minimal fine scale over <5% of the plaque.

Study II also evaluated the proportion of patients who achieved a score of "clear" or "excellent" by the relative Physician's Global Assessment (rPGA). The rPGA is a 6-category scale ranging from "6 = worse" to "1 = clear" that was assessed relative to baseline. Overall lesions were graded with consideration to the percent of body involvement as well as overall induration, scaling, and erythema. Treatment success, defined as "clear" or "excellent," consisted of some residual pinkness or pigmentation to marked improvement (nearly normal skin texture; some erythema may be present). The results of these studies are presented in Table 12.

Table 12: Adult Psoriasis Studies I, II, and III, Week 10 Percentage of Patients Who Achieved PASI 75 and Percentage Who Achieved Treatment "Success" with Physician's Global Assessment at Week 10

	Placebo	**Infliximab**	
		3 mg/kg	**5 mg/kg**
Psoriasis Study I - patients randomized[a]	77	—	301
PASI 75	2 (3%)	—	242 (80%)*
sPGA	3 (4%)	—	242 (80%)*
Psoriasis Study II - patients randomized[a]	208	313	314
PASI 75	4 (2%)	220 (70%)*	237 (75%)*
rPGA	2 (1%)	217 (69%)*	234 (75%)*
Psoriasis Study III - patients randomized[b]	51	99	99

	Placebo	Infliximab	
		3 mg/kg	5 mg/kg
PASI 75	3 (6%)	71 (72%)*	87 (88%)*
sPGA	5 (10%)	71 (72%)*	89 (90%)*

* *P*<0.001 compared with placebo.

[a] Patients with missing data at Week 10 were considered as nonresponders.

[b] Patients with missing data at Week 10 were imputed by last observation.

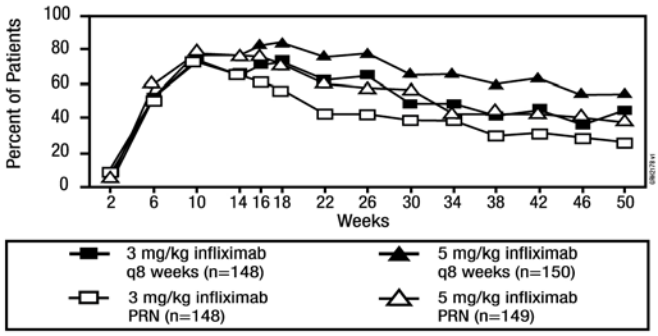
In Study I, in the subgroup of patients with more extensive Ps who had previously received phototherapy, 85% of patients on 5 mg/kg infliximab achieved a PASI 75 at Week 10 compared with 4% of patients on placebo.

In Study II, in the subgroup of patients with more extensive Ps who had previously received phototherapy, 72% and 77% of patients on 3 mg/kg and 5 mg/kg infliximab achieved a PASI 75 at Week 10 respectively compared with 1% on placebo. In Study II, among patients with more extensive Ps who had failed or were intolerant to phototherapy, 70% and 78% of patients on 3 mg/kg and 5 mg/kg infliximab achieved a PASI 75 at Week 10 respectively, compared with 2% on placebo.

Maintenance of response was studied in a subset of 292 and 297 infliximab-treated patients in the 3 mg/kg and 5 mg/kg groups; respectively, in Study II. Stratified by PASI response at Week 10 and investigational site, patients in the active treatment groups were re-randomized to either a scheduled or as needed maintenance (PRN) therapy, beginning on Week 14.

The groups that received a maintenance dose every 8 weeks appear to have a greater percentage of patients maintaining a PASI 75 through Week 50 as compared to patients who received the as needed or PRN doses, and the best response was maintained with the 5 mg/kg every 8-week dose. These results are shown in Figure 4. At Week 46, when infliximab serum concentrations were at trough level, in the every 8-week dose group, 54% of patients in the 5 mg/kg group compared to 36% in the 3 mg/kg group achieved PASI 75. The lower percentage of PASI 75 responders in the 3 mg/kg every 8-week dose group compared to the 5 mg/kg group was associated with a lower percentage of patients with detectable trough serum infliximab levels. This may be related in part to higher antibody rates *[see Adverse Reactions (6.1)]*. In addition, in a subset of patients who had achieved a response at Week 10, maintenance of response appears to be greater in patients who received infliximab every 8 weeks at the 5 mg/kg dose. Regardless of whether the maintenance doses are PRN or every 8 weeks, there is a decline in response in a subpopulation of patients in each group over time. The results of Study I through Week 50 in the 5 mg/kg every 8 weeks maintenance dose group were similar to the results from Study II.

Figure 4: Proportion of Adult Ps Patients Who Achieved ≥75% Improvement in PASI from Baseline through Week 50 (patients randomized at Week 14)



Efficacy and safety of infliximab treatment beyond 50 weeks have not been evaluated in patients with Ps.

15 REFERENCES

1. Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: A prospective multicenter study. *Gastroenterology*. 2007;133:423–432.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

AVSOLA (infliximab-axxq) for injection is supplied as one single-dose vial individually packaged in a carton (NDC 55513-670-01). Each single-dose vial contains 100 mg of infliximab-axxq as a sterile, preservative-free, white to slightly yellow lyophilized powder for reconstitution and dilution (more than one vial may be needed for a full dose) *[see Dosage and Administration (2.11)]*.

Storage and Handling

Store unopened AVSOLA vials in a refrigerator at 2°C to 8°C (36°F to 46°F). Protect from light.

If needed, unopened AVSOLA vials may be stored at room temperatures up to a maximum of 30°C (86°F) for a single period of up to 6 months but not exceeding the original expiration date. The new expiration date must be written in the space provided on the carton. Once removed from the refrigerator AVSOLA cannot be returned to the refrigerator.

For storage conditions of the reconstituted and diluted product, *see Dosage and Administration (2.11)*.

17 PATIENT COUNSELING INFORMATION

Advise the patient or their caregiver to read the FDA-approved patient labeling (Medication Guide).

Patients or their caregivers should be advised of the potential benefits and risks of AVSOLA. Healthcare providers should instruct their patients or their caregivers to read the Medication Guide before starting AVSOLA therapy and to reread it each time they receive an infusion.

Infections

Inform patients that AVSOLA increases the risk for developing serious infections. Instruct patients of the importance of contacting their healthcare provider if they develop any symptoms of an infection, including tuberculosis, invasive fungal infections, and reactivation of hepatitis B virus infections *[see Warnings and Precautions (5.1, 5.3)]*.

Malignancies

Malignancies have been reported among children, adolescents and young adults who received treatment with TNF blockers. Patients should be counseled about the risk of lymphoma and other malignancies while receiving AVSOLA *[see Warnings and Precautions (5.2)]*.

Hepatotoxicity

Instruct patients to seek medical attention if they develop signs or symptoms of hepatotoxicity (e.g., jaundice) *[see Warnings and Precautions (5.4)]*.

Heart Failure

Instruct patients to seek medical attention and consult their prescriber if they develop signs or symptoms of heart failure *[see Contraindications (4) and Warnings and Precautions (5.5)]*.

Hematologic Reactions

Instruct patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever) while on AVSOLA *[see Warnings and Precautions (5.6)]*.

Hypersensitivity

Advise patients to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions *[see Warnings and Precautions (5.7)]*.

Cardiovascular and Cerebrovascular Reactions During and After Infusion

Advise patients to seek immediate medical attention if they develop any new or worsening symptoms of cardiovascular and cerebrovascular reactions which have been reported during and within 24 hours of initiation of AVSOLA infusion *[see Warnings and Precautions (5.8)]*.

Neurologic Reactions

Advise patients to seek medical attention if they develop signs or symptoms of neurologic reactions *[see Warnings and Precautions (5.9)]*.

Live Vaccines/Therapeutic Infectious Agents

Instruct patients treated with AVSOLA to avoid receiving live vaccines or therapeutic infectious agents *[see Warnings and Precautions (5.13)]*.

Manufactured by:
Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
U.S. License No. 1080

[part number] v2

MEDICATION GUIDE
AVSOLA®
(infliximab-axxq)

for injection, for intravenous use

Read the Medication Guide that comes with AVSOLA before you receive the first treatment, and before each time you get a treatment of AVSOLA. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment.

What is the most important information I should know about AVSOLA?
AVSOLA may cause serious side effects, including:

1. Risk of infection
AVSOLA is a medicine that affects your immune system. AVSOLA can lower the ability of your immune system to fight infections. Serious infections have happened in patients receiving AVSOLA. These infections include tuberculosis (TB) and infections caused by viruses, fungi or bacteria that have spread throughout the body. Some patients have died from these infections.

- Your doctor should test you for TB before starting AVSOLA.
- Your doctor should monitor you closely for signs and symptoms of TB during treatment with AVSOLA.

Before starting AVSOLA, tell your doctor if you:
- think you have an infection. You should not start receiving AVSOLA if you have any kind of infection.
- are being treated for an infection.
- have signs of an infection, such as a fever, cough, flu-like symptoms.
- have any open cuts or sores on your body.
- get a lot of infections or have infections that keep coming back.
- have diabetes or an immune system problem. People with these conditions have a higher chance for infections.
- have TB, or have been in close contact with someone with TB.
- live or have lived in certain parts of the country (such as the Ohio and Mississippi River valleys) where there is an increased risk for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, or blastomycosis). These infections may develop or become more severe if you receive AVSOLA. If you do not know if you have lived in an area where histoplasmosis, coccidioidomycosis, or blastomycosis is common, ask your doctor.
- have or have had hepatitis B.
- use the medicines KINERET (anakinra), ORENCIA (abatacept), ACTEMRA (tocilizumab), or other medicines called biologics used to treat the same conditions as AVSOLA.

After starting AVSOLA, if you have an infection, any sign of an infection including a fever, cough, flu-like symptoms, or have open cuts or sores on your body, call your doctor right away. AVSOLA can make you more likely to get infections or make any infection that you have worse.

2. Risk of Cancer
- There have been cases of unusual cancers in children and teenage patients using tumor necrosis factor (TNF) blocker medicines, such as AVSOLA.
- For children and adults receiving TNF blocker medicines, including AVSOLA, the chances of getting lymphoma or other cancers may increase.
- Some people receiving TNF blockers, including AVSOLA, developed a rare type of cancer called hepatosplenic T-cell lymphoma. This type of cancer often results in death. Most of these people were male teenagers or young men. Also, most people were being treated for Crohn's disease or ulcerative colitis with a TNF blocker and another medicine called azathioprine or 6-mercaptopurine.
- People who have been treated for rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis for a long time may be more likely to develop lymphoma. This is especially true for people with very active disease.
- Some people treated with infliximab products, such as AVSOLA, have developed certain kinds of skin cancer. If any changes in the appearance of your skin or growths on your skin occur during or after your treatment with AVSOLA, tell your doctor.
- Patients with Chronic Obstructive Pulmonary Disease (COPD), a specific type of lung disease, may have an increased risk for getting cancer while being treated with AVSOLA.

- Some women being treated for rheumatoid arthritis with infliximab products have developed cervical cancer. For women receiving AVSOLA, including those over 60 years of age, your doctor may recommend that you continue to be regularly screened for cervical cancer.
- Tell your doctor if you have ever had any type of cancer. Discuss with your doctor any need to adjust medicines you may be taking.

See the section "**What are the possible side effects of AVSOLA?**" below for more information.

What is AVSOLA?

AVSOLA is a prescription medicine that is approved for patients with:

- Rheumatoid Arthritis - adults with moderately to severely active rheumatoid arthritis, along with the medicine methotrexate.
- Crohn's Disease - children 6 years and older and adults with Crohn's disease who have not responded well to other medicines.
- Ankylosing Spondylitis in adults.
- Psoriatic Arthritis in adults.
- Plaque Psoriasis - adult patients with plaque psoriasis that is chronic (does not go away), severe, extensive, and/or disabling.
- Ulcerative Colitis - children 6 years and older and adults with moderately to severely active ulcerative colitis who have not responded well to other medicines.

AVSOLA blocks the action of a protein in your body called tumor necrosis factor-alpha (TNF-alpha). TNF-alpha is made by your body's immune system. People with certain diseases have too much TNF-alpha that can cause the immune system to attack normal healthy parts of the body. AVSOLA can block the damage caused by too much TNF-alpha.

It is not known if AVSOLA is safe and effective in children under 6 years of age.

Who should not receive AVSOLA?

You should not receive AVSOLA if you have:

- heart failure, unless your doctor has examined you and decided that you are able to receive AVSOLA. Talk to your doctor about your heart failure.
- had an allergic reaction to infliximab products, or any of the ingredients in AVSOLA. See the end of this Medication Guide for a complete list of ingredients in AVSOLA.

What should I tell my doctor before starting treatment with AVSOLA?

Your doctor will assess your health before each treatment.

Tell your doctor about all of your medical conditions, including if you:

- have an infection (see "**What is the most important information I should know about AVSOLA?**").
- have other liver problems including liver failure.
- have heart failure or other heart conditions. If you have heart failure, it may get worse while you receive AVSOLA.
- have or have had any type of cancer.
- have had phototherapy (treatment with ultraviolet light or sunlight along with a medicine to make your skin sensitive to light) for psoriasis. You may have a higher chance of getting skin cancer while receiving AVSOLA.
- have COPD, a specific type of lung disease. Patients with COPD may have an increased risk of getting cancer while receiving AVSOLA.
- have or have had a condition that affects your nervous system such as:
    - multiple sclerosis, or Guillain-Barré syndrome, or
    - if you experience any numbness or tingling, or
    - if you have had a seizure.
- have recently received or are scheduled to receive a vaccine. **Adults and children receiving AVSOLA should not receive live vaccines (for example, the Bacille Calmette-Guérin [BCG] vaccine) or treatment with a weakened bacteria** (such as BCG for bladder cancer). Adults and children should have all of their vaccines brought up to date before starting treatment with AVSOLA.
- are pregnant or plan to become pregnant, are breastfeeding or plan to breastfeed. You and your doctor should decide if you should receive AVSOLA while you are pregnant or breastfeeding.

If you have a baby and you were receiving AVSOLA during your pregnancy, it is important to tell your baby's doctor and other health care professionals about your AVSOLA use so they can decide when your baby should receive any vaccine. Certain vaccinations can cause infections.

If you received AVSOLA while you were pregnant, your baby may be at higher risk for getting an infection. If your baby receives a live vaccine within 6 months after birth, your baby may develop infections with serious complications

that can lead to death. This includes live vaccines such as the BCG, rotavirus, or any other live vaccines. For other types of vaccines, talk with your doctor.

How should I receive AVSOLA?

- You will be given AVSOLA through a needle placed in a vein (IV or intravenous infusion) in your arm.
- Your doctor may decide to give you medicine before starting the AVSOLA infusion to prevent or lessen side effects.
- Only a healthcare professional should prepare the medicine and administer it to you.
- AVSOLA will be given to you over a period of about 2 hours.
- If you have side effects from AVSOLA, the infusion may need to be adjusted or stopped. In addition, your healthcare professional may decide to treat your symptoms.
- A healthcare professional will monitor you during the AVSOLA infusion and for a period of time afterward for side effects. Your doctor may do certain tests while you are receiving AVSOLA to monitor you for side effects and to see how well you respond to the treatment.
- Your doctor will determine the right dose of AVSOLA for you and how often you should receive it. Make sure to discuss with your doctor when you will receive infusions and to come in for all your infusions and follow-up appointments.

What should I avoid while receiving AVSOLA?

Do not take AVSOLA together with medicines such as KINERET (anakinra), ORENCIA (abatacept), ACTEMRA (tocilizumab), or other medicines called biologics that are used to treat the same conditions as AVSOLA.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. These include any other medicines to treat Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis or psoriasis.

Know the medicines you take. Keep a list of your medicines and show them to your doctor and pharmacist when you get a new medicine.

What are the possible side effects of AVSOLA?

AVSOLA can cause serious side effects, including:

See "**What is the most important information I should know about AVSOLA?**"

Serious Infections

- Some patients, especially those 65 years and older have had serious infections while receiving infliximab products, such as AVSOLA. These serious infections include TB and infections caused by viruses, fungi, or bacteria that have spread throughout the body or cause infections in certain areas (such as skin). Some patients die from these infections. If you get an infection while receiving treatment with AVSOLA your doctor will treat your infection and may need to stop your AVSOLA treatment.
- Tell your doctor right away if you have any of the following signs of an infection while receiving or after receiving AVSOLA:
  - o a fever
  - o feel very tired
  - o have a cough
  - o have flu-like symptoms
  - o warm, red, or painful skin
- Your doctor will examine you for TB and perform a test to see if you have TB. If your doctor feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with AVSOLA and during treatment with AVSOLA.
- Even if your TB test is negative, your doctor should carefully monitor you for TB infections while you are receiving AVSOLA. Patients who had a **negative** TB skin test before receiving infliximab products have developed active TB.
- If you are a chronic carrier of the hepatitis B virus, the virus can become active while you are being treated with AVSOLA. In some cases, patients have died as a result of hepatitis B virus being reactivated. Your doctor should do a blood test for hepatitis B virus before you start treatment with AVSOLA and occasionally while you are being treated. Tell your doctor if you have any of the following symptoms:
  - o feel unwell
  - o poor appetite
  - o tiredness (fatigue)
  - o fever, skin rash, or joint pain

Heart Failure
If you have a heart problem called congestive heart failure, your doctor should check you closely while you are receiving AVSOLA. Your congestive heart failure may get worse while you are receiving AVSOLA. Be sure to tell your doctor of any new or worse symptoms including:

- shortness of breath
- sudden weight gain
- swelling of ankles or feet

Treatment with AVSOLA may need to be stopped if you get new or worse congestive heart failure.

Other Heart Problems
Some patients have experienced a heart attack (some of which led to death), low blood flow to the heart, or abnormal heart rhythm within 24 hours of beginning their infusion of infliximab products. Symptoms may include chest discomfort or pain, arm pain, stomach pain, shortness of breath, anxiety, lightheadedness, dizziness, fainting, sweating, nausea, vomiting, fluttering or pounding in your chest, and/or a fast or a slow heartbeat. Tell your doctor right away if you have any of these symptoms.

Liver Injury
Some patients receiving infliximab products have developed serious liver problems. Tell your doctor if you have:

- jaundice (skin and eyes turning yellow)
- fever
- dark brown-colored urine
- extreme tiredness (severe fatigue)
- pain on the right side of your stomach area (right-sided abdominal pain)

Blood Problems
In some patients receiving infliximab products, the body may not make enough of the blood cells that help fight infections or help stop bleeding. Tell your doctor if you:

- have a fever that does not go away
- look very pale
- bruise or bleed very easily

Nervous System Disorders
Some patients receiving infliximab products have developed problems with their nervous system. Tell your doctor if you have:

- changes in your vision
- seizures
- numbness or tingling in any part of your body
- weakness in your arms or legs

Some patients have experienced a stroke within approximately 24 hours of their infusion with infliximab products. Tell your doctor right away if you have symptoms of a stroke which may include: numbness or weakness of the face, arm or leg, especially on one side of the body; sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes, sudden trouble walking, dizziness, loss of balance or coordination or a sudden, severe headache.

Allergic Reactions
Some patients have had allergic reactions to infliximab products. Some of these reactions were severe. These reactions can happen while you are getting your AVSOLA treatment or shortly afterward. Your doctor may need to stop or pause your treatment with AVSOLA and may give you medicines to treat the allergic reaction. Signs of an allergic reaction can include:

- hives (red, raised, itchy patches of skin)
- high or low blood pressure
- difficulty breathing
- fever
- chest pain
- chills

Some patients treated with infliximab products have had delayed allergic reactions. The delayed reactions occurred 3 to 12 days after receiving treatment with infliximab products. Tell your doctor right away if you have any of these signs of delayed allergic reaction to AVSOLA:

- fever
- muscle or joint pain
- rash
- swelling of the face and hands
- headache
- difficulty swallowing
- sore throat

Lupus-like Syndrome
Some patients have developed symptoms that are like the symptoms of Lupus. If you develop any of the following symptoms, your doctor may decide to stop your treatment with AVSOLA.

- chest discomfort or pain that does not go away
- shortness of breath
- joint pain
- rash on the cheeks or arms that gets worse in the sun

Psoriasis
Some people receiving infliximab products had new psoriasis or worsening of psoriasis they already had. Tell your doctor if you develop red scaly patches or raised bumps on the skin that are filled with pus. Your doctor may decide to stop your treatment with AVSOLA.

The most common side effects of infliximab products include:

- respiratory infections, such as sinus infections and sore throat
- headache
- coughing
- stomach pain

Infusion reactions can happen up to 2 hours after your infusion of AVSOLA.
Symptoms of infusion reactions may include:

- fever
- chills
- chest pain
- low blood pressure or high blood pressure
- shortness of breath
- rash
- itching

Children with Crohn's disease showed some differences in side effects of treatment compared with adults with Crohn's disease. The side effects that happened more in children were: anemia (low red blood cells), leukopenia (low white blood cells), flushing (redness or blushing), viral infections, neutropenia (low neutrophils, the white blood cells that fight infection), bone fracture, bacterial infection and allergic reactions of the breathing tract. Among patients who received infliximab for ulcerative colitis in clinical studies, more children had infections as compared with adults.
Tell your doctor about any side effect that bothers you or does not go away.
These are not all of the side effects with AVSOLA. Ask your doctor or pharmacist for more information.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about AVSOLA
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
You can ask your doctor or pharmacist for information about AVSOLA that is written for health professionals.
For more information go to www.AVSOLA.com, or call 1- 800-77-AMGEN (1-800-772-6436).

What are the ingredients in AVSOLA?
The active ingredient is infliximab-axxq.
The inactive ingredients in AVSOLA include: dibasic sodium phosphate anhydrous, monobasic sodium phosphate monohydrate, polysorbate 80, and sucrose. No preservatives are present.

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